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Comparison of an experimental bone cement with a commercial control, Hydroset™

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Abstract Glass polyalkenoate cements based on strontium calcium zinc silicate glasses (Zn-GPCs) and high molecular weight polyacrylic acids (PAA) (MW; 52,000–210,000) have been shown to exhibit mechanical properties and in vitro bioactivity suitable for arthroplasty applications. Unfortunately, these formulations exhibit working times and setting times which are too short for invasive surgical applications such as bone void filling and fracture fixation. In this study, Zn-GPCs were formulated using a low molecular weight PAA (MW; 12,700) and a modifying agent, trisodium citrate dihydrate (TSC), with the aim of improving the rheological properties of Zn-GPCs. These novel formulations were then compared with commercial self-setting calcium phosphate cement, Hydroset™, in terms of compressive strength, biaxial flexural strength and Young's modulus, as well as working time, setting time and injectability. The novel Zn-GPC formulations performed well, with prolonged mechanical strength (39 MPa, compression) greater than both vertebral bone (18.4 MPa) and the commercial control (14 MPa). However, working times (2 min) and rheological properties of Zn-GPCs, though improved, require further modifications prior to their use in minimally invasive surgical techniques.

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1 Introduction

The use of surgical cement to fill traumatic or surgically induced bone voids and gaps in the skeletal system is widespread, with three main material types dominating the literature on the subject: acrylics, composites and calcium phosphates.

Acrylic bone cements are employed for the repair of the human skeleton. However, concerns such as (but not limited to) impaired functioning of the immune system [1, 2], thermal and chemical necrosis [3] and lack of direct bone apposition around acrylic implants [4] has encouraged other material developments.

Composite materials like Cortoss® (Orthovita, Malvern, USA), a Bisphenol-A-glycidyl dimethacrylate (BIS-GMA) resin enriched with ceramic particles, are being investigated as alternatives to conventional acrylics [5, 6]. However, drawbacks are also associated with the use of these materials, including; deletions in DNA sequences [7] decreasing strength with respect to time [8], impaired immune response [7] and excessive elastic modulus [8]. However, these materials display sufficient radiopacity and mechanical properties [9] for clinical applications and as such, some compositions are undergoing clinical trials for vertebroplasty [10].

The final material group, which is of particular relevance to the work contained herein are the self setting calcium phosphates and include materials like Bonesource™ (Stryker Orthopaedics, Limerick, Ireland) [11], Norian® SRS (Synthes Inc., West Chester, Pennsylvania, USA) [12], and Hydroset™ (Stryker Orthopaedics, Limerick, Ireland) [13]. Calcium phosphate cements (CPCs) have established clinical interest due to their potential to be resorbed and replaced with new bone as part of the natural bone remodelling cycle without provoking an inflammatory response [11, 14–16]. Whilst some CPCs suffer from delayed setting

in the wet field environment, and viscosity contrary to injectable surgical procedures, their biocompatibility is not matched by acrylic or composite bone cements. The main deficiency associated with CPCs is their poor mechanical properties. For example, compressive strengths after 24 h for Bonesource™ and Alpha BSM® CPCs have been recorded as <10 MPa and 5 MPa respectively [17]. As such, limited structural support is offered by these materials and complications are likely [18].

Glass polyalkenoate cements (GPCs) are a group of materials that have potential for skeletal cementation. They are formed by the reaction of an acid degradable alumino–silicate glass with an aqueous solution of polyalkenoic acid, usually polyacrylic acid (PAA) [19]. GPCs are bioactive materials [20] with mechanical properties similar to bone, and have an established record of success in dental applications. However, cases of aluminium induced encephalopathy have been reported [21–24], due to the release of the neurotoxic Al^{3+} ion from the mantle of set GPCs in vivo. Subsequently, aluminium based GPCs were contraindicated for use in skeletal applications, particularly for procedures where the cement could come into contact with cerebrospinal fluid (CSF). The authors have previously reported the development of aluminium-free GPCs for consideration as skeletal materials [25–30]. These materials are based on predicate dental materials and exhibit similar properties to their predecessors but are formed from a calcium–strontium–zinc–silicate glass, thus eliminating the threat of aluminium induced neurotoxicity. The novel zinc based GPCs (Zn-GPCs) have strengths suitable for load bearing applications [25], demonstrable bioactivity in vitro [26], and are inherently antibacterial [27] due to the release of bacteriocidal ions from the cement mantle.

