Bone cements and fillers: A review

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Charnley [1] developed the first bone cement in the 1960s using poly(methyl methacrylate) (PMMA), which remains the most widely used material for fixation of orthopaedic joint replacements. In the field of dentistry, zinc polycarboxylate and glass polyalkenoate cements received major research interest from the 1970s to the present day. The discovery of a well-integrated intermediate layer between bone and many bioactive ceramic phases from the calcium–phosphate system, such as hydroxyapatite (HA), resulted in the development of new cements incorporating such phases. These investigations ranged from the development of castable bioactive materials to modified bioactive composites. This paper attempts to give a broad overview of the many different types of cements that have being developed in the past and those which are being researched at the present time. It has lead to a set of fundamental design criteria that should be considered prior to the development of a cement for use as a bone cement or in applications requiring a bone substitute.

1. Introduction

Fixation of the majority of prostheses in the past has been performed using poly(methyl methacrylate) (PMMA) bone cement[1] [1]. However, although used universally for many years, PMMA bone cement is not without its problems, as it has to cure before it sets hence suffering both biologically and mechanically. These problems lead to the failure of the cement and hence the prosthetic it holds in place, via aseptic loosening [2].

Thus, in an effort to prolong the lifetime of the prosthetic, investigations have been carried out on many different types of cements. Ionic polymer cements set via a neutralization reaction, therefore eliminating the complications associated with the exotherm accompanying the PMMA cement. Zinc and glass polyalkenoate cements first came to prominence as dental cements in the late 1960s [3] and early 1970s [4]. Although biocompatible, the zinc component results in the formation of a fibrous collagen capsule around the zinc polycarboxylate cement *in vivo* [5], which compromises the strength of the intermediate region between the bone and the cement. Previous to an *in vivo* assessment of glass polyalkenoate cements [6] it was anticipated that these materials had potential in orthopaedic applications. However, demineralization of pre-existing bone local to the site of implantation, accumulation of aluminum both locally and at a distance from the site of implantation, and defective mineralization of newly formed osteoid were observed after the cement was implanted in the femur of rabbits for 6 weeks. These results, though disappointing, did not stop investigations into the cements' mechanical properties.

A fourth type of biomaterial was introduced with the synthesis of bioglass [7]. These materials were designed to induce a specific biological activity [8]. However, their fragile nature limits their applicability in the orthopaedic area. Thus, in order to overcome this limitation, research branched out in the area of apatite/wollastonite glass–ceramics [9]. Various compositions of these glass–ceramics have been investigated [10–12] and numerous bioactive ceramics are now fabricated commercially in various shapes and forms for orthopaedic applications [13].

Investigations into bioglass and apatite/wollastonite glass–ceramics prompted the development of off-the-shelf bone graft substitute materials. Synthetic hydroxyapatite can be created commercially and serves primarily as a scaffold in order to facilitate the bone regeneration process [14].

Calcium phosphate cements possess an additional characteristic in that they can be shaped intraoperatively. Examples for cement formulations are powder mixtures of tetracalcium phosphate (TTCP) and dicalcium phosphate anhydride (DCPA) or dicalcium phosphate dihydrate (DCPD) or β-tricalcium phosphate (β-TCP), which react in the presence of water to form hydroxyapatite without any acidic or basic byproducts [15]. The aqueous environment is used for mass transport; the reactants form a supersaturated micro-environment in solution with regard to hydroxyapatite.

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In an effort to combine the biological properties of glass polyalkenoate cements with the mechanical properties of resin-based components, resin-modified cements have being examined [16, 17]. These types of materials are easy to handle and place with good aesthetics as well as possessing immediate strength. Hence, they have become quite popular. However, high polymerization shrinkage results in a less than well-integrated cement with the adjacent bone [18].

In an attempt to match the stiffness of the bone cement to that of bone, examination of the microstructure of bone [19] has suggested a possible solution. A material with a low elastic modulus and high strength can be achieved by reinforcing a suitable biocompatible polymer with a bioactive second phase material. Control of the properties and design of the cement can be achieved by using various volume fractions of each phase, thus tailoring the mechanical and physiological conditions to best suit the host tissue.

Each of the various types of cements have been discussed individually in this paper, giving details relating to their mechanical, rheological, and biocompatible properties.

2. Poly(methyl methacrylate) cements

Mainly through the pioneering efforts of Charnley [1] the two-part self-polymerizing PMMA bone cement emerged as one of the premier synthetic biomaterials in contemporary orthopaedics. Since its inception, PMMA cement has widely been used in various prosthetic replacement operations. In these applications the main functions of the cement are to transfer body weight and service loads from the prosthesis to the bone and/or increase the load carrying capacity of the prosthesis–bone cement–bone system. The cement performs these functions admirably because of the array of properties it possesses. However, in recent years it has been recognized that to achieve a long lasting bone replacement requires the establishment of a stable bone–implant interface. Therefore, because of the non-bone bonding character of the PMMA cement, aseptic loosening is reported to be the most common cause of failure in cemented arthroplasties using PMMA cement.

3. Zinc phosphate cements

Zinc phosphate cements were mainly developed for dental applications such as lining materials and as adhesives for cementing appliances to the external surfaces of teeth. The main component of the powder is zinc oxide, with an addition of 2–10% magnesium oxide. The liquid is an aqueous solution of 45–60% phosphoric acid.

The setting reaction between the positive zinc ions and the negative phosphate groups results in a brittle cement, but this has relatively high compressive strength [3]. Despite the use of the term cement when referring to zinc–phosphate materials, this is not a characteristic of the material in the fully hardened condition. The retaining action in its hardened state is almost totally one of mechanical interlocking between the surface irregularities of the tooth and the restoration.

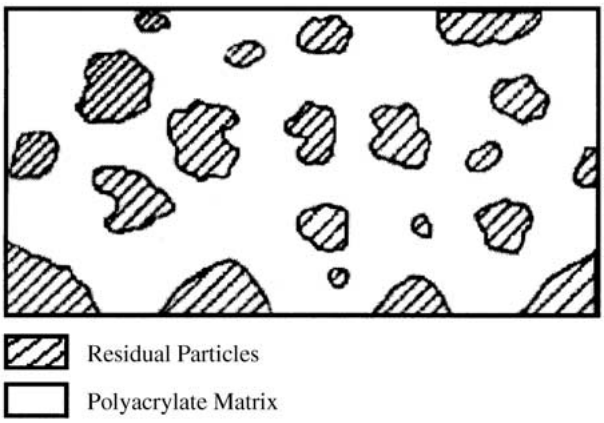


Figure 1 Un-reacted metal oxide particles embedded in a zinc polyacrylate matrix.

The disintegration of these cements within the oral cavity is accelerated via the attack of food decomposition products, wear and abrasion. These cements exhibit limited compressive strengths of approximately 104 MPa [20].

4. Zinc polycarboxylate cements

Developed by Smith in 1968 [3], zinc polycarboxylate cements are modified zinc phosphate cements and have been widely used clinically, including: cavity liners, as adhesives for the placement of crowns and for the adhesion of orthodontic applications [21]. Roughly speaking, these cements are fabricated by the chemical mixing of a metal oxide and a polyelectrolyte polymer. They belong to the class of materials known as acid–base reaction cements, which set at body temperature, thereby eliminating any problems associated with the thermal necrosis of surrounding tissue. The constituents are a polycarboxylic acid, usually poly(acrylic acid) (PAA), and a modified zinc oxide (ZnO) powder. The modified ZnO is prepared by mixing pure ZnO with small amounts of magnesium oxide and fusing the mixture at 1100–1200 °C [22]. The heat treatment causes the ZnO to become slightly yellow in color, due to evaporation of oxygen to give a non-stoichiometric material [23]. This process reduces the reactivity of the ZnO towards the acid, and therefore the cement paste sets sufficiently slowly to be mixed and placed.

