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# Biomedical Physics & Engineering Express

# Injectable glass polyalkenoate cements: evaluation of their rheological and mechanical properties with and without the incorporation of lidocaine hydrochloride

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## Abstract

Lidocaine hydrochloride is used as an anesthetic in many clinical applications. This short communication investigates the effect of complete substitution of lidocaine hydrochloride for deionized (DI) water on the physico-chemical properties of two novel glass polyalkenoate cements. Substituting DI water with lidocaine hydrochloride resulted in cements with shorter working times but comparable setting times and mechanical properties. Fourier transform infrared spectroscopy confirmed that the setting reaction in cements containing DI water and lidocaine hydrochloride was completed within 24 h, post cement preparation and maturation. Further, it was explained that lidocaine hydrochloride binds to poly(acrylic) acid (PAA) due to electrostatic forces between the positively charged amino group of lidocaine hydrochloride and the carboxylic group of the PAA, resulting in a compact poly-complex precipitate.

## 1. Introduction

Bioactive glasses are implanted for tissue replacement or regeneration [1]. Such glasses elicit a biological response at their surface which stimulates cell growth and gene response for the formation of a bond between the material and living tissues [2, 3].

Glass polyalkenoate cements (GPCs) are formed by an acid–base reaction between a water-soluble poly (acrylic) acid (PAA) and an acid-degradable fluoro-alumino-silicate bioactive glass [4]. GPCs were initially developed in the early 1970's for use in restorative dentistry [5]. A poly-salt matrix is formed in GPCs through the degradation of the glass, leading to the release of free cations which associate with the carboxylic anions from the PAA [6]. The crosslinking mechanism is a continuous process during which acrylate networks are established, leading to the increase in strength over time [7, 8]. The physical properties of GPCs have been shown to vary with alteration of the powder-liquid ratio, acid concentration, molecular weight of the PAA and methods of curing [9]. However, there has been little research reported concerning the changes in physical properties of the GPC upon the replacement of deionized (DI) water with a different agent.

Lidocaine hydrochloride is used as an anesthetic in many clinical applications [10, 11]. It functions by inhibiting the flow of sodium ions into the membranes of neurons when activated through an exterior stimulant, causing temporary relief from pain [12]. Of the local anesthetics clinically available, lidocaine is the most widely used [12]. Substituting lidocaine for water in a GPC is a novel proposal, given the expansive range of its use. Injection of the resultant GPC could provide stabilization to the fracture whilst relieving patient pain.

The objective of this preliminary study is to determine the change in mechanical and rheological properties in GPCs that result from the complete substitution of lidocaine hydrochloride for water in the starting composition. The objective is realized by utilizing two distinct aluminum-free glass compositions and observing any variation in GPC properties prepared from them as a result of substituting lidocaine hydrochloride for DI water.

Table 1. Composition of glass series in mole fraction.

|        | $SiO_2$ | ZnO   | CaO  | SrO  | $P_2O_5$ | $Ta_2O_5$ |
|--------|---------|-------|------|------|----------|-----------|
| **BT101** | 0.48 | 0.36  | 0.12 | 0.04 | —        | —         |
| **TA2**   | 0.48 | 0.355 | 0.06 | 0.08 | 0.02     | 0.005     |

# 2. Materials and methods

## 2.1. Glass synthesis

Two glass compositions (BT101 and TA2) were utilized in this study (table 1). The glasses were prepared by weighing out appropriate amounts of the analytical grade reagents (Fisher Scientific, Ottawa and Sigma-Aldrich, Oakville, Canada) and mixing them in a container. Platinum (Pt) crucibles and a Lindberg/Blue M model furnace (Lindberg/Blue M, Asheville, NC USA) with a UP-550 controller were used for melting the powders. BT101 glass was melted at 1500 °C for 1 h while TA2 glass was melted at 1650 °C for 1.5 h. The melts were shock quenched in water to obtain frit which was then dried in the oven (100 °C, 1 h), ground using a ball mill (400 rounds per minute, 15 min), and sieved to obtain particle size of 45 $\mu$m and 20 $\mu$m < $x$ < 45 $\mu$m for TA2 and BT101, respectively. BT101 was then annealed at 630 °C for 12 h, to relieve internal stresses within the glass network and to extend the handling properties of the GPCs made from them. The furnace (Lindberg/Blue M, Asheville, NC USA) was programmed to reach annealing temperature within 3 h and to cool down to room temperature (25 ± 2 °C) in a further 3 h. The glass powders of the selected compositions were then sieved and utilized for subsequent cement preparation and characterization. TA2 glass was not annealed because that would have resulted in handling properties longer than clinically applicable.