The working and setting time requirements for an injectable bone cement are outlined by Lewis as 6–10 min and 15 min, respectively [31]. Injectable bone void filler, Norion SRS® has a working time of 5 min and a setting time of 10–15 min [31]. It is noted in the literature that, for the best injectability results, a setting dough viscosity that does not change much between mixing and delivery is preferred [31]. A number of different methods have been used to investigate the rheology of bone cements [32–37]. These studies have investigated PMMA, calcium phosphate and GPC viscosity during setting and have recorded viscosity effects of varying cement composition. From these studies GPCs have been observed as Newtonian, behaving as power law fluids which become progressively dilatant as setting proceeds, making it suitable for injectable applications [35].

It is the aim of this paper to compare a selection of the physical and mechanical properties of Zn-GPCs with a commercially available CPC bone substitute, Hydroset™, with the objective of offering a critical review of which materials are most suitable to clinical applications.

2 Material and methods

2.1 Glass synthesis

One glass was synthesised; $0.04SrO/0.12CaO/0.36ZnO/0.48SiO_2$ (mol. fraction). Appropriate amounts of analytical grade calcium carbonate, strontium carbonate, zinc oxide and silicon dioxide (Sigma Aldrich, Dublin, Ireland), were weighed out in a plastic tub and mixed in a ball mill for 1 h, then dried (100°C, 1 h). The pre-fired glass batch was then transferred to a platinum crucible for firing (1480°C, 1 h). The glass melt was subsequently quenched into water and the resulting frit was dried, ground and sieved to retrieve a <25 μm glass powder. The glass was then annealed (645°C, 3 h) to relieve internal stresses within the glass network, such that Zn-GPC specimen preparation was possible. The glass composition in this study is the result of optimisation of cement performance from preceding studies [38, 39].

2.2 Commercial bone cements

One commercial bone cement was reviewed in this study; Hydroset™ (Stryker International, Limerick, Ireland), lot # IC06276A.

2.3 Cement preparation

Two Zn-GPC formulations were prepared by mixing the glass with 40 wt% (formulation A) and 50 wt% (formulation B) PAA (MW, 12,700) (Advanced Healthcare Ltd., Kent, UK), with 10 wt% trisodium citrate dihydrate (TSC), at a glass-solution ratio of 2:1.5, as shown in Table 1. Mixing of GPCs was carried out on a clean glass slab using a dental spatula and was completed within 20 s. All commercial materials were produced in strict compliance with manufacturer's instructions.

2.4 Determination of working and setting times

The working times (t_w) were evaluated as described in ISO9917, which specifies the standard for dental water based cements, as "the period of time, measured from the start of mixing, during which it is possible to manipulate a dental material without an adverse effect on its properties". Setting times (t_s) of the cement series were determined in accordance with ISO9917 [40].

Table 1 Zn-GPC cement compositions

Cement	Glass (g)	Acid (g)	TSC (g)	Water (ml)
Formulation A	1.00	0.30	0.075	0.45
Formulation B	1.00	0.37	0.075	0.37

2.5 Determination of compressive strength

The compressive strengths of the cements were evaluated in accordance with ISO9917E [40]. Cylindrical samples (6 mm h × 4 mm Ø) were incubated in distilled water for 1, 7 and 30 days ($n = 5$). Compression testing was undertaken using an Instron 4082 (Bucks, UK) fitted with a 5 kN load cell at a crosshead speed of 1 mm min^{-1}.

2.6 Determination of biaxial flexural strength

The biaxial flexural strengths of the cements were evaluated by a method described by Williams et al. [41]. Cement discs (2 mm h × 12 mm Ø) were incubated in distilled water for 1, 7 and 30 days ($n = 5$). Testing of the discs was undertaken using an Instron 4082 (Instron, Bucks, UK) fitted with a 1 kN load cell, at a crosshead speed of 1 mm min^{-1}. Biaxial flexural strength (BFS) was calculated according to Eq. 1

$$BFS = \frac{\rho}{t^2}\{0.63\ln(r/t) + 1.156\} \quad (1)$$

[41], where ρ is the fracture load (N), t the sample thickness (mm), and r is the radius of the support diameter (mm).