The set cement consists of unreacted metal oxide particles embedded in a zinc polyacrylate matrix (Fig. 1). The zinc ions released from the ZnO particles crosslink the PAA chains and effectively render them insoluble. However, there is some controversy surrounding the nature of the set cement in the literature. Padilla and his co-workers [24] reported that a decrease in porosity occurred as the ZnO/PAA ratio was increased. The chemical reaction between PAA and ZnO was used to explain this phenomena:

$$\mathrm{ZnO} + 2(\mathrm{–CH2–CHCOOH–}) \rightarrow (\mathrm{–CH2–CHCOO–})2\mathrm{Zn} + 2\mathrm{H2O}$$

Crosslinking was reported to take place via a sort of ''bridge'' between the divalent zinc cation and the hydrophilic functional groups on the polymeric chain. In

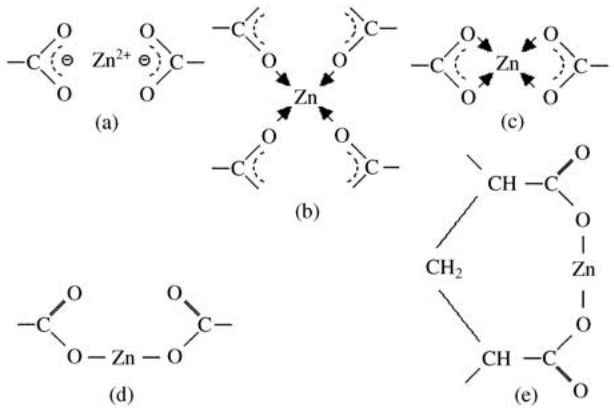


Figure 2 Possible modes of bonding of Zn^{2+} to carboxylate groups in zinc polycarboxylate cements ((a) ionic, (b) bridging bidentate (c) chelating bidentate (d) asymmetric unidentate (e) chelate bidentate (8-membered ring)) (after Nicholson [25]).

fact, Nicholson *et al*. [25], conducting a study using Fourier transform infrared spectroscopy (FTIR), concluded that there were a number of types of zinc carboxylate units, including purely ionic but also a variety of covalent structures (Fig. 2). Studies by Anstice *et al*. [26] and Moharran *et al*. [27] were in agreement with this hypothesis. However, Wilson [28] suggested that zinc polyacrylate is a simple salt and that there is no evidence for chelate formation from FTIR studies. Hill *et al*. [29] concluded that these cements behave in many ways like thermoplastic composites, as the chain length of the PAA had significant influence over the fracture properties. They suggested that rather than treat the linkages between the polymer chains as crosslinks, it would be better to treat them as interchain attractions, therefore supporting the idea that the polymer chains can slip past one another. It was found [29] that the fracture toughness, as well as other fracture properties and the Young's modulus of the zinc polycarboxylate cements, are influenced by the molar mass of the PAA to a much higher degree compared to the glass polyalkenoate cements. This greater influence of PAA chain length may well reflect the weaker linkages between the polymer chains.

Also, the inherent flaw size did not vary systematically with molecular weight but instead was found to correspond to the macroscopic pores, or surface cracks as these cements are quite porous. Padilla *et al*. [24] suggested that there is a clear dependence of the final porosity of this cement on the chemical composition of the composite concluding that the ZnO/PAA ratio of 0.6 resulted in minimal porosity. This behavior was associated with specific physicochemical conditions whereby the reaction could be reversed and some of the water would act as a solvent for both the reacted and the un-reacted substances.

As PAA is a polyelectrolyte it will dissociate into polymeric ions and numerous small ions (counter-ions), which remain in the vicinity of the polymeric ions via electrostatic attractions [30]. Therefore, in water the hydrocarbon backbone will be hydrophobic and therefore insoluble, whilst, in contrast, it is the polar functional groups which confer solubility. Small amounts of water were found to be particularly tightly bound within these cement structures [22]. As the PAA has been shown to experience complete neutralization within these cements [28, 31] then any tightly bound water molecules maybe associated with the Zn^{2+} and Mg^{2+} ions. As these small amounts of water were retained under an extremely desiccating environment, it can be assumed to be present within a coordination sphere of the metal ions. Nicholson and his co-workers [22] also showed that the zinc polycarboxylate cements achieved their maximum strength usually after 7 days, after which time there was little or no increase in strength. Neutralization in the zinc polycarboxylate cements, was found to occur more rapidly than that which occurred in the glass polyalkenoate cements, with the rate controlling step determined as being the diffusion of the metal ions [31]. The rate of elution of Zn^{2+} and Mg^{2+} ions from polycarboxylate cements decreases with aging time. This phenomenon is explained by the setting reaction in which these cations are liberated from the oxide powder by an exchange with protons from the polyacid and in this state are vulnerable to water leaching [32]. Subsequently, these cations become more resistant to water leaching as they bind to the polyanion chain. Loosely and tightly bound forms of water are absorbed by polycarboxylate cements. The ionization of the polyacid during the course of the reaction apparently creates a demand for water, and the cement where the COOH:C ratio in the polyacid is highest absorbs the most water. Reaction in the zinc polycarboxylate cements is therefore relatively rapid and occurs within the first few days of mixing.

Zinc is an essential metal, which a wide variety of metabolic processes rely on for the function of many enzymes [33–34]. The relatively low toxicity of zinc *in vivo* may be ascribed to a combination of homeostatic mechanisms that regulate gastrointestinal absorption and excretion of zinc [33], the action of a variety of hormonal stimuli which control cellular metabolism [34], rapid redistribution of Zn in the body and cellular adaptive mechanisms [35]. For cells in culture exposed to relatively high concentrations of Zn the maintenance of homeostasis is more difficult since the adaptive mechanisms are the only available way of regulating Zn levels and this may make them more vulnerable. The sensitivity of cells *in vitro* to the toxic effects of zinc may be dependent on the rate of zinc uptake [36]. Compared to other trace elements, zinc is relatively non-toxic *in vivo* [33, 37]. In dental applications, zinc polycarboxylate cements have shown very good chemical stability on long-term use *in vivo* [38]. The composition of the cements (unreacted ZnO and zinc polycarboxylate matrix) was found to be independent of their age, except that older cements did appear to have a greater amount of water. Low levels of Zn^{2+} ions released *in vivo* are also believed to assist in the prevention of bacterial infection [39]. Zinc is fundamental for cell growth, development and differentiation [40]. Yamaguchi *et al*. [41] suggested that zinc may be localized largely in the osteoblasts of bone and can stimulate bone formation, playing a physiologically important role as an activator in bone metabolism. In a study undertaken by Peters and his co-workers [39] it was found that the zinc ions were non-toxic *in vivo* over a one year study period. Also, the bond between the zinc ions and the PAA appeared to be more stable than that

TABLE I Covalent, atomic, ionic radius and electronegativity of the Ca and Zn ions

Property	Calcium	Zinc
Covalent radius (Å)	1.74	1.25
Atomic radius (Å)	1.97	1.38
Ionic radius (Å)	0.99	0.74
Electronegativity	1.00	1.65

between the calcium ions and the PAA. This may be due to the fact that the calcium ions are more easily hydrolyzed than zinc ions because they are less strongly bound to the polyanion chain. Zinc ions are apparently more strongly bound to a polyacid as they have a smaller radius and greater electronegativity than the Ca^{2+} ions (Table I).

The uptake of ^{45}Ca by the poly(acrylic acid) was reported to be complete after 2 h, at a concentration of 2 g/mol. There was no change in the ^{65}Zn bound to the cement when the Ca^{2+} concentration was increased. A fibrous collagen capsule layer was observed between the zinc polycarboxylate cement and bone in a study conducted by Lawerence *et al*. [42] suggesting the material is biocompatible. However, it must be remembered that zinc is a highly potent and selective inhibitor of osteoclastic bone resorption *in vitro* [36, 43].

5. Glass polyalkenoate cements

In spite of their novel properties, zinc and other metal oxide cements are opaque and unaesthetic. Formulations using zinc-containing glass–ceramics and silicate cement powders were developed [3] but they do not set rapidly or satisfactorily when mixed with PAA solutions. Similar observations were made by Wilson *et al*. [44] who carried out extensive studies on the basic chemistry of dental silicate cements. By modification of the Al_2O_3/SiO_2 ratio in the silicate glass Wilson and Kent [4] were able to produce usable cements with PAA.

The setting reaction in glass polyalkenoate cements has been studied in detail over the past 30 years or so. They are formed from acid–decomposable glasses and aqueous solutions of poly(alkenoaic acids), usually PAA [45]. In addition, (+)-tartaric acid (Fig. 3) is incorporated as it delays the onset of the hardening reaction whilst speeding up the latter stages of this process. Fluidity is retained for longer and setting occurring more sharply compared to cements without (+)-tartaric acid. It was established quite quickly that neutralization of the aqueous acid by the glass [46] lead to a set material and therefore were referred to as acid–base reaction cements

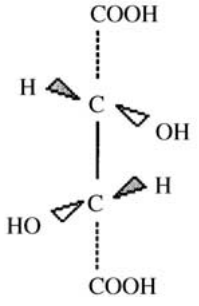


Figure 3 Chemical structure of (+)-tartaric acid.