## 2.2. Cement preparation

Cement samples were prepared by mixing BT101 with poly(acrylic acid) (PAA 40, Mw = 30 000, Advanced Healthcare Ltd, Tonbridge, UK) and TA2 with PAA 35 (Mw = 55 000, Advanced Healthcare Ltd, Tonbridge, UK). The glasses were thoroughly mixed with their respective acids and DI water on a glass plate. The cement using BT101 was formulated at a P:L ratio of 1:2, where 1 g of glass was mixed with 1 g PAA 40 and 1 ml DI water. The cement using TA2 was formulated at a P:L ratio of 1:1.6, where 1 g of glass was mixed with 0.6 g PAA 35 and 1 ml DI water. The process was repeated with identical powder–liquid ratios for both glasses when formulating samples using lidocaine hydrochloride as opposed to DI water. Complete mixing was undertaken within 30 s in ambient room temperature (23 ± 1 °C). Cements were subsequently named (BT101-W, BT101-L, TA2-W and TA2-L) after the glasses and aqueous solvents (W for Water, L for lidocaine) that they were fabricated from.

## 2.3. Working and net setting times

The working time ($T_w$) of the cements ($n$ = 5) was measured in ambient air (23 ± 1 °C) using a digital stopwatch, and was defined as the period of time from the start of mixing during which it was possible to manipulate the material without having an adverse effect on its properties [13].

The setting time ($T_s$) of each of the cements ($n$ = 5) was measured in accordance with ISO 9917 [13]. An empty mold with internal dimensions 10 mm × 8 mm was placed on aluminum foil and filled to a level surface with mixed cement. Sixty seconds after mixing commenced, the entire assembly was placed on a metal block (8 mm × 75 mm × 100 mm) in an oven maintained at 37 °C. Ninety seconds after mixing, a Vicat needle indenter (mass 400 g) was lowered onto the surface of the cement. The needle was allowed to remain on the surface for 5 s, the indent it made was then observed and the process was repeated every 30 s until the needle failed to make a complete circular indent when viewed at ×2 magnification.

## 2.4. Fourier transform infrared (FTIR) spectroscopic study

Three cement cylinders (6 mm high, 4 mm diameter) of both compositions were prepared and aged for 1 day in DI water. ~0.3 g powdered versions (<90 $\mu$m) of each cement were used as samples. Spectra were collected using a FTIR spectrometer (Spectrum One FTIR spectrometer, Perkin Elmer Instruments, USA) and background contributions were removed. The sample and the reference background spectra were collected for each cement formulation in ambient air (23 ± 1 °C). Analysis was performed in the wavenumber ranging from 4000 to 650 cm$^{-1}$ with a spectral resolution of 4 cm$^{-1}$. Measurements were performed by attenuated total reflectance technique with a ZnSe crystal.
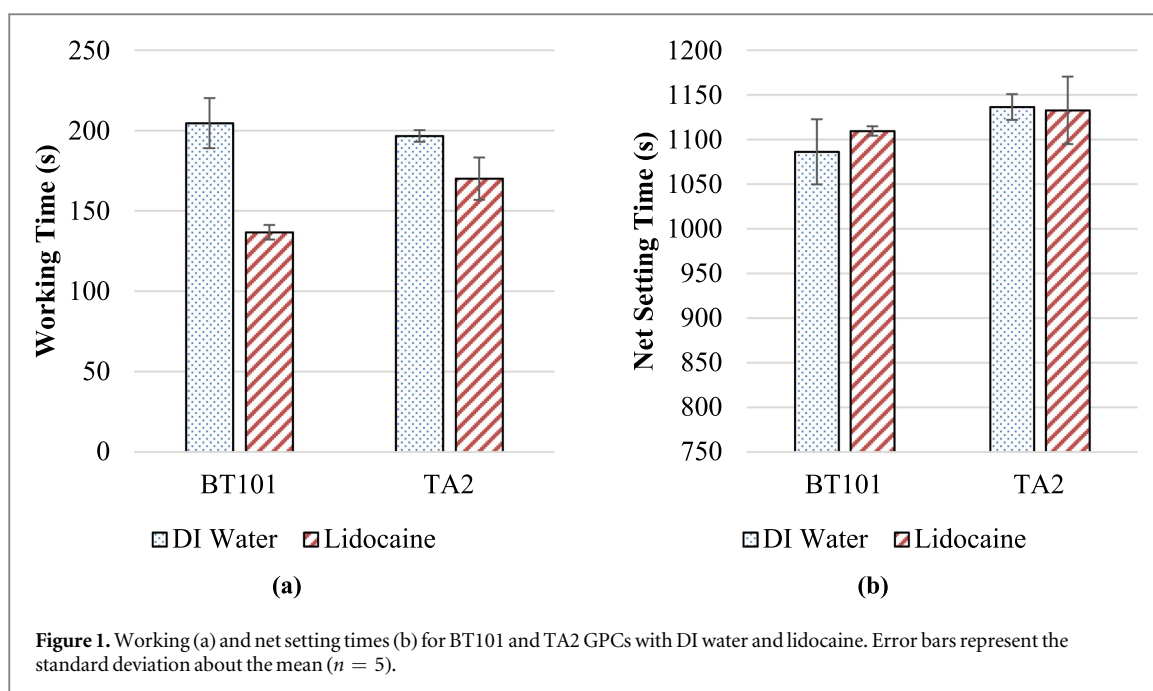
## 2.5. Evaluation of mechanical properties

