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Release of sodium fusidate from glass-ionomer dental cement

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Abstract Restorative grade glass-ionomer cement has been studied for its potential as a controlled release material for the antimicrobial compound sodium fusidate. Sodium fusidate powder was incorporated into the cement at the mixing stage at levels of 1% and 5% by mass, and disc shaped specimens (6 mm diameter × 2 mm depth) prepared. After curing for 1 hour at 37°C, specimens were placed in water and release of sodium fusidate at set time intervals determined using reverse-phase HPLC. Sets of five specimens were used in all experiments. Early release of sodium fusidate was shown to occur by diffusion for each level of addition, as shown by M_t/M_∞ being linear with respect to $\sqrt{}$time in both cases. Diffusion coefficients were calculated as 4.4×10^{-8} cm^2 s^{-1} and 3.0×10^{-8} cm^2 s^{-1} for 1 and 5% respectively. These were an order of magnitude lower than had been found previously for water transport in glass-ionomer cements, a result that is attributed to the greater size of the sodium fusidate molecule compared with that of water. Cements released 20.4 and 22.8% respectively of the total sodium fusidate added after 2 weeks, values which were not significantly different from each other, and which exceeded total release previously reported for benzalkonium chloride and chlorhexidine.

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1 Introduction

Glass-ionomer cements are widely used in clinical dentistry [1]. They are employed mainly as liners and bases, and as direct filling materials. They are also used to cement orthodontic brackets [2] and to seal root canals in endodontics [3]. In addition, they have been used as bone cements [4–6].

They are formed by reaction of special basic glass powders with aqueous polymeric acid [7]. The glass is typically a calcium or strontium fluoro-aluminosilicate, though other experimental types have been reported [8]. The polymer is either polyacrylic acid or acrylic acid/maleic acid copolymer in clinical brands, though other polymers have also been studied, such as polyvinyl phosphonic acid [9] and amino acid-modified polyacrylic acid [10].

Setting is a complex process involving neutralization of the acid and crosslinking by multi-valent ions, e.g. Ca^{2+} and Al^{3+} [11]. Other chemical reactions occur that increase the degree of hydration [12] and reduce the proportion of 4-coordinate Al with concomitant increase in the proportion of 6-coordinate Al [12].

In view of their clinical usefulness, glass-ionomers have been considered as controlled release materials. Controlled release is a topic of considerable scientific interest in the field of pharmacy [13], and the possibility of using glass-ionomers in this way has been explored with a view to enhancing their antimicrobial properties for dental use. The active ingredient studied in greatest detail has been chlorhexidine [14].

Addition of chlorhexidine at levels of between 0.5 and 13.0% by mass has been reported [14]. At higher levels in particular, chlorhexidine was shown to slow down the setting and to weaken the resulting cement, as determined

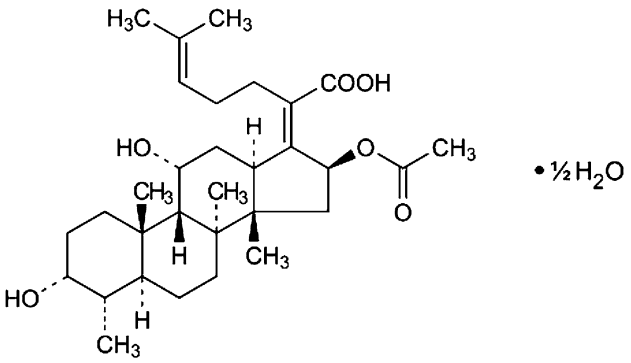

Fig. 1 Fusidic acid structure

by compressive strength studies [14]. Chlorhexidine was released in what was shown to be a diffusion process, in that release was linear with respect to square root of time; however, diffusion coefficients were not reported [14]. At equilibrium the majority of the chlorhexidine was retained within the cement.

Other additives have also been studied, including benzalkonium chloride and cetyl pyridinium chloride [15, 16]. Studies of the effect of these additives on cements were less comprehensive than those for chlorhexidine, but microbiological studies showed that benzalkonium chloride in particular was released in amounts sufficient to enhance significantly the antibacterial properties of the glass-ionomer [15]. This was despite the fact that, at the highest level of loading used, 4%, around 96% of the added benzalkonium chloride was retained in the cement.

Studies so far have employed either bases or quaternary ammonium salts. The aim of the present work was to extend this knowledge to the study of a different type of antimicrobial compound, namely the sodium salt of fusidic acid (see Fig. 1). Fusidic acid has a steroid skeleton and is employed against staphylococcus infections and other gram positive bacteria [17]. It prevents these bacteria producing essential proteins. Its sodium salt is widely used to treat skin, wound, bone and joint infections, and also pneumonia and endocarditis [18]. It might thus be a useful antimicrobial compound to employ in glass-ionomers designed for bone repair applications.

2 Materials and methods

Experiments were carried out using a hand mixed glass-ionomer cement (Ionoexpress, ex Kent Dental, UK). Sodium fusidate (ex Sigma-Aldrich, Poole, UK) was incorporated during the mixing process by spatulating the required amount (1 or 5% respectively) on a ceramic tile.

Freshly mixed cement pastes were placed in silicone rubber moulds (dimensions 6 mm diameter by 2 mm depth) placed between glass microscope slides, then cured at 37°C for 1 h. Five specimens were prepared for each sample.

After 1 h these specimens were weighed and placed in individual 5 ml volumes of deionised water in plastic centrifuge tubes. The specimen tubes were stored at room temperature (20–22°C). For each specimen at appropriate time intervals (1, 2, 3, 4, and 24 h, 1 and 2 weeks) a 10 µl aliquot was removed and analysed using HPLC. After 2 weeks the specimens were weighed again.

HPLC analysis used an Agilent 1200 series high-performance liquid chromatograph, fitted with a C18 column. Isocratic elution was used, with a mobile phase comprising acetonitrile, methanol and 0.01 M aqueous ortho-phosphoric acid in the volume ratios 5:2:3. All solvents were HPLC grade (ex Fisher, Loughborough, UK) and the blended mobile phase was degassed before use. The LC system employed a pump (type G1310A), injector (type G1328A) and UV detector (type G13314B). The detector was pre-calibrated and set at 235 nm wavelength. Flow rate was 2 cm^3/min and the system operated at room temperature and approximately 100 bars of pressure. Under these conditions, retention of sodium fusidate was 5.0 ± 0.1 min.

Using the data obtained, plots were made of M_t/M_∞ versus $\sqrt{}$time, to determine whether Fick's second law of diffusion is obeyed [19]. Where appropriate, differences in numerical values were tested for significance using Student's t test and differences where $P > 0.05$ were not considered significant.

3 Results

All samples were found to release sodium fusidate at all time intervals tested. After two weeks, this release had almost reached equilibrium, and the 2-week release value was taken as a reasonable estimate of the M_∞ value. Release was accompanied by a mass gain as the specimens took up water from the storage medium.

Release profiles based on mean levels of release are shown in Figs. 2 and 3. These were re-calculated and plotted as graphs of M_t/M_∞ versus $\sqrt{}$time, as shown in Fig. 4, using the value of release at 2 weeks as an approximate indication of M_∞. In both cases, this plot was linear for the first 4 h, showing that release occurred by a diffusion mechanism. For the 5% addition, this plot was still almost linear at 24 h, suggesting that diffusion-based release continues much longer at this higher loading.

Table 1 shows a summary of the release results for both sets of specimens. The differences between the mass gains and the proportions of additive released were not significant.