[47]. The acid degrades the glass structure and hydrolyzes the bonds of the glass network. Aluminum–oxygen–silicon bonds [48] and phosphorus–oxygen bonds [49] of the glass network are hydrolyzed releasing aluminum and calcium cations, which are chelated by the carboxylate groups and serve to ''crosslink'' the PAA chains.

Initally, setting within these cements was believed to occur via a two-step mechanism [45]. The primary hardening step was completed after approximately 3–5 min and was followed by a secondary post-hardening step. During the early stages of the reaction, FTIR studies revealed that a calcium salt alone was formed [46] leading to gelation and initial set. The latter step involved the formation of an aluminum salt, the precise nature of which is in doubt. Therefore, a sequential release of, first calcium ions followed by aluminum ions was believed to occur [45–47]. The latter reaction, resulting in an aluminum–polyacrylate species, was associated with improvements in mechanical properties of these cements, which were found to occur with time [50]. Conversely, studies by Cook [31, 51] questioned this idea of sequential release of Ca^{2+} and Al^{3+} ions and suggested that Al^{3+} ions are also involved in the initial setting reaction. However, Wasson and Nicholson [52] maintain that, even though aluminum ions are released early in the setting process, a delay between when the ions are released and the formation of an aluminum polyacrylate species is due to the slow decomposition of the anionic form of aluminum $\{[Al_{13}O_4(OH)_{24}(OH_2)_{12}]^{7+}\}$ in aqueous solution.

However, in recent years the improvement in mechanical properties with time has been related to an additional reaction. The presence of Ca^{2+} and Al^{3+} ions, which were originally believed to be as a result of an ion-exchange process, are now thought to result from the complete dissolution of a fraction of the glass [53]. The setting of the cements was still related to the neutralization reaction involving calcium and aluminum ions, together with a more gradual one involving the reconstruction of the silicate network of the glass. It was this latter reaction that was associated with changes on maturation [52, 54]. The initial leaching of ions from the glass is believed to leave behind an ion-depleted layer of silica gel around unreacted glass particles. The fact that zinc polycarboxylate cements behave in a different manner to glass polyalkenoate cements with respect to toughness was used to explain the significance of a hydrated silicate phase. The toughness of zinc polycarboxylate cements was found to depend on the molar mass of the polymer component, with the slope of the log G_I versus log M plot being approximately 1 [29]. However, the slope of such a plot for the glass polyalkenoate cements is 0.5. Thus the presence of a silicate network was held responsible for the difficulty in pulling polymer chains through the cement matrix [54]. This phenomenon was supported by work carried out by Hatton and Brook [55] which revealed, via transmission electron microscopy (TEM), glass particles surrounded by a siliceous layer set in a hydrogel matrix. The presence of these regions was verified by X-ray microanalysis data, which detected such ions throughout the matrix.

Maeda and his co-workers [56] provide evidence that

TABLE II Types of tissue attachment of biomaterials

Type of implant	Type of attachment	Example
1. Nearly inert	Mechanical interlock (morphological fixation)	Metals, Alumina, Zirconia. Polyethylene (PE).
2. Porous	Ingrowth of tissues into pores (biological fixation)	Hydroxyapatite (HA), HA coated porous metals
3. Bioactive	Interfacial bonding with tissues (bioactive fixation)	Bioactive glasses, HA, Bioactive glass–ceramics
4. Resorbable	Replacement with tissues	TCP, Polylactic acid (PLA)

the surface of the glass dissolves and changes into a siliceous gel, by means of secondary ion mass spectroscopy (SIMS). However, it was also confirmed that Si^{4+} ions are not distributed uniformly throughout the matrix areas, but remain in high concentrations around undissolved glass core. It was proposed that the protons migrate from the matrix to the glass, while Al^{3+} ions migrate in the reverse direction. It is also believed that the migration of Al^{3+} ions could continue for long periods, accumulating in regions of bone formation, both locally and at a distance from the implant material, inhibiting mineralization [6]. Therefore, the development of a glass polyalkenoate cement with low/no aluminum release from the unset cement dough is a priority in the further development of these cements for possible orthopaedic applications.

One of the major disadvantages of glass polyalkenoate cements is their poor fracture toughness ($1.39\,MPa\sqrt{m}$ [57]). These cements can achieve Young's modulus values in the range 4–8 GPa and flexural strengths between 25 and 35 MPa. Fluoride and phosphate ions are known to complex aluminum and calcium ions and reduce their ability to crosslink polyacrylate chains. For example, in the presence of F^- ions hydrated AlF^{2+} ions, rather than hydrated Al^{3+}, are likely to exist [58]. In contrast to the acrylic cements, this setting reaction does not generate significant heat and so will not cause thermal damage to tissues at the implant site.

Glass polyalkenoate cements do not have to rely exclusively on a mechanical bond to achieve fixation. Although mechanically inferior to acrylic cements, the possibility of chemical adhesion to the surrounding tissue and prosthesis, may overcome this deficiency. Their potential for bioactivity is illustrated in their ability to release osteoconductive ions such as calcium and fluoride for prolonged periods post-setting [55]. Implantation of set glass polyalkenoate rods resulted in the formation of variably mineralized osteoid/woven bone at the bone–cement interface. However, the bone of animals implanted with cement dough exhibited demineralization of pre-existing bone local to the site of implantation with aluminum accumulating in regions of bone formation, both locally and at a distance from the implant material, inhibiting mineralization [6]. Therefore the development of a glass polyalkenoate cement with low/no aluminum release from the unset cement dough is a priority in the further development of these cements for possible orthopaedic applications.

6. Bioglass

Hench and his co-workers at the University of Florida synthesized a surface-active material that underwent chemical bonding to bone [7]. This new type of ''biomaterial'' was a soda lime phosphosilicate glass labeled ''Bioglass'' which was composed of 46.1% SiO_2, 24.4% NaO_2, 26.9% CaO and 2.6% P_2O_5, all in weight percent.

Since their discovery, an ever-increasing amount of new types of bioactive glasses have been developed and used in prosthetic applications and in repair of bone defects, due to their well documented biocompatibility, as well as their osteoconductive and bone-bonding properties [59–60]. According to the different types of implant–tissue attachment, biomaterials were classified into three types, which are summarized in Table II, bioglass introduced a fourth response; the formation of a mechanically strong chemical bond across the tissue/implant interface. This attachment is called ''bioactive fixation''. It is capable of withstanding more complex stress states than dense nearly inert implants that achieve only ''morphological fixation''.

The bioglasses used in orthopaedic surgeries:

- Allow the prosthesis to adapt to the bone cavity.
- Prevent the formation of fibrous tissue at the prosthetic–bone interface.
- Favor a strong chemical bond between implant and bone tissue.

The reaction kinetics at the interface of 45S5 Bioglass have been studied extensively and apparently proceed via five stages after implantation [61]. These five stages occur on the material side of the interface and do not depend on the presence of tissues. Initially there is an ion exchange between the implant surface and the surrounding physiological environment with Na^+ being replaced by H^+ or H_3O^+. The second stage involves the break-up of the silicate network to form silanols:

$$Si–O–Si + H_2O \rightarrow 2Si–OH_{(aq)}$$

The third stage involves the equilibrium condensation and partial repolymerization of these silanols to form a SiO_2-rich gel layer at the interface. The open gel structure then permits rapid migration of Ca^{2+} and PO_4^{3-} to the interface region, which subsequently produces a $CaO–P_2O_5$ rich film on the gel layer that develops into a thicker and denser amorphous layer. The final stage involves crystallization of the amorphous calcium–phosphate into a mixed hydroxyl, carbonate and fluoro-apatite layer, the necessary OH^-, CO_3^{2-} and F^- anions again being derived from host tissue. Successfully, a calcium phosphate layer will recrystallize onto this layer of hydroxycarbonate apatite [62]. Bone-bonding properties of bioglasses are based on the formation of this layer. Compared to synthetic hydroxyapatite, the surface layer of bioactive glasses is more similar, in terms of crystallinity, to the apatite of bone

tissue and consequently a greater proportion of bone bonding has been reported for bioactive glasses than for HA [59].

Hill [63] provided a supplementary explanation on the bioactivity of bioglasses through a discussion of the composition of bioglasses and the effect on its network connectivity. Silicate glasses can be regarded as inorganic polymers of oxygen crosslinked by silicon atoms. The reactivity and solubility of inorganic glasses change dramatically at the point where the glass moves from being a continuous crosslinked network to a linear polymer of ever decreasing molar mass. The transition occurs at a crosslink density[2] of 0 or network connectivity of 2. The network connectivity of 45S5 is 1.90. Therefore, the silicate structural units present are of low molar mass and thus capable of dissolving without any breakage of the Si–O–Si bonds, contrary to Hench's model.