### 2.5.1. Determination of compressive strength

The compressive strength ($\sigma_c$) of the four GPC compositions (section 2.2) were evaluated in ambient air (23 ± 1 °C) according to ISO 9917-1:2007 [13]. Cylindrical samples (4 mm Ø, 6 mm height, $n$ = 5) were tested after 1, 7 and 30 days ageing (DI water, 37 °C). Testing was undertaken on an Instron Universal Testing Machine (Instron Corp., Massachusetts, USA) using a ±2 kN load cell at a crosshead speed of 1 mm min$^{-1}$. The fracture load was noted for each sample. Compressive strength was calculated according to equation (1).

$$C = \frac{4\,\rho}{\pi\,d^2}, \tag{1}$$

where $\rho$ is the fracture load (N) and $d$ is the sample diameter (mm).

**Figure 1.** Working (a) and net setting times (b) for BT101 and TA2 GPCs with DI water and lidocaine. Error bars represent the standard deviation about the mean ($n = 5$).

*2.5.2. Determination of biaxial flexural strength*

The biaxial flexural strengths ($\sigma_f$) of the four cement compositions ($n = 5$) were evaluated using the method as described by Williams *et al* [14]. Cement disks (12 mm Ø, 2 mm thick) were tested, in the wet state, after being aged for 1, 7 and 30 days (DI water, 37 °C). Testing was undertaken on an Instron Universal Testing Machine (Instron Corp., Massachusetts, USA) using a ±2 kN load cell at a crosshead speed of 1 mm min$^{-1}$. The fracture strength was noted for each sample. Biaxial flexural strength was calculated according to equation (2).

$$ \mathrm{BFS} = \frac{\rho(N)}{t^2} \left\{ 0.63 \ln \frac{r}{t} + 1.156 \right\}, \qquad (2) $$

where $\rho$ is the fracture load (N), $t$ is the sample thickness (mm) and $r$ is the radius of the support diameter (mm).

**2.6. Statistical analysis**

A non-parametric Kruskal–Wallis H Test was used to analyze the data. Mann–Whitney U test was used to compare the relative means and to report the statistically significant differences when $P \leqslant 0.05$. Statistical analysis was performed using SPSS software (IBM SPSS statistics 21, IBM Corp., Armonk, NY, USA).

# 3. Results and discussion

## 3.1. Evaluation of rheological properties

The working and net setting times for BT101 and TA2 with DI water and lidocaine hydrochloride were evaluated and are presented in figure 1. The mean working times for BT101-W, BT101-L, TA2-W and TA2-L were recorded as ∼205, 137, 197 and 170 s, respectively (figure 1(a)). There was a statistically significant difference ($P = 0.050$) between the working times for the DI water/lidocaine hydrochloride cement pairs. The net setting times were also recorded. BT101-W and BT101-F had a similar mean setting time of ∼1100 s ($P = 0.513$). A similar trend was observed with the TA2 cement pair as TA2-W and TA2-F had a setting time of ∼1140 s ($P = 0.513$).