Young's modulus was determined from the biaxial flexural test using the method of Higgs et al., this method displays Young's modulus as a function of the slope of the load-displacement curve of the failed disc, along with disc radius, disc thickness and testing parameters [42]. Poisson's ratio for this analysis was assumed to be 0.34, as determined from other glass poly(alkenoate) cements [43].

2.7 Injectability

Injectability testing was carried using a Tinius Olsen H10KS test machine (Tinius Olsen Ltd., Pennsylvania, USA) fitted with a HTE 1 kN load cell as depicted in Fig. 1. A 25 mm min^{-1} cross-head speed was used for all testing. The cement was mixed by hand in a mixing bowl and placed into a 20 cc syringe and was forced through a 10 gauge cannula. Cements were mixed and placed into the syringe within 35 s, the syringe was loaded in the test rig and testing commenced 45 s after the beginning of mixing. The time to reach a load of 225 N was recorded ($n = 3$). This load was used as it is just above the limit of physical injectability by hand [44].

3 Results

3.1 Working and setting times

The working times (t_w) and setting times (t_s) were evaluated as described in the materials and methods. Working time (t_w) and setting time (t_s) results are illustrated in Table 2 [40].

From Table 2 it can be seen that the working times of the GPC formulations are shorter than that of commercial

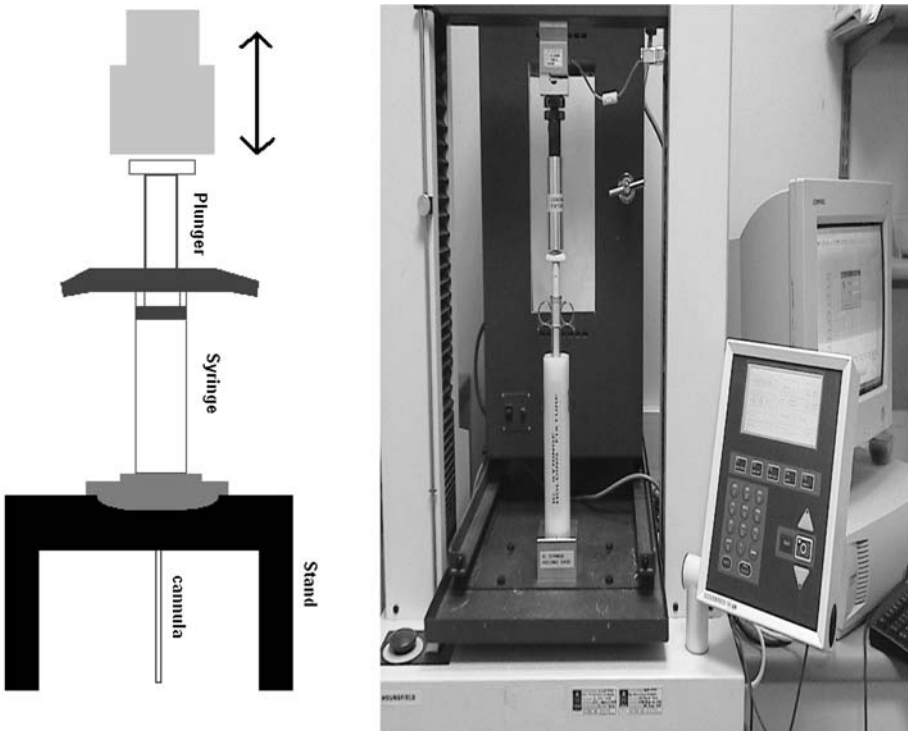

Fig. 1 Injectability test apparatus. **a** schematically; **b** photographically

Table 2 Working and setting times of cement formulations

Cement	Working time	Setting time
Hydroset™	4 min 20 s	5 min 20 s
Formulation A	2 min	9 min
Formulation B	1 min 20 s	7 min 30 s

cement, however setting times of the GPC formulations are longer than that of the commercial control.