A network connectivity greater than 2 will usually result in a 3D network, decreasing the reactivity of the glass and therefore the bioactivity. For example, incorporation of aluminum into the glass converts the glass from a low molar mass polymer to a less reactive three-dimensional network. Therefore, the inhibition of bone bonding with glasses containing aluminum may be due to changes in reactivity rather than to aluminum directly inhibiting the bone bonding ability of the glass.

Whilst the network connectivity of glass can give an insight into the properties of bioglass, calculation of it is crude, assuming once a bridging oxygen is replaced by two non-bridging oxygens, the bond is completely broken. However, when a divalent metal such as calcium is used as a network modifying oxide the bond between the two silicate chains will be a weaker one with a more ionic character. Therefore, Hill argues that the importance of the second step in Hench's mechanism will depend critically on the network connectivity of the glass. In glasses with no phosphate content and a network connectivity well above 2, it is a critical step, but with glasses with a network connectivity below 2 it will not be so important [63].

Many of these materials have the capacity to form a hydroxycarbonate apatite layer (CHA) on their surfaces *in vitro* and *in vivo* [13], compatible with the mineral phase of bone. Although some materials display favorable physical and mechanical properties, they are often very hard, brittle, and difficult to machine. Their fragile nature thus limits the production of suitable shapes for implantation to treat various bone defects in orthopaedic and dental applications. The addition of HA to bioactive glasses has been reported to increase the mechanical properties [64, 65]. However, it has been found that $CaO–P_2O_5–SiO_2–(MgO)$ glass can crystallise apatite and wollastonite after appropriate heat treatment and are stronger than hard tissue [66]. Yoshihara *et al.* [67] reported that bioactive $CaO–P_2O_5–SiO_2$ glass, reacted with 3.7 M ammonium phosphate solution at pH 7.4, achieves a compressive strength of 25 MPa on hardening. However, immersion in simulated body fluid results in an increase in compressive strength (about 80 MPa) due to the formation of hydroxyapatite in the cement.

The nature of the relationship between the structure of these glasses on their compositions allows for their exploitation and development. The degree of reactivity and solubility can be manipulated via the addition of network modifiers, such as CaO and Na_2O. The incorporation of such compounds interrupt the physical nature of the glasses, while the proportion of CaO determines the dissolution times [68]. These constituent atoms are found in the inorganic mineral phase of bone and therefore they have a chemical affinity with bone. Therefore, the ease of manufacture and ability to control the solubility makes them potentially clinically useful for promoting the regeneration of soft as well as hard connective tissues. Hence, bioactive glass materials are available in a range of compositions that are able to bond to soft tissue and/or bone. These materials vary in their reactivity and speed of bonding and in the ability of the bone to provide mechanical strength. They have been successfully applied as solids and particulates and may be combined with other materials, both natural and synthetic, to provide treatment for many disparate clinical conditions [69–73].

7. Apatite/wollastonite glass–ceramics

As a result of different requirements in the development of biocompatible and bioactive glass–ceramics, distinct chemical systems are used, with the development of glass–ceramic materials being concentrated on different main crystal phases.

According to the principles of controlled surface crystallization of powdered glass, Kokubo *et al.* [9] developed an apatite–wollastonite (AW) glass–ceramic with composition 34% SiO_2, 44.7% CaO, 4.6% MgO, 16.2% P_2O_5, 0.5% CaF_2 all in weight percent. This glass ceramic is known to form a tight chemical bond with bone and a high mechanical strength [74, 75] can be produced through sintering and subsequent crystallization of glass powders. Fine crystals such as apatite wollastonite ($CaOSiO_3$) and whitlockite ($3CaO \cdot P_2O_5$) precipitate from the glass matrix and enhance the mechanical strength whilst promoting bioactivity of the glass ceramic. The effect of compositional changes on the bioactivity [10] and crystallization behavior of these glass ceramics has been the subject of many investigations [76]. As with bioglass, the effect of SiO_2 content is of interest in the study of their bioactive and mechanical properties. Marghussian and his co-workers [11] studied the effect of P_2O_5 replacement by SiO_2 and found that the amount of wollastonite precipitated in the glasses increased at the expense of apatite precipitation. This resulted in an increase in compressive strength and fracture toughness. It was also concluded that the presence of apatite was not essential for a bioactive characteristic and it was thus suggested that further reduction (or complete exclusion) of P_2O_5 could increase the strength and toughness of these materials, with a positive effect on bioactivity. Ebisawa *et al.* [12], in a study investigating the bioactivity of these materials, also concluded that the formation of this apatite layer occurred with P_2O_5-free $CaO \cdot SiO_2$ glass. The bone bonding ability of the glass decreased with the addition of P_2O_5 and Na_2O. The osteoconductive properties of these materials were evaluated by Ikeda *et al.* [77] and

TABLE III Physical properties of AW glass–ceramics (after Kokubo [80])

Physical property	Value
Density (g/cm^3)	3.07
Bending strength (MPa)	215
Compressive strength (MPa)	1080
Young's modulus (GPa)	118
Vicker's hardness (HV)	680
Fracture toughness (MPam$^{1/2}$)	2.0

after the effects of size and porosity were investigated, it was concluded that dense granules were not easily handed and due to their smooth surfaces they did not stay in place satisfactorily. However, bone adsorption was facilitated by porous granules, which were easy to handle, because of their rough surfaces, as well as having the ability to be molded into the desired shape at the time of operation.

The apatite layer is believed to form by a chemical reaction of the calcium and silicate ions dissolved from the glass–ceramic with the phosphate ion in the surrounding body fluid [78]. The exact mechanism of apatite formation on the surfaces of these glass-based glass–ceramics in the body is thought to involve the dissolution of Ca^{2+} ions from the glass, which increases the ion activity product of the apatite in surrounding body fluid. The hydrated silica on the surface of the glass and glass–ceramic provides sites for nucleation of apatite. The role of the silica hydrogel layer on the cement surface was investigated by Kokubo *et al*. [79] and the addition of silicate ion in combination with simulated body fluid (SBF), which consequently combines with the silanol group to form a highly hydrated silicate structure on the surface of the glass-ceramic, is said to be the major requirement for apatite nucleation. Consequently, the apatite nuclei are rapidly formed on their surfaces and spontaneously grow by consuming calcium and phosphate ions from the surrounding body fluid.

This glass–ceramic has a bending strength that is almost twice that of dense sintered hydroxyapatite (115 MPa) and higher than human cortical bone (160 MPa) (Table III). As the parent glass and the glass–ceramic (precipitating only apatite) have bending strengths of 72 and 88 MPa respectively it is apparent that it is the precipitation of wollastonite, as well as apatite, which is responsible for its high bending strength [80]. AW glass–ceramic has a roughened fracture surface, and as the glass and apatite have fairly smooth fracture surfaces, then this means that the wollastonite effectively prevents straight propagation of cracks. Therefore, AW glass–ceramics achieve high fracture surface energy, which results in high fracture toughness.

Bioactive ceramics of various sizes and forms are now fabricated commercially for orthopaedic applications [13]. Bioactive ceramic blocks are used for vertebral replacement, reconstruction of the iliac crest and filling the cavities left after excision of bone tumors and the granular forms are often used for filling interstices surrounding a block/defect with skeletal surface irregularities such as those encountered during revision surgery for aseptically loosened hip prostheses.

8. Synthetic hydroxyapatite

Analysis of various failed implants over the last 30 years has indicated that their failure mainly originates at the tissue/biomaterial interface [81]. The formation of the fibrous capsule and the dimineralization of bone surrounding the implant are thought to be the main causes of this interface failure. Clinical success requires the simultaneous achievement of a stable interface with connective tissue and a match of the mechanical behavior of the implant with the tissue to be replaced. Particulate bone grafts are often required for reconstructive orthopaedic, maxillofacial, craniofacial, oral and plastic surgery procedures. However, donor site morbidity remains a problem associated with the use of autografts[3] [82].

Moreover, more bone graft than can be obtained from autogenous bone sites is often required. Concerns with allograft[4] bone include [82]:

- Transmission of disease.
- Difficulty of procurement and processing.
- Uncertain immune response.
- Premature resorption.

