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Zinc polycarboxylate dental cement for the controlled release of an active organic substance: proof of concept

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Abstract The potential of employing zinc polycarboxylate dental cement as a controlled release material has been studied. Benzalkonium chloride was used as the active ingredient, and incorporated at concentrations of 1, 2 and 3% by mass within the cement. At these levels, there was no observable effect on the speed of setting. Release was followed using an ion-selective electrode to determine changes in chloride ion concentration with time. This technique showed that the additive was released when the cured cement was placed in water, with release occurring by a diffusion mechanism for the first 3 h, but continuing beyond that for up to 1 week. Diffusion coefficients were in the range 5.62×10^{-6} cm^2 s^{-1} (for 1% concentration) to 10.90×10^{-6} cm^2 s^{-1} (for 3% concentration). Up to 3% of the total loading of benzalkonium chloride was released from the zinc polycarboxylate after a week, which is similar to that found in previous studies with glass-ionomer cement. It is concluded that zinc polycarboxylate cement is capable of acting as a useful material for the controlled release of active organic compounds.

1 Introduction

Dental cements are based on mixtures of an acid and a base [1]. The base is a solid, typically powdered zinc oxide or a special ion-leachable glass, whereas the liquid is and acidic solution, either of phosphoric acid or polyacrylic acid. The cements set by a process of neutralization to give a phosphate or polyacrylate salt matrix and leave some unreacted base to act as reinforcing filler.

The zinc polycarboxylate cement is formed from heat-treated zinc oxide and aqueous polyacrylic acid [1]. The zinc oxide is very slightly non-stoichiometric, and usually mixed with about 10% magnesium oxide. The polyacrylic acid is typically of molar mass 40,000–50,000 [2]. Zinc polycaboxylate was first reported (by Smith) in 1968 [3] and was an important invention, as it was the first adhesive dental cement. It was also found to have low irritancy towards oral tissues [4].

Zinc polycarboxylate is related to the glass-ionomer dental cement, in that a similar aqueous polymer solution is used in its preparation. Glass-ionomer, which consists of special ion-leachable glass powders reacted with aqueous polyacrylic acid, is considered extremely versatile in clinical dentistry [1, 5]. One aspect that has been explored is its potential as a controlled release material.

Controlled release is an important concept in modern pharmaceutical science [6]. A variety of devices, many of them polymer based, have been studied to release active organic molecules at a sustained rate. Preferably this occurs close to the site at which the pharmaceutical treatment is needed.

Glass-ionomers have been studied for the ability to deliver a variety of active organic molecules. The most extensive studies have been with chlorhexidine [7–10], a substance which is widely used in mouthwashes and in skin cleansers [11].

Pearson et al. have shown that chlorhexidine can be incorporated into glass-ionomer cements with only minor changes in setting behaviour for low levels of addition [7]. Release followed a diffusion mechanism as shown by linearity of graphs of release against square root of time [7]. Chlorhexidine was found to cause small but significant

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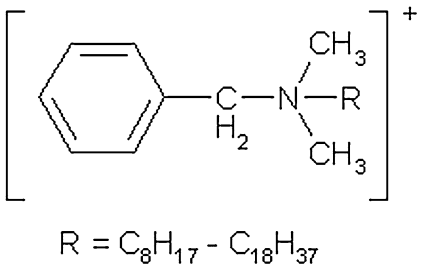

Fig. 1 Structure of benzalkonium chloride

reductions in compressive strength of the glass-ionomer cement specimens [7, 9], but to be effective as an anti-microbial agent against a variety of oral bacteria [8, 10].

Other organic species have also been studied for delivery by glass-ionomer cements [9]. These include benzalkonium chloride, cetyl pyridinium chloride and cetrimide. All have been shown to have similar effects on the properties of the glass-ionomer, namely increasing the working and setting times and reducing the compressive strength [9].