3.2 Compressive and biaxial flexural strength testing

Figures 2 and 3 illustrate the effect of maturation time on the compressive and biaxial flexure strength of each Zn-GPC and the control. It can be observed from Fig. 2 that the compressive strength of Hydroset™ and both Zn-GPCs are similar after 24 h incubation in deionised water. However, with increased maturation time, the mean compressive strength of Hydroset™ decreases, whereas the compressive strengths of both Zn-GPCs increase between 1 and 30 days. Compressive strengths of up to 40 MPa can be observed in Zn-GPC formulations after 30 days of incubation.

From Fig. 3, after a 24 h incubation period, Hydroset™ is observed to have superior biaxial flexural strength to both Zn-GPCs. However, similarly to trends observed in compression, the mean biaxial flexural strength of Hydroset™ is seen to decrease with prolonged maturation whereas, in contrast, the biaxial flexural strength of each Zn-GPC is seen to increase with maturation time. Though increases in biaxial flexural strength with maturation time are less significant in formulation A, than formulation B, a

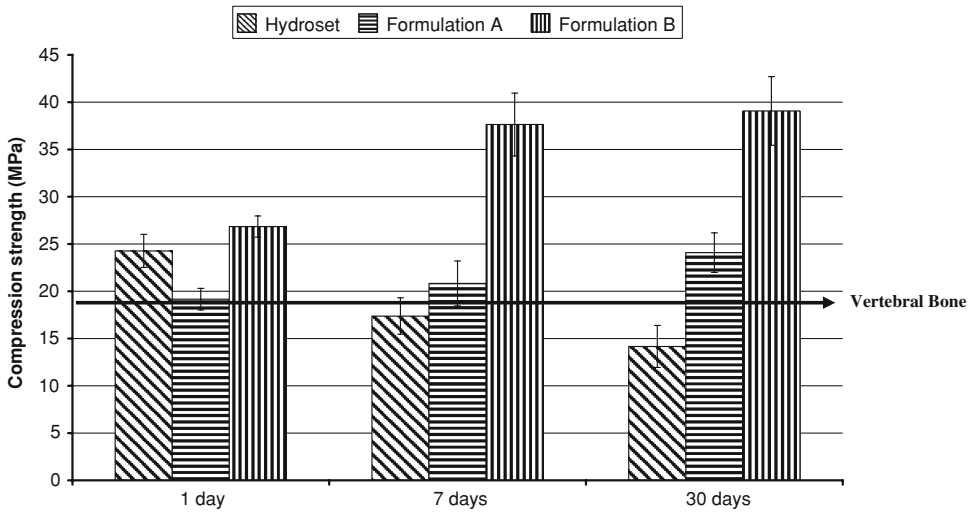

Fig. 2 Compressive strength results of two Zn-GPC formulations and Hydroset™

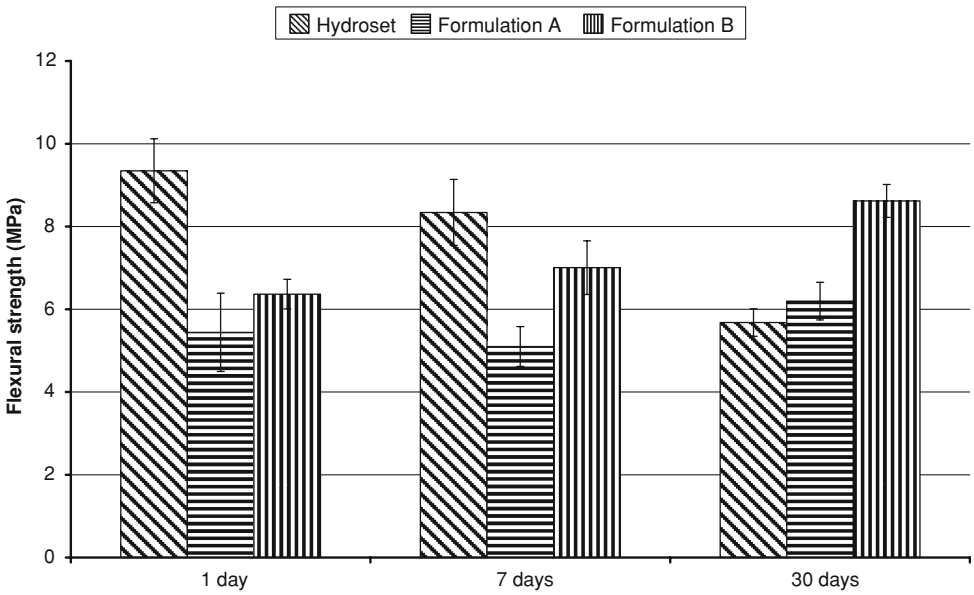

Fig. 3 Biaxial Flexure strength results of two Zn-GPC formulations and Hydroset™