The significant decrease in the initial working time can be attributed to complexation caused by the binding of lidocaine hydrochloride to PAA. Complexation of the polymer can cause conformational changes in the polymer chain leading to a decrease in viscosity [9]. In a study by Nurkeeva *et al* [15], the authors reported that lidocaine hydrochloride binds to PAA, leading to a significant decrease in the viscosity of the polymer. The binding occurred due to electrostatic forces and is accompanied by the formation of compact poly-complex precipitate. The electrostatic forces can be explained by the formation of ionic bonds between the positively charged amino group of lidocaine hydrochloride and the carboxylic group of the PAA [15].

## 3.2. FTIR spectroscopic study

FTIR transmittance spectra of the cements are shown in figure 2 in the range 4000–650 cm$^{-1}$. Figure 2(a) shows the FTIR transmittance spectra for BT101-W and BT101-L. Figure 2(b) shows the FTIR transmittance spectra for TA2-W and TA2-L. It is obvious that both BT101 and TA2 have similar FTIR bands. The obtained bands are centered at ∼3300, 2100, 1550, 1400, 1320, 1170, 1060 and 960 cm$^{-1}$. This indicates that both materials have similar chemical bonds when observed one day, post cement preparation and maturation.

The broad peak centered at 3268 cm$^{-1}$ is assigned to hydrogen-bonded OH stretching vibrations of
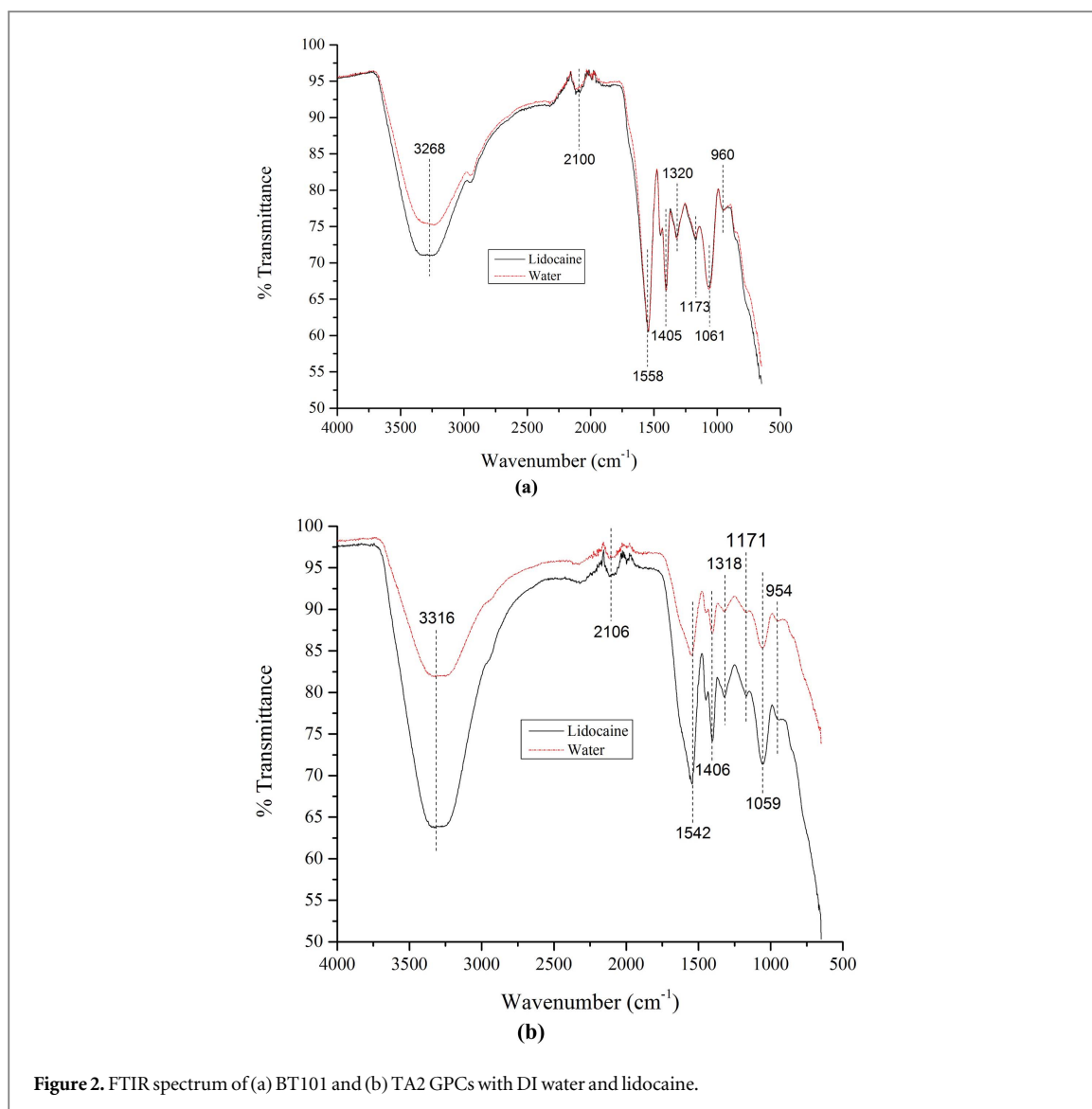
**Figure 2.** FTIR spectrum of (a) BT101 and (b) TA2 GPCs with DI water and lidocaine.
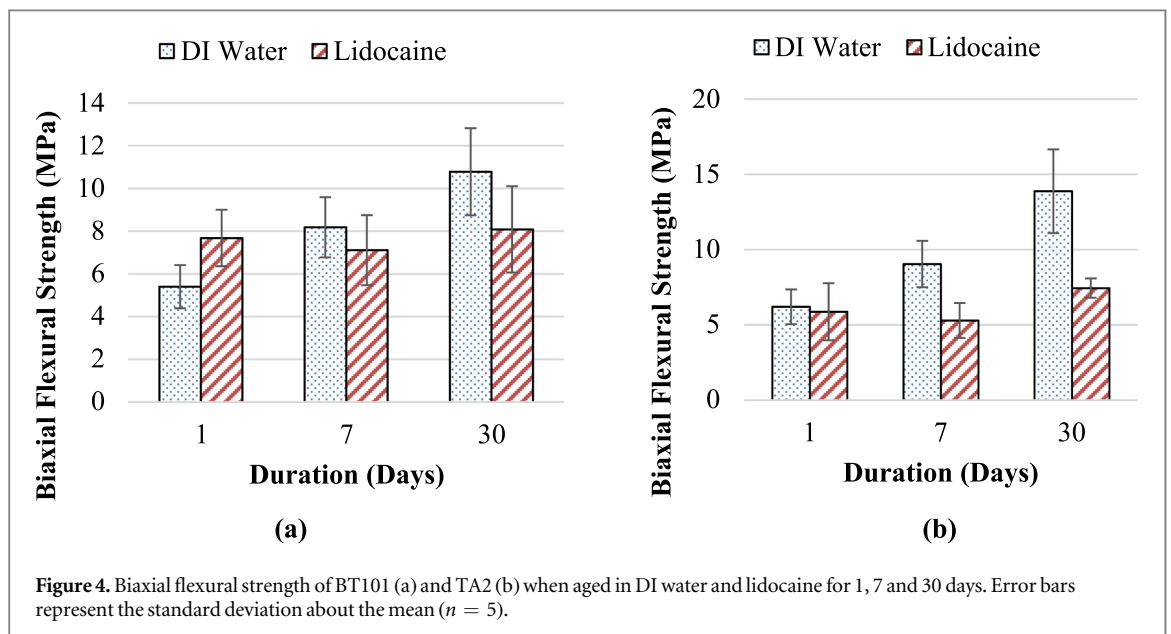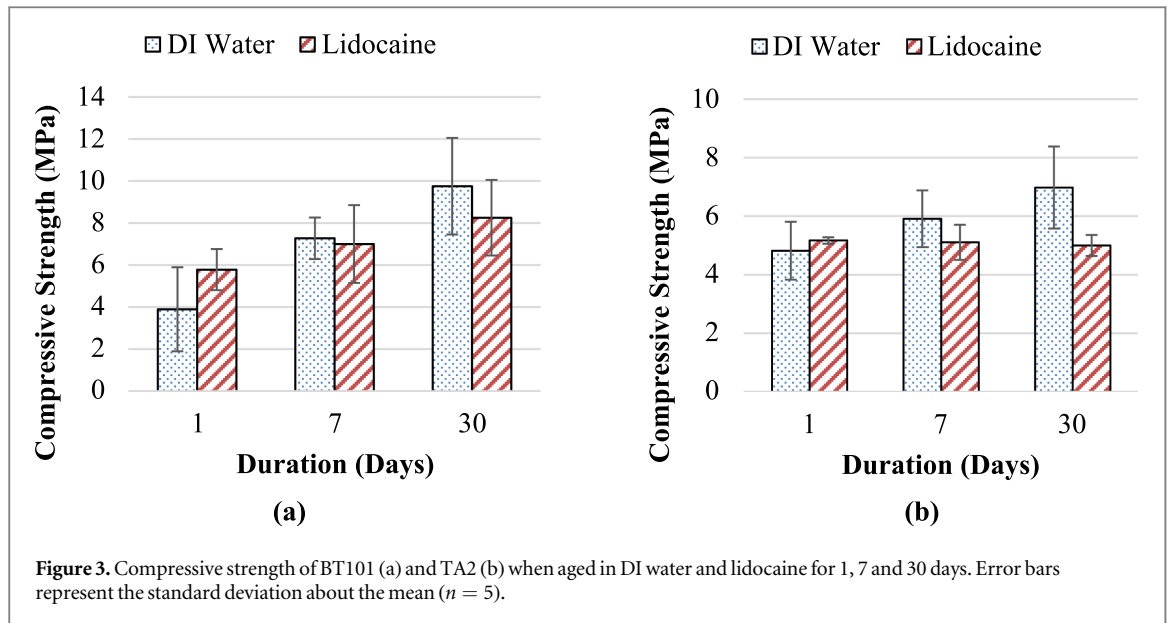
absorbed water within the poly-salt matrix [16]. The intensity of this peak was found to drop from ~75 (BT101-W) to ~70 cm$^{-1}$ (BT101-L) and from ~82 (TA2-W) to ~64 cm$^{-1}$ (TA2-L) when the water component was fully replaced with lidocaine. It is apparent that replacing DI water with lidocaine hydrochloride results in a poly-salt matrix containing larger amounts of water, evident from the drop in %transmittance. The spectra for all materials have shown peaks surrounded by noise in the region 2300–1800 cm$^{-1}$. Therefore, the peaks in the region 2300–1800 cm$^{-1}$ were not analyzed. The peaks centered at 1550, 1400, 1320, 1170, 1060 and 960 cm$^{-1}$ were observed in a similar study utilizing tantalum-containing glasses including the one used here [16]. The peaks centered at 1550, 1400 and 1320 cm$^{-1}$ are assigned to the asymmetric/symmetric stretching vibrations of the dissociated carboxyl COO groups with the glass cations, for example Ca$^{2+}$ and Sr$^{2+}$ [17, 18]. Confirming that the reaction between PAA and glass cations was completed within 24 h, post cement preparation and maturation. The peaks centered at 1170 and 1060