These issues have prompted investigation and development of off-the-shelf bone graft substitute materials. The availability of such substances has benefited other indications, such as the treatment of periodontal[5] defects [83], for which bone autografts and allografts were not generally used. Bone graft substitute materials are employed primarily to serve as scaffold to facilitate the bone regeneration process [14]. Therefore, if a bone cement, which achieves approximately the same mechanical and biological make up of bone itself, is developed, then similar compositions should perform as effective bone substitutes. Some properties may need to be manipulated but this should easily be overcome. To function successfully in this capacity, the bone substitute needs to serve as a substrate for osteogenesis (i.e. be osteoconductive). In doing so it becomes incorporated into host bone thus preventing its migration or movement relative to surrounding bone that might interfere with the bone formation process. The incorporated bone graft substitute particles are mechanically coupled (i.e. bone-bonded) to the host bone that forms on the surface of the particles and in the interstices. In effect, this creates a particulate-filled composite material, with the trabecular bone serving as the ''matrix'' material of the composite. As with any composite, the mechanical properties of the particulate filler have a profound effect on the mechanical properties of the composite. Hydroxyapatite (HA) is the main component of hard tissues such as bones and teeth of vertebrate animals and humans. Consequently HA is readily considered as a bioactive material for artificial bone substitution because of its biocompatibility and chemical and biological affinity with bony tissue [84, 85].

While calcium hydroxyapatite ($Ca_5(PO_4)_3OH$) is the primary inorganic component of natural bone [86] trace elements are also present. HA is but one of a number of calcium–phosphorus (Ca–P) compounds which are biocompatible. Others include octacalcium phosphate and both forms of TCP ($Ca_3(PO_4)_2$). Compounds,

particularly HA, may show differing degrees of stoichiometry with the Ca:P ratio ranging from 1.55 to 2.2 [87]. Such materials can be artificially created by conventional high-temperature ceramic processing or by low-temperature aqueous chemistry [88]. Many such artificial materials show good bio compatibility so that bone cells tolerate their presence with few deleterious effects, and indeed enhanced bone mineralization may occur [13].

The apatite structure is a very hospitable one, allowing the substitution of many other ions. Changes in properties like lattice parameter, morphology solubility (etc.) occur as a result of substitutions for (Ca), (PO_4) or (OH) groups. For example, when the CO_3^{2-} substitutes for PO_4^{3-}, it is called B-type carbonate hydroxyapatite (CHA), which results in a decrease of the *a*-axis and an increase of the *c*-axis [89]. This contraction of the *a*-axis occurs as the smaller planar CO_3^{2-} group substitutes for the larger PO_4^{3-} tetrahedral group. The position of the carbonate group in this site has been found to reduce crystallinity and size of precipitates [90].

Expansion of the *a*-axis and contraction of the *c*-axis occurs as a consequence of substitution in the OH^- sites with CO_3^{2-} groups, as expected when the smaller linear OH group is replaced by the larger planar CO_3 group. The presence of carbonate in the apatite structure weakens the bonds, increases the dissolution rate and the solubility [89]. The occurrence of CO_3^{2-} in the apatite structure can be elucidated from X-ray diffractions patterns and FTIR spectra. To confirm substitution of carbonate in apatite via XRD, patterns around the main peak ($2\theta = 31$–$35°$) are examined. An upward shift in the expanded (300) reflection peak (around 32.5°) is an indication that CO_3^{2-} ions substitute into the PO_4^{3-} positions [91]. From FTIR analysis the CO_3 band has been reported in the region 1400 cm^{-1} (in the range 1108–1414 cm^{-1}). Absorption bands in the range 865–1039 and 1108–1414 cm^{-1} indicate the presence of PO_4, whilst absorption band representing OH are observed at about 3568 cm^{-1} [92].

The rate of calcium dissolution has been correlated to the pH of the surrounding environment [93]. Higher HA crystallinity appears to result in less change in medium pH. Normal cell lines grow well at pH 7.4, however, as the pH falls from pH 7.0 to pH 6.5, cell growth will stop, with cell viability being lost between pH 6.5 and pH 6.0 [94] It has been reported, however, that the *in vivo* cellular response could be compromised by highly crystalline HA ceramics. Some amorphous or more soluble phases may be desirable and may result in a more stable interface with the biological environment [95]. Yamaguchi [96] reported that HA blocks were biocompatible and demonstrated a character resistant to degradation. However, the degradation resistant character of porous HA blocks indicated that they would not be subjected to osteoclastic resorption, a process which controls bone remodeling. Therefore, it was suggested that porous HA might make a mechanical weak point if the cortex of long bones were filled with them [96].

Dense HA like other Ca–P biomaterials is osteoconductive but not osteoinductive [84]. As stated earlier, an osteoconductive material allows the formation of bone on its surface by serving as a scaffold or a template. The role of dense HA is not a passive one and it contributes to the formation of the CO_3^{2-} apatite on surfaces and promotes the adhesion of matrix-producing cells and organic molecules as a result of surface chemistry and surface charges.

The use of low density HA, with highly interconnected porosity has also been advocated as a viable alternative to bone grafts without the complications of sterilization, infection and inadequate supply. Furthermore, porous structures invite ingrowth of bone into the implant, leading to a more securely fixed and integrated repair particularly in cancellous bone where the structure closely mirrors that of the host [7, 97].

The interfacial strength between bone and the implant material is much greater for these bioactive implant materials compared to other materials, such as Ti, Zr, or Al. With bioactive materials, the fracture occurs either in the material or the bone, but not at the interface as opposed to inert materials, where the separation occurs at the interface.

In the Ca–P system, HA [$Ca_{10}(PO_4)_6OH_2$] and TCP [$Ca_3(PO_4)_2$] are excellent bioactive materials suitable for hard tissue prosthetics. The biocompatibility of HA and the similarities between the crystal structure of HA and bone mineral [98] have led to great interest in the potential of dense HA as a mineral for the augmentation of osseous defects.

9. Calcium phosphate cements

Bone mineral is an apatite calcium phosphate containing carbonate and small amounts of sodium, magnesium and other trace components [99]. This carbonate apatite, termed dahllite, contains 4–6% carbonate by weight and is also a constituent of teeth and of some invertebrate skeletons [100].

Bone tissue replaces itself through the action of osteoclasts, which produce acids to dissolve (resorb) hydroxyapatite and enzymes to break down collagen. The resulting release of calcium and protein prompts other cells (i.e.) osteoblasts to lay down a new matrix that mineralizes forming HA and collagen. In normal conditions bone density is maintained due to the dynamic equilibrium between the functions of osteoclasts and osteoblasts. Any change in this equilibrium, by uncoupling between bone resorption by osteoclasts and bone formation by osteoblasts causes an absolute reduction in the amount of bone in osteoporosis. Bone cells themselves manufacture some growth factors in order to either increase or decrease bone remodeling.

In hard tissue replacement, involving permanent attachment of limb prostheses, a biomaterial must interface with bone. The biocompatibility of implant materials is optimal when the material elicits the formation of normal tissues at its surface and establishes a continuous interface capable of transferring the loads that normally occur at the implantation site. To what extent bone-plus-implant will be able to function as an integrated mechanical unit depends on:

- Mechanical and physiological properties of the implant.
- Interaction between bone and implant.

Calcium phosphate implant materials are composed of the same ions that make up the bulk of the natural bone mineral. Grüninger and his co-workers [101] introduced the term ''calcium phosphate cements''. Such a cement may be described as:

> a powder or as a mixture of powders which, upon mixing with water or an aqueous solution to a paste, reacts around room or body temperature by the formation of a precipitate containing crystals of one or more calcium phosphates and sets by the entanglement of the crystals of that precipitate [102].