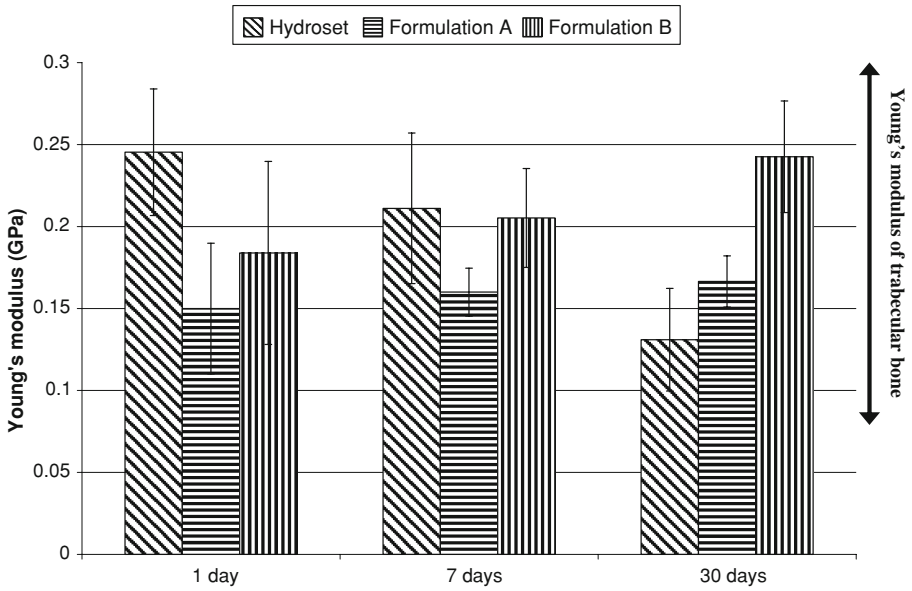

Fig. 4 Young's Modulus results of two Zn-GPC formulations and Hydroset™

significant increase is observed between 7 and 30 days of maturation. Finally with both trends in progress, after 30 days of maturation, Hydroset™'s biaxial flexure strength is lower than that of Zn-GPC formulation A, which, is significantly lower than that of formulation B.

As observed in Fig. 4, Young's modulus remains relatively constant for Zn-GPCs over the examined period, with no significant increase observed over 30 days of maturation. However, the modulus of Hydroset™ is seen to decrease slightly with prolonged maturation.

3.3 Injectability

From the injectability results in Table 3, the time taken to reach 225 N for Zn-GPC B was significantly less than for A. Both Zn-GPC formulations had significantly less injectability time than Hydroset™.

Figures 5, 6 and 7 illustrate the force-displacement relationship of each cement as it is extruded through the 10 gauge cannula. From these figures it can be seen that during the test regime, for Zn-GPC formulation A, approximately 5 mm of material is displaced from the syringe by the time the syringe has reached 225 N; this figure is considerably less for Zn-GPC formulation B (*c*.3 mm) and all cement is expelled from the syringe for Hydroset™ before reaching 225 N.