corresponds to the vibrational mode of the stretching of Si–O–Si [19]. The transmittance peak centered at 960 cm$^{-1}$ corresponds to Si–OH deformation vibration [20].

It is obvious from FTIR spectra that Ta-based cements contained more DI water than BT-based cements when the DI phase was replaced with lidocaine hydrochloride, ne day post cement preparation and maturation. This could be due to the presence of Ta$^{5+}$ ions in the cement matrix delaying the gelation process thus facilitating larger amounts of water to be absorbed by the poly-salt matrix [16] in the Ta-containing GPCs. The delay in the gelation process results from the former role of Ta in these materials and its slow reactivity with PAA [16].

### 3.3. Evaluation of mechanical properties
The compressive strengths ($\sigma_c$) for the four cement compositions were tested over 1, 7, and 30 days and are presented in figure 3. Both BT101-W and TA2-W recorded their lowest $\sigma_c$ at 1 day with values of ~5 MPa and highest $\sigma_c$ at 30 days with respective

**Figure 3.** Compressive strength of BT101 (a) and TA2 (b) when aged in DI water and lidocaine for 1, 7 and 30 days. Error bars represent the standard deviation about the mean ($n = 5$).



**Figure 4.** Biaxial flexural strength of BT101 (a) and TA2 (b) when aged in DI water and lidocaine for 1, 7 and 30 days. Error bars represent the standard deviation about the mean ($n = 5$).

values of ~10 and 7 MPa (figure 3). The increase in compressive strength over time was significant for BT101-W ($P = 0.005$) but insignificant for TA2-W ($P = 0.056$). BT101-L ($P = 0.102$) and TA2-L ($P = 0.403$) did not exhibit any significant change in $\sigma_c$ over time. However, the change in $\sigma_c$ between DI water and lidocaine samples were found to be insignificant ($P > 0.05$) for both BT101 and TA2 across all maturation periods.

Biaxial flexural strengths ($\sigma_f$) were also evaluated over 1, 7 and 30 days for the formulated GPCs and are presented in figure 4. The minimum and maximum $\sigma_f$ were recorded at 1 and 30 days for both BT101-W and TA2-W samples with respective values of ~5 (BT101-W) and ~6 (TA2-W) MPa at 1 day and ~11 (BT101-W) and ~14 (TA2-W) MPa at 30 days. The increasing trend was found to be significant for both BT101-W ($P = 0.003$) and TA2-W ($P = 0.003$). Biaxial flexural

strength results of BT101-L and TA2-L did not show any specific trend over time and the differences in the mean $\sigma_f$ values for both samples were found to be insignificant ($P > 0.05$). There were, however, significant changes for certain maturation periods when comparing the differences between DI water and lidocaine hydrochloride samples. For BT101, the changes between 1 day ($P = 0.009$) and 30 days ($P = 0.047$) for the DI water/lidocaine pairs were significant. The TA2 DI water/lidocaine pairs had significant changes for 7 day ($P = 0.009$) and 30 day ($P = 0.009$) maturation periods.

The increase in $\sigma_c$ and $\sigma_f$ over time for DI water-based cements is the expected trend seen by comparable GPCs in the literature [7, 21, 22] and is attributed to the continuous cross-linking process between the carboxyl groups from the polymer and the released cations from the glass [21, 23, 24]. The process is

initiated by the release of protons from the PAA in the presence of water at neutral pH (equation (3)) [9]. The released protons attack the glass particles in an acid–base reaction that liberates the cations to form the acrylate networks. The $\sigma_c$ and $\sigma_f$ of lidocaine hydrochloride-containing GPCs however, showed lower or comparable strengths during maturation. When lidocaine hydrochloride is mixed with PAA and deionised water, protons are released due to the formation of ionic bonds between the carboxylic groups of the PAA and positively charged amino groups in lidocaine hydrochloride [15]. The ionic bond that forms slows down the process of cross-linking between the PAA and the cations from the glass. This behavior was shown to affect the strength of lidocaine hydrochloride-containing GPCs when compared to water-based GPCs. This agrees with the obtained FTIR results. The lidocaine hydrochloride-containing GPCs were found to contain more water, which could explain the reduced strengths recorded.

$$\eta\ CH_2 = CH - CO_2H + H_2O \xrightarrow{pH=7.0}$$
$$\eta\ CH_2 = CH - H_2O + COOH. \tag{3}$$
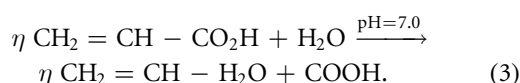
## 4. Conclusion

To the best of our knowledge, this communication reports for the first time that the local anesthetic lidocaine hydrochloride can fully substitute for the water phase in GPC systems, but this substitution results in cements with shorter working times but comparable setting times and mechanical properties. This may lead to the development of injectable GPCs with suitable working and setting times for various skeletal applications such as wrist and shoulder fixation which can also minimize pain for recipients.

Due to the low strengths of the cements under study, the authors recommend the use of these cements in conjunction with plates or wires to offer additional fixation. Further *ex-vivo* and *in-vivo* studies are necessary to prove the suitability of the studied GPC systems for skeletal applications.

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