The production of calcium phosphate bioceramics usually involves sintering at high temperatures with the exclusion of water vapor. However, their fate after implantation depends on their stability at ambient and body temperatures. The solid state reactions hardly ever occur at room temperature; solid unstable phases will only react at their surfaces. When in contact with aqueous solutions, only two calcium phosphate phases are stable at room temperature and it is the pH of the solution that determines which one is stable [103]. Dicalcium phosphate [(DCPD), (Brushite), ($CaHPO_4 \cdot 2H_2O$)] is most stable at pH less than 4.2, above this value hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$) is the stable phase. The various crystallization mechanisms that occur during the formation of hydroxyapatite cement where described in a study by Lacout [104]. Dicalcium phosphate dihydrate was found to form according to the following reactions:

$$Ca(H_2PO_4)_2 \cdot H_2O + Ca_3(PO_4)_2 + H_2O \rightarrow 4Ca(HPO_4) \cdot 2H_2O$$

$$Ca_4(PO_4)_2O + 2H_3PO_4 + 7H_2O \rightarrow 4Ca(HPO_4) \cdot 2H_2O$$

In the subsequent stage, tetracalcium phosphate [(TTCP), ($Ca_4(PO_4)_2O$)] reacts with the previously formed DCPD and with tricalcium phosphate [(TCP), ($Ca_3(PO_4)_2$)] to give a final product with an apatite composition according to

$$2Ca_4(PO_4)_2O + 2Ca(HPO_4) \cdot 2H_2O \rightarrow Ca_{10}(PO_4)_6(OH)_2 + 4H_2O$$

$$Ca_4(PO_4)_2O + 2Ca_3(PO_4)_2 + H_2O \rightarrow Ca_{10}(PO_4)_6(OH)_2$$

The reactions in the formation of DCPD are very rapid, corresponding to the setting stage. The hardening stage was found to be quite slow, involving the formation of the apatitic phase. Also dicalcium phosphate does not evolve directly into apatite. Octacalcium phosphate [(OCP), ($Ca_8(HPO_4)_2(PO_4)_25H_2O$)] phase, which consists of alternating layers of PO_4^{3-} groups interspersed with Ca^{2+} ions and layers of more widely spaced PO_4^{3-} and Ca^{2+} with H_2O interspersed, is known to occur. Its formation is followed by its hydrolysis into apatite.

The critical problem of low mechanical strengths in calcium phosphate bioceramics encouraged researchers to reinforce the ceramics with polymers. These types of cements have the advantage of biocompatibility and bone replacing behavior of calcium phosphates, as well as *in situ* handling and shaping abilities, due to the addition of certain polymers [105].

From the above discussion it is clear that different Ca–P cements may be classified according to the type of calcium phosphate formed during the setting reaction. Many researchers have opted to use various Ca–P phases as they yield a calcium-deficient HA phase similar to bone mineral [106, 107]. Studies involving an amorphous calcium phosphate (ACP)-filled polymer, ACP being an intermediate in the formation of HA, revealed that Ca^{2+} and PO_4 ions were released in proportions favorable to the formation of HA [108]. Further studies which employed Bis-GMA resin as a matrix produced cements with tensile strengths comparable to glass–ionomer cements [109]. The internal formation of HA resulted in a stronger cement compared to the ACP-filled material, and the remaining ACP provided sufficient release of Ca^{2+} and PO_4 ions to encourage bone growth on the surface of the cement. Dos Santos *et al*. [106] found that incorporating a low molar mass PAA resulted in an increase in the strength of an α-TCP filled cement compared to the unmodified cement. Similarly, the mechanical strengths of zinc polycarboxylate cements were matched by a calcium phosphate cement composed of TTCP, dicalcium phosphate anhydrous and poly-(methyl vinyl ether-maleic acid) (PMVE-Ma) [110]. The hardening mechanism of these types of polymeric Ca–P cements depends primarily on the acid–base reaction between the carboxylic acid groups on the backbone of the polymer and the basic ceramic component [111], similar to the neutralization reaction which occurs in zinc polycarboxylate and glass polyalkenoate cements. The solubility of these polymeric-based cements will decrease with HA formation as HA is thermodynamically more stable than the other Ca–P phases mentioned [112]. It would appear that majority of strength achieved earlier on in the reaction is due to the interaction between ions released from the ceramic component and the carboxylic acid groups on the polymeric chains, whilst continuation in strength development occurs as a result of HA formation. Fundamental studies and clinical applications in the past three decades have demonstrated that calcium phosphate biomaterials (HA ceramic, tricalcium phosphate ceramic and HA/TCP ceramic) are biocompatible and osteoconductive [113, 114]. When implanted *in vivo* these materials are non-toxic, antigenically inactive, do not induce cancer and bond directly to bone without any intervening connective tissue layer. Most of the studies on these cements are in the preliminary stages with work concentrating on *in vitro* or *in vivo* investigations, however, and their clinical use is still limited.

10. Resin modified glass ionomer

Original glass–ionomer cements, which were discussed previously, set sluggishly, showed relatively prolonged sensitivity to moisture and set to be opaque materials [115]. Incremental changes to the cement system have been responsible for some improvements in their properties. Modifications to these early cements have resulted in a number of alternative materials. One category of alternative includes resin-modified cements. In these materials the original acid–base reactions have been

complemented with monomers and initiators capable of undergoing photochemical polymerization. Usually the organic matrix is based on methacrylate chemistry, where especially dimethacrylates are used. Therefore the monomers react simultaneously with methacrylate groups by free-radical polymerization and by an acid–base neutralization reaction, with the cations released from the glass particles in the presence of water. The selection of monomers strongly influences the reactivity, viscosity and polymerization shrinkage of the composite paste, as well as mechanical properties, water uptake and swelling by water uptake of the cured composite.

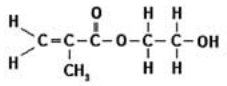
The first reported attempt to make a hybrid of a glass–ionomer and a composite involved the blending of components of a commercial glass–ionomer and resin [16]. This initial investigation revealed that it was possible to combine acid–base and resin polymerization setting in a single material. Developments have since mushroomed and include:

- *Modified composites*, which set through a polymerization mechanism, but also contain ion-leachable glasses in order to achieve fluoride release.
- *Hybrid type products*, which set via both an acid–base reaction and through polymerization (light and/or chemical activation).
- *Compomers* (from *comp*osites and glass–ion*omers*), contain all the major components of both composites and glass–ionomers *except for water*. Premature setting is thus prevented and setting occurs via polymerization.

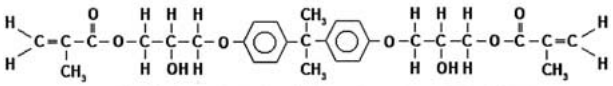
A plethora of products have flooded onto the market, some simply glass ionomer cements with small amounts of resin components (Fig. 4), such as hydroxyethyl methacrylate (HEMA) and bisphenol A-glycidylmethacrylate (Bis-GMA) [16], others are quite complex with the glass ionomer polyacid being modified by light polymerizing side chains [17].

The popularity of these glass–ionomer hybrid systems is due in no small measure to their ease of handling and good aesthetics. In fact, such cements are generally better than glass polyalkenoate cements in terms of immediate strength, aesthetics and water stability after placement, but high polymerization shrinkage can cause problems with marginal sealing and retention [18]. In order to attain adhesion to enamel and dentine, they require a separate adhesive to produce a micro-mechanical bond [116].

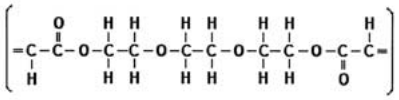
In recent years, attempts have been made to improve the *in vivo* behavior of these cements. Incorporation of HA [117 118] and bioactive glass–ceramic [119] has been used in an attempt to achieve improved bioactivity. However, as PMMA cures via 2D polymerization, a tight link between it and the bioactive filler is not obtained. In the 1960s Bowen developed a composite resin consisting of Bis-GMA and silica powder as a dental cement [120], which subsequently became the most popular dental cement in place of PMMA. Because Bis-GMA forms a 3D crosslinked polymerization structure it provides a tight physical binding. Furthermore, silane treatment of the filler surface results in chemical binding with the filler and the base resin [120]. Recently, composite



(a) Hydroxyethyl methacrylate (HEMA)



(b) Bisphenol A-glycidylmethacrylate (Bis-GMA)



(c) Triethylene glycol dimethacrylate (TEGDMA)

Figure 4 Chemical structure of (a) HEMA (b) Bis-GMA and (c) TEGDMA; three of the many resin components used in the production of resin-modified glass–ionomers.

cements of bioactive ceramics with Bis-GMA and triethylene glycol dimethacrylate (TEGDMA) (Fig. 4) resin have been prepared [121, 122] These cements form apatite on their surfaces in the body environment and bond to the bone through this apatite layer. Unpolymerized monomers, however, dissolve from the surface of these cements and hence a less dense layer forms [122]. As this less dense layer may be unstable, the bonding between these cements and the bone may be liable to degradation over prolonged periods. Together with this drawback, the dissolution of monomers from the cements is undesirable. The main advantages and disadvantages of these cements are listed in Table IV.

Due to the presence of hydrophilic OH groups, these materials absorb water. However, according to Nicholson and Anstice [123] they set by various competing reactions, and a complex structure results, containing both ionic and covalent crosslinks. These products have a tendency to undergo phase separation and may contain domains of different hydrophobic and hydrophilic phases. Hence, the absorbed water would be expected to migrate preferentially to the hydrophilic sites and may provoke the dissolution and leakage of ionic species (including fluoride ions). The advantages of fluoride release from glass polyalkenoate cements are well established [124–126]. Resin modified glass–ionomers are also known to release fluoride ions into the surrounding environment for extended periods. In fact, the set cement is capable of reabsorbing fluoride ions from the surrounding environment [127]. Therefore, this latter aspect of uptake and re-release of fluoride, is thought to be unique to these type of glass–ionomers.