Table 3 Injectability results of Zn-GPC cement formulations

Sample number	Formulation A	Formulation B	Hydroset™
1	1 min 1 s	58 s	3 min 30 s
2	1 min 1 s	54 s	3 min 30 s
3	1 min 1 s	54 s	3 min 30 s

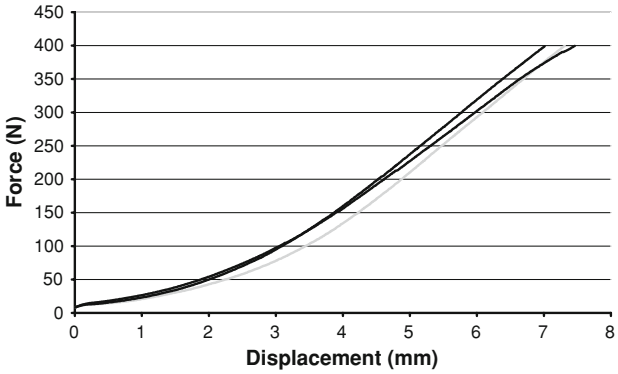

Fig. 5 Injectability curve for Zn-GPC formulation A

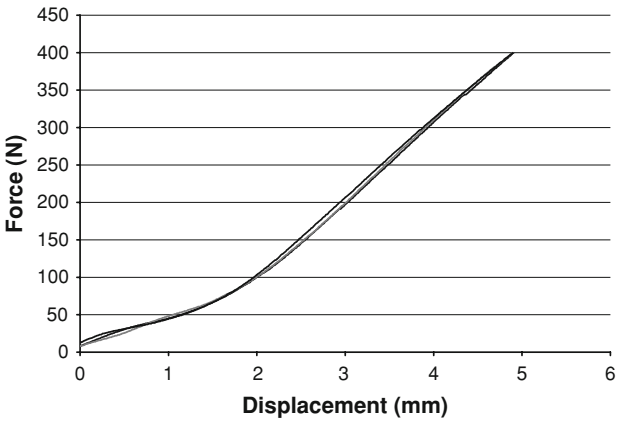

Fig. 6 Injectability curve for Zn-GPC formulation B

4 Discussion

4.1 Working and setting times

The working time of Hydroset™ is significantly longer than both Zn-GPC formulations and it has a more rapid set once

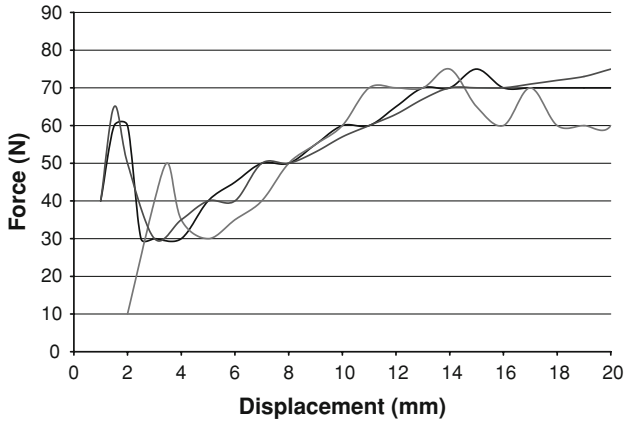

Fig. 7 Injectability curve for Hydroset™

working time has ended. The working and setting time requirements for an injectable bone cement are 6–10 min and 15 min, respectively [31]. This indicates that further lengthening of the working time and shortening of the setting time is required to make these novel cement formulations clinically suitable. However, the significant variation in working and setting time between the two Zn-GPCs studied highlights the ability to tailor such working times to specific requirements. Formulation B exhibited a shorter working and setting time than formulation A as a result of its increased PAA concentration. Such an increased reaction rate would be expected with increased PAA concentration, as stated by the 'law of mass action', which dictates that the rate of an elementary reaction is proportional to the product of the concentrations of the participating molecules [45]. This increased concentration results in a faster neutralisation of PAA and faster formation of a hydrated salt matrix. Similar trends have been observed in preceding studies and studies on conventional GPCs [38, 46, 47]. The hydroxyacid salt, trisodium citrate dihydrate, was incorporated into this formulation. The rise of viscosity observed during GPC setting was observed to be retarded by the addition of some hydroxyacids to the cement formulation [36], similarly retardation of setting was observed with application of vibration [37], decreasing powder to liquid (P–L) ratio [48], increasing particle size of the glass constituent [49] and acid washing of the glass powder [50]. Many of these methods of increasing working time have trade offs with strength but not all in equal measure. Increasing particle size of the glass increases fracture toughness [51], decrease compressive strength [52] and result in no significant alteration in biaxial flexure strength [49]. Reduction in P–L ratio does not affect fracture toughness appreciably but does have an effect on other mechanical properties [51]. Many of the adjustments which can be made to Zn-GPC formulations to improve their viscosity will most likely be made at the expense of some mechanical integrity; however optimisation of these novel cements can undoubtedly be carried out to produce a clinically applicable material.