To date, glass-ionomers are the only acid–base cements that have been reported as possible controlled release devices. In the current study, we have extended this to study the potential of zinc polycarboxylate to act in this way, using benzalkonium chloride as the model active ingredient.

There has been one previous study of this system, which was an in vivo study in which benzalkonium chloride was added to a zinc polycarboxylate prior to placement in the mouth [20]. The presence of the benzalkonium chloride led to elevated salivary chloride levels and also a decreased deposition of plaque. This suggests that the system has the capacity to inhibit bacterial growth under clinical conditions.

Benzalkonium chloride (Fig. 1) is a widely used anti-microbial preservative [12, 13]. It is a mixture of alkyl-benzyldimetylammonium chlorides with the general formula $[C_6H_5CH_2N(CH_3)_2R]Cl$, in which R represents a mixture of alkyl groups [14]. The alkyl groups have chain lengths in the range C_8 to C_{18} and the typical molar mass of the compound is about 340.

Benzalkonium chloride is effective against gram negative bacteria, and operates by causing cytolytic leakage of cytoplasmic materials at low concentrations, after acting on general membrane permeability [15]. It has mild surfactant properties, which assist in its anti-microbial behaviour [16] and it is of relatively low toxicity towards humans [12].

2 Materials and methods

Experiments employed the commercial zinc polycarboxylate cement Polykent (ex Kent Dental, Gillingham, Kent, UK). This is a water-activated cement that is mixed at a powder:water ratio of 5.0:1. Benzalkonium chloride (Sigma-Aldrich, Poole, Dorset, UK) was used as the active ingredient. It is supplied at a stated purity of ≥95.0%. Cements were mixed on a ceramic tile using a stainless steel spatula, with mixing taking approximately 1–1.5 min.

Freshly mixed cement pastes were then placed in silicone rubber moulds of dimensions 6 mm diameter and 2 mm depth. Six specimens were prepared for each concentration of additive. Three sets of specimens were made, containing, respectively, 1, 2 and 3% benzalkonium chloride by mass. In addition, a set of control specimens containing no additive was prepared.

Once packed into the moulds, specimens were cured in an incubator for 10 min at 37°C. After curing, the specimens were being removed carefully from the rubber mould, weighed, then placed in individual plastic centrifuge tubes (capacity: 50 ml), and deionised water (5 ml) added to each tube.

Chloride release was then determined from each specimen at intervals of 15, 30 and 45 min, then 1, 2, 3, 4, 5, 24 h, and 1, 2 and 3 weeks, respectively, using a chloride ion-selective electrode (Ionplus Sure-Flow electrode, ex Thermo Electron Corporation, Basingstoke, Hampshire, UK) (Table 1). The storage liquid was unchanged throughout the experiments. The chloride electrode was kept in a solution of sodium chloride of concentration 0.1 ppm between readings and all specimens were stored at room temperature for the duration of the experiments.

Release profiles were recorded using figures for the mean release at each time interval. Graphs M_t/M_∞ against square root time were plotted to determine whether the release occurred by a diffusion mechanism. Lines of best fit were determined by least squares regression.

Table 1 Chloride release levels/ppm in 5 ml of water from zinc polycarboxylate cement specimens (SD in parentheses)

Time/min	1% benzalkonium chloride	2% benzalkonium chloride	3% benzalkonium chloride
0	0.5 (0.0)	0.5 (0.0)	0.5 (0.0)
15	0.7 (0.1)	1.2 (0.2)	1.9 (0.3)
30	1.0 (0.2)	1.7 (0.2)	2.0 (0.3)
45	1.3 (0.2)	2.1 (0.3)	2.3 (0.2)
60	1.5 (0.3)	2.5 (0.3)	2.7 (0.4)
120	1.7 (0.3)	2.7 (0.3)	3.8 (0.5)
180	1.9 (0.3)	3.2 (0.5)	4.3 (0.4)
240	2.0 (0.4)	3.9 (0.6)	5.3 (0.7)
1 week	4.3 (0.5)	13.9 (1.6)	27.8 (3.4)

3 Results

For all three concentrations of benzalkonium chloride, measurable amounts of chloride were found using the ion-selective electrode at all time intervals. Release was steady throughout the early release times, and there was no initial burst of release. Negligible amounts of chloride were detected from the control cement with no additive (circa 1.0 ppm, SD 0.5 ppm, after 1 week). A typical release profile for one of the benzalkonium chloride cements (1%) is shown in Fig. 2.