The influence of fillers of various volume fractions on the mechanical properties of cured composites has been studied in order to test conformity with theoretical predictions that the properties of cured composites should increase monotonically as the volume fraction of the filler is increased. Properties evaluated by various authors, which have been found to agree with this exception, include indentation hardness, compressive strength, yield strength and fatigue limit [128, 129]. In another study [130] the relationships between filler type and content, matrix resin composition and viscosity and flow characteristics were investigated and a characteristic maximum filler content was found to be dependent on the nature of the filler. A reduction in the filler

TABLE IV Main advantages and disadvantages of resin-modified glass–ionomer cements

Advantages	Disadvantages
Improved setting characteristics	Setting shrinkage is greater than conventional glass ionomer cements
Working times can be manipulated by photo-curing	Depth of cure problematic with more opaque lining cements
Rapid development of early strength	Long term exposure to moisture may result in degradation of physical properties
Less tolerant to moisture loss/gain	Shrinkage as a result of dehydration

increased plasticity with lower viscosity mixes accepting higher filler contents, at a constant plasticity. Kawanabe *et al*. [131] developed a bioactive bone cement consisting of silane-treated $CaO–SiO_2–P_2O_5–CaF_2$ glass powder as the filler particles and an organic matrix consisting of Bis-GMA/triethylene-glycol dimethacrylate resin. It was found that this new cement achieved better mechanical properties than existing PMMA-based cements, and it adheres directly to bone. Therefore, one of the major disadvantages of these resin-based cements, that is dimensional change during and following placement, can be combated by increasing the filler content. However, water will leach out free unreacted monomers and ions [132].

The fluoride release and caries control properties of the glass–ionomer materials lends it to novel and increasingly conservative techniques of restoring teeth. At present, poor strength and wear resistance renders glass–ionomers less than ideal, and it is not yet possible to make them as strong as an amalgam.

11. Composites

One of the major problems associated with orthopaedic surgery is the mismatch of stiffness between the bone and metallic/ceramic implant. The amount of stress carried by the bone and the implant is directly related to their stiffness. As bone is a dynamic material, changing continuously to meet the requirements of its surroundings, prolonged reduction of stress on a bone may result in a phenomenon known as ''stress shielding'', leading to increased bone porosity. However, by matching the stiffness of the implant with that of the host tissue this effect can be limited and used to produce desired tissue remodeling.

Cortical bone at the ultrastructural level is a HA-reinforced composite [19]. Therefore, the development of a cement analogous to the natural tissue requires materials with equivalent microstructural and deformational characteristics. Thus, the use of reinforced polymers simultaneously with a bioactive second phase material (e.g. ceramic, glass, etc.) offers the low elastic modulus associated with the polymer and high strength as a result of the chosen filler. Additional merit related to the use of composite materials is that by controlling the volume fractions and arrangement of the reinforcing phase, the properties and design of an implant can be varied and tailored to suit the mechanical and physiological conditions of the host tissue. Achieving a stable implant–tissue interface during physiological loading, in contrast to that obtained with current orthopaedic implants, is top of the agenda. Previous studies have shown that bioactive glass and glass–ceramics can bond chemically with host bone [133–135]. Their primary advantage is the ability to produce fast tissue bonding via a rapid rate of surface reaction. However, their main disadvantage lies in the fact that they form an amorphous 2D glass network [136]. The inherent low strength, fracture toughness and short critical crack propagation length that they experience means that they are confined to applications in low loaded or compressively loaded devices [137]. Glasses are thus not suitable as load bearing implants because they are brittle.

Calcium phosphates are being developed as bone cements for application in osseous sites and for bone reconstruction, filling and augmentation. Research involving calcium phosphate cement (CPC) has led to numerous patents since the mid-1980s [15, 138–140]. Biocompatibility is a common property of calcium phosphate biomaterials and many Ca–P-based biomaterials including HA, bioglass ceramic, TCP, DCPD have demonstrated biocompatiblity [141–145]. The main reason for biocompatibility of calcium phosphate biomaterials is that calcium phosphate is the main inorganic constituent of hard tissues and the free calcium and phosphorus ions can be used in bone metabolism [144]. Biocompatibility of calcium phosphate cement has been reported in other studies where it was related to the constituents of the cement [146–150]. However, low strength and susceptibility to brittle catastrophic fracture of the cement have also severely limited its use to only non-load-bearing applications [151–153]. The use of the cement is ''limited to the reconstruction of non-stress-bearing bone'' as ''clinical usage was limited by brittleness'' [154].

The important calcium phosphate phase, HA, is also a brittle material. However, a possible solution may be to incorporate it, in order to confer bioactivity, in a polymeric matrix, which will result in a combination of strength and elasticity, producing a strong, bioactive cement as a consequence. A number of researchers have investigated various new composite materials, and the results being reported appear very promising. A large number of these new materials exist and variations include PMMA reinforced with hydroxyapatite [155] PMMA reinforced with bioactive glass [156] polyethylmethacrylate (PEMA) reinforced with HA [157] and polyethylene reinforced with HA [158] to name but a few.

PMMA cements were the first to be used in orthopaedic surgery [1] with a success rate of 90% at 15 years post implantation [159]; it therefore stands to reason why it has received such interest in the development of a new composite cement. Even though it provides immediate structural support, the bone–cement interface is considered to be the weak link in cement-held prostheses providing a barrier to direct fracture healing. With HA being considered a bioactive material, it seems reasonable to attempt to fill the PMMA

cement with HA in order to improve the bone–cement interface. It was suggested that the extent of bioactivity in these composite materials is dependent on the volume of HA incorporated in the PMMA cement [155]. This study found that the composite material supported normal osteoblast cell growth and HA demonstrated preferential anchoring of human osteoblast-like cells (HOB), rather than the cement polymer. However, the cement was prepared prior to placement and this eliminated any effects related to the exothermic polymerization of PMMA. On the surface area of the composite cones where PMMA was present between the spots of bioactive material, a dense fibrous layer was always observed which increased with time preventing bone contact. It was therefore concluded that, by using SEM and energy dispersive X-ray analysis (EDXA), the osteoconductive bone formation in the interface between the bioactive glass or HA and bone was impeded by PMMA at the border area adjoining bioactive glass or HA with PMMA. In a similar study [156], the heat factor was also ruled out, but efforts were instead concentrated on the effect of PMMA on bone formation at the surface of the bioactive material. The control PMMA cement showed no bone contact at the interface. It was Weightman *et al*. [160] who first published a report on a bone cement based on PEMA and *n*-butylmethacrylate (*n*-BMA) monomer. This polymer matrix was chosen as it possesses a low exotherm (55 °C) compared to PMMA (100 °C). It has a relatively low modulus (700 MPa) and high ductility (50% strain to failure) thereby yield/flow would occur before fracture and result in a more even stress distribution. It has been shown that relatively speaking, these cements showed lower extractability of n-butylmethacrylate compared to methmethylacylate monomer [161] and an investigation into their biological response demonstrated excellent biocompatibility [162] of the PEMA–nBMA cement. However, these cements were found to be highly susceptible to creep, and in order to overcome this effect and to offer the potential of increased bioactivity, HA particles were introduced [163]. It was subsequently found [164] that although the incorporation of 10% vol. HA did have bioactive effects, such as preferential adhesion, raised proliferation and increased matrix organization, the effects were not as notable as would have been expected. It is thought that loading the cement with large volumes of HA may have given rise to the release of unreacted monomer.

Hydroxyapatite reinforced high-density polyethylene (HDPE) composite (HAPEX™) has been developed since the early 1980s as an analog for bone replacement [165]. The addition of reinforcing particles of HA has been shown to increase the modulus [166] and the bioactivity of the composite material [151]. The optimum filler volume traction for both mechanical and bioactive properties was originally found to be 0.4 vol. fraction [167], where the modulus of the composite reached the lower band of the modulus of bone, while the fracture toughness was higher than that of bone and the tensile failure was ductile. Biochemical and morphological analysis showed the material surface was suitable for cell proliferation and maintenance of osteoblast phenotype [158] at a filler volume fraction of 0.2. However, in the clinical application of polyethylene for the bearing surfaces of, for instance, joint replacements, creep is a problem, which alters mechanical performance and can lead to wear of the material causing adverse tissue response and eventually to revision [168].