4.2 Mechanical properties

The mechanical properties of the novel GPC formulations examined in this study are befitting to the purpose of bone void filling and, over prolonged periods, are superior to the mechanical properties of the commercial cement examined. The novel GPCs have the advantage of increasing strength with maturation time, ensuring stability of the implant after prolonged immersion in an aqueous environment. After 24 h of incubation all cements exhibited compressive strengths superior to the maximum compressive strength of vertebral bone. However, after 30 days of incubation, Hydroset™'s compressive strength can be seen to drop below that of vertebral bone, whereas Zn-GPCs exhibit compressive strengths of up to 40 MPa [53]. It might be argued that the reduction in Hydroset™'s compressive strength, below that of vertebral bone may be offset by the support of bony integration into the cement body, assuming a healthy bone metabolism. However, in many surgical applications this is not the case. Hydroset™ is designed as a bone void filler, bone void fillers are not designed for load-bearing capacity and Hydroset™ is used in such applications for its injectability, biocompatibility and osteoconductive properties.

In both compression and biaxial flexure, Zn-GPC B is superior to A after 30 days maturation. This is solely due to the increased PAA concentration. Such trends have been observed in other studies of GPCs and have been attributed to an increased acid degradation of the glass phase, resulting in a higher ion crosslink density in the cement matrix [38, 46, 47, 54].

Young's modulus in those Zn-GPCs examined appears to remain relatively constant, whereas for Hydroset™, the mean value is seen to decrease with prolonged incubation. However, all cements examined have Young's moduli which are in the range of trabecular bone and are unlikely to cause significant stress raising or shielding when used in trabecular bone void filling applications [55, 56].

4.3 Injectability

The importance of injectability can not be understated in the current clinical environment, with minimally invasive surgical techniques becoming ever more prevalent, reducing morbidity to patients, risk of infection, operating and recovery times. In bone void filling procedures such as craniotomy, fixation of vertebral compression fractures, frontal sinus obliteration and fixation of comminuted fractures, open invasive procedures are becoming rare and there is a growing demand for strong, injectable, biocompatible and bioactive cements.

It is clear from the results in Figs. 5 and 6 that the novel GPCs examined have unsuitable injectability for injection in a clinical setting. Hydroset™ is injectable (below 225 N) until it approaches the working time (Tables 2 and 3). Although GPC A, with a longer working time, has better injectability, it is fair to say that a considerably longer working time is required to allow sufficient flow and rheological properties for Zn-GPC's injectability.

Working and setting times more suited to injectability may be achieved by further modification of the cement compositions. In this study TSC was used at a concentration of 10 wt% but further increases in TSC content have been shown to result in deterioration of strength in Zn-GPCs [57]. The use of alpha-hydroxy acids and their salts, other than TSC, has been investigated for modification of calcium phosphate and zinc polycarboxylate cements [58–62]. Two alpha-hydroxy acids appear most promising; glycolic acid and lactic acid. Numerous salts of these acids exist (ammonium glycolate, sodium glycolate, ammonium lactate, calcium lactate, potassium lactate, and sodium lactate). Future studies into the effects of such modifications on Zn-GPCs rheological properties may reveal favourable results and produce a more injectable cement.

5 Conclusion

Formulations of glass polyalkenoate cements based on strontium calcium zinc silicate glasses and low molecular weight poly(acrylic acid) exhibit suitable mechanical properties for use in bone void filling and fracture fixation applications and perform admirably when compared to a commercial self-setting calcium phosphate cement. Though such GPCs do exhibit some injectability, working times, at present, remain too short for use in minimally invasive surgical techniques.

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