After 1 week, release levels had levelled out and they did not change significantly in the two subsequent weeks. The 1 week value was used as the M_∞ when substituting into the equation for Fick's 2nd Law, i.e., Diffusion coefficient,

$$D = \frac{s^2 \pi l^2}{4}$$

where s = slope of the graph of M_t/M_∞ against $\sqrt{t}$; 2 l = specimen thickness (i.e., 1 mm for the specimens used in these experiments) [17]. From the 1 week figures, total release of benzalkonium chloride was estimated, assuming a molar mass of 340 (Table 2). The proportion of the total contained in the cements was calculated and expressed as percentage (also Table 2).

The plots of M_t/M_∞ against $\sqrt{t}$ for all three concentrations of benzalknoium chloride for the period of linearity (i.e. the first 3 h of release) are shown in Fig. 3 and the best fit equations are shown in Table 3. All three plots had correlation coefficients of 0.985 or better. From the slopes,

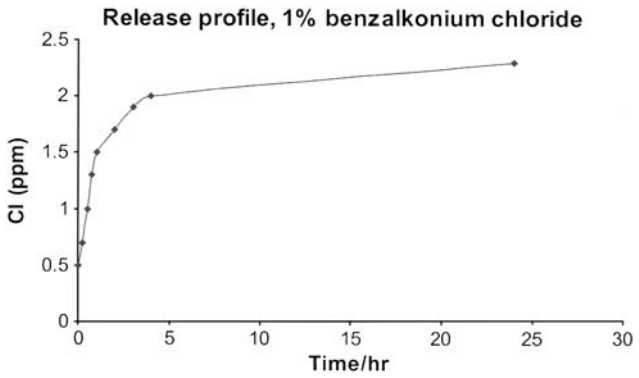

Fig. 2 Release profile for 1% benzalkonium chloride from zinc polycarboxylate

Table 2 Calculated recovery of benzalkonium chloride after 1 week (SD in parentheses)

1% addition	2% addition	3% addition
41.2 (4.8) ppm	133.1 (15.3) ppm	266.2 (32.6) ppm
1.4%	2.2%	3.0%

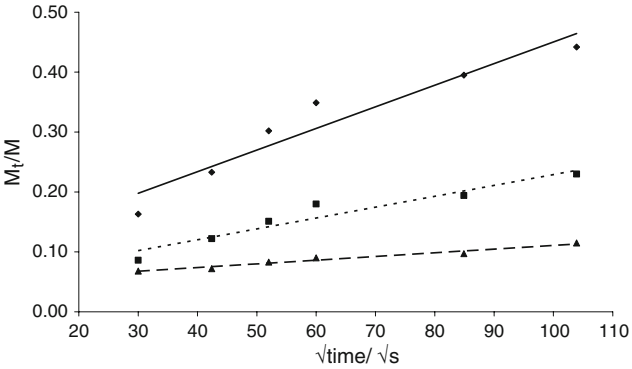

Fig. 3 Diffusion plot for benzalkonium chloride at levels of 1, 2 and 3% in cement (*Filled diamond* = 1%; *filled square* = 2%; *filled triangle* = 3%)

Table 3 Diffusion equations and regression coefficients for benzalkonium chloride release from zinc polycarboxylate cement

Initial concentration (%)	Equation	Regression coefficient (r)
1	$y = 0.02676x - 0.11$	0.998
2	$y = 0.02797x + 0.52$	0.985
3	$y = 0.03731x + 0.54$	0.992

Table 4 Diffusion coefficients for benzalkonium chloride release from zinc polycarboxylate cement

Initial concentration (%)	Diffusion coefficient ($cm^2\ s^{-1}$)
1	5.62×10^{-6}
2	6.14×10^{-6}
3	10.90×10^{-6}

diffusion coefficients were determined and are shown in Table 4.