Poly(ethylene-co-maleic acid) (EMa) along with PAA were both used to improve the interface between HA and a polyester–ether in Polyactive™ 30/70 [169]. Polyactive™ is a copolymer of polyethylene glycol (PEG) and poly(butylene terephthalate) (PBT) that has good biocompatibility. In order to introduce interfacial bonding between HA and Polyactive™ 30/70 the effects of polyelectrolytes PAA and EMa have been investigated [169, 170]. The principle is that both PAA and EMa can be firmly adsorbed on to the surface of HA and result in a composite material, which will possess sufficient strength. The use of PAA and EMa was demonstrated to be an effective way to improve the interface between HA and Polyactive™ 30/70, with surface modified HA particles maintaining better mechanical properties [169].

A number of biocompatibility studies on mixtures of tetracalcium phosphate ($Ca_4(PO_4)_2O$ or TTCP) and PAA as bone cements have shown there is no adverse tissue reaction, the cement bonds both chemically and mechanically to bone and osteogenesis can and will occur in areas adjacent to the cement restorations [95, 171]. It is possible to produce HA-calcium polyacrylate cements [172] by reactions similar to those of glass ionomer or zinc polycarboxylate (ZP) cements [29]. However, all these cements are investigated for use in dental environments.

As mentioned earlier, the bond between zinc ions and PAA appears to be more stable than that between calcium ions and PAA [39]. This finding was discussed in a study carried out on a zinc polycarboxylate dental cement, where it was also discovered that zinc ions are non-toxic, *in vivo*, and indeed are believed to have an antibacterial effect [5]. The setting reaction of these types of cements is that of a neutralization reaction with little accompanying temperature rise. However, these cements have again originally been used in dental applications, their mechanical properties restricting their use within these realms. Values for fracture toughness reached $0.8\,\mathrm{MPam}^{1/2}$ with a PAA molar mass of 3.83×10^5 (E11) [29]. In the 1991 study by Hill and Labok [29], it was concluded that the chain length of the PAA had a significant influence on the fracture properties, toughness, fracture toughness and flexural strength of zinc polyalkenoate cements.

In 1973, a cement based on conventional zinc phosphate–zinc polycarboxylate cements was patented [173]. This cement was investigated more as a deterrent against tooth decay rather than to achieve better mechanical properties. It releases fluoride ions which migrate from the cement into the underlying tooth structure, consequently increasing the resistance to further tooth decay. Difference phases of calcium phosphate together with fluoride additions are used. However, the concentration of the PAA used was too low to achieve improved strength. In 1985, a slight variation on this dental cement was patented which promised to overcome the problems associated with cements already

TABLE V Inorganic and carboxylic acid powders used in Aoki's [174] cement composition

Inorganic powder	Use	Acid	Use
Calcium tertiary phosphate	Increases strength	Acrylic acid	
Calcium oxide	Shortens working time and reacts with acid which reduces disintegration property	Methacrylic acid	
Zinc oxide		Ethacrylic acid	Conveys water-hardening property
Silicon oxide Alumina Magnesium oxide Calcium fluoride	Increases compressive strength	Itaconic acid Fumeric acid	

on the market [174]. It was stated that this water hardenable cement had a ''high compressive strength and excellent operational adaptability, being capable of providing a hardened body without disintegration''.

This cement comprised of HA as the main component and an inorganic powder and hardening agent. A highly crystalline powder form of HA was used together with the inorganic powder, which may be one of the powders listed in Table V.

The unsaturated carboxylic acid could be any of those listed above in Table V, which convey the water-hardening property. However, these materials also resulted in low compressive strengths, although the strength was found to increase proportionally to the amount of HA present. It was also found that the toxicity of these cements was much lower than that obtained with comparable cements *in vitro*.

Composition based on the aforementioned cements, consisting of hydroxyapatite and zinc oxide were investigated in an attempt to improve the mechanical properties of the cements [175–177]. The molar mass and concentration of the PAA were found to exert a pronounced influence on the fracture toughness, flexural strength and compressive strength of the cements. Fracture toughness, flexural strength and compressive strength all increased with increases in the polymer molar mass. The PAA molar mass was also found to influence the Young's modulus of the cements, which had not been observed previously with polyalkenoate cements. This result suggested that chain entanglements [178] contributed to the stability and stiffness of these cements, an argument which was strengthened by increases in modulus, fracture toughness and flexural strength as the PAA concentration was increased. The fact that higher polymer molar mass based cements exhibited increases in modulus with time indicated a continuation in the crosslinking reaction with time.

12. Summary

In conclusion it is clear that any attempt to develop a bone cement should include a fundamental examination of all items listed in Table VI. A number of potential research paths that could result in new types of bone replacement materials have arisen as a result of this review, the solutions of which may lead to the development of a bioactive, mechanically able cement.

It would appear that the most likely solution to the development of a successful bone cement should include a biocompatible polymer of low elastic modulus, reinforced by a bioactive second phase of high strength, analogous to bone. The majority of these types of composites include a Ca–P ceramic as the second phase and usually a polymer with carboxylate groups on the backbone. HA has been identified as the most stable Ca–P phase the incorporation of which results in much better mechanical properties than any obtained with other Ca–P filler phase. The integrity of any new material produced is of the upper most importance. Therefore, investigations on the chemical interactions and localized strength of cement matrices need to be carried out in order to have a greater understanding and knowledge of the mechanisms at play. Many researchers have chosen such composites [155–158, 169–172] to attempt to produce a bone replacement. However, various questions remain unanswered and may prove instrumental to the development of such a cement.

- Do the formation of crosslinks between the (polymer) carboxylate groups and ions released from the second phase (usually di- and trivalent) result in a reduction in diffusion of ions from the soluble second phase?
- In glass polyalkenoate cements, the release of Ca^{2+}, PO_4^{3-} and Al^{3+} ions are thought to result in a silica ''gel'' phase which encourages diffusion

TABLE VI List of criteria for the design of a new bone cement

Criterion	Purpose
Mechanical properties to match that of bone	Enhance the elimination of the phenomenon known as stress shielding
Quick setting (5–15 min)	To assist in clinical use and after care of patient
In situ setting at body temperature	Elimination of necrosis of the adjacent tissue
Bonding to bone and medical grade alloys	Elimination of fibrous capsule and thus loosening of the implant
Bioactive bone in-growth	Enhancing both stress transfer and chemical attachment of the implant
Radio opaque	Subsequent monitoring of implant

[54–56]. Can this type of gel phase be used in future cements to help direct the diffusion of bioactive ions and crosslinking ions to specific locations?

- If the cement matrix forms around individual particles inhibiting the diffusion of ions and leaving behind unreacted filler particles, particles with a soluble Ca–P outer phase surrounding a stable HA phase should provide bioactivity together with mechanical properties comparable to those of bone.

Particle size is also known to have an effect on many properties such as:

- Solubility.
- Bioactivity/bone ingrowth.
- Strength/reactivity.
- Working and setting times.

The formation of new phases during the maturation of a cement could be manipulated in such a way as to produce materials that could be engineered for specific applications. For instance, in the human body the rate of repair changes with age. Through the incorporation of components with varying solubility rates, bone replacement materials could be tailored to suit the needs of individual patients, depending on their age, in order to provide faster recovery times through the scheduled release of bioactive ions. Similar ideas are used in the engineering of drug coated stents [179] where ''reservoir'' systems are used to control the release of drugs over time. The environmental surroundings of each application would need to be considered prior to the development of such a material so that the manipulation of these characteristics could lead to improved bioactive solutions.

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Notes

1 Bone cements are mainly used in the fixation of orthopaedic prosthetic materials for hips, knees, and shoulders as they can withstand the stresses of a loaded environment. Bone substitute materials are used primarily as a scaffold for the bone regeneration process and are used in applications such as maxillofacial and craniofacial surgery.

2 The crosslink density is defined as the average number of additional crosslinking bonds above 2 for the elements other than oxygen forming the glass network backbone. A glass with a network connectivity of 2, equivalent to a crosslink density of 0, corresponds to a linear polymer chain, while a pure silica glass has a network connectivity of 4 and has a 3D network structure.

3 Autograft: A transplanted tissue or organ transferred from one part of a body to another part of the same body.

4 Allograft: Transplanted tissue or organ between unrelated individuals of the same species. Also called homograft.

5 Periodontal ligament: Periodontium; the connective tissue (ligament) joining the tooth to the alveolar bone.

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