4 Discussion

The incorporation of benzalkonium chloride at levels of 3% or less was found to have a negligible effect on the setting behaviour of zinc polycarboxylate cement. This is probably a reflection of the low concentrations involved, as previous studies have shown that ionic additives, such as sodium chloride, at higher concentrations speed up the setting process of zinc polycarboxylates [18]. This is because the presence of ions stabilises the charge-separated forms of the polyacrylic acid component, thus reducing the pH of the acid solution and increasing its overall reactivity [18].

With the benzalkonium chloride added, cured cements were found to release chloride ion in a process that

followed Fick's second law of diffusion for the first 3 h [17]. It is assumed that this chloride was released in association with the benzalkonium counter-ion in order that the system maintained electroneutrality, though this was not established experimentally in the current work. Diffusion coefficients varied with initial concentration of additive present, and ranged from 5.62×10^{-6} cm^2 s^{-1} (for 1% concentration) to 10.90×10^{-6} cm^2 s^{-1} (for 3% concentration).

Release beyond 3 h showed deviation from Fickian diffusion, though release continued for up to 1 week. The value of release at 1 week was not significantly different from those found at 2 and 3 weeks for all concentrations used in the cement, from which it was concluded that release had equilibrated by 1 week.

The amount of additive released at equilibrium was low, i.e., only 3% of the total addition or less. This is similar to the amount of compares with a figure of 4% for benzalkonium chloride released from glass-ionomer cement (4%) [9] to which up to 4% by mass of benzalkonium chloride by mass had been added. Similarly, it compares with a range of from 0.5 to 13.0% for chlorhexidine acetate release from glass-ionomer [7]. This means that, as with glass-ionomer, the majority of the additive is retained in the zinc polycarboxylate cement. The mechanism of retention is unclear. However, these cements are formulated from acidic polymers that are crosslinked by metal ions on setting, and all of these species have high affinities for quanternary ammonium salts. Hence it is not surprising that total release volumes are low for both zinc polycarboxylate and glass-ionomer cements.

Overall, these findings demonstrate that zinc polycarboxylate cement is capable of acting as a satisfactory controlled release material, at least over relatively short durations. At the levels of additive incorporated, its setting was not obviously affected, and the amounts released compared favourably with those previously observed for release from the closely related glass-ionomer cement.

5 Conclusions

Benzalkonium chloride can be incorporated into zinc polycarboxylate cement at low concentrations with little or no observable effect on the speed of setting. This additive can then be released from the cured cement into water in a process that was diffusion-controlled for at least the first 3 h, but continued releasing additive well beyond this limit, so that values at 1 week were much higher than those at 3 h. Values at 2 and 3 weeks were not significantly different from that at 1 week. Diffusion coefficients in the initial 3 h lay in the range 5.62×10^{-6} cm^2 s^{-1} (for 1% concentration) to 10.90×10^{-6} cm^2 s^{-1} (for 3% concentration). Only up to 3% of the total loading of benzalkonium chloride was released from this cement at equilibrium, so most of it was retained rather than released. The amount released is similar to the figure of 4% previously observed for release of benzalkonium chloride from glass-ionomer cement [9]. This high retention is attributed to the high affinity of the quaternary ammonium additive for the salt matrix derived from polyacrylic acid from which these cements are formed.

These results demonstrate that zinc polycarboxylate cement, like the glass-ionomer, is capable of acting as a controlled release material and may be worth exploring further for use in this role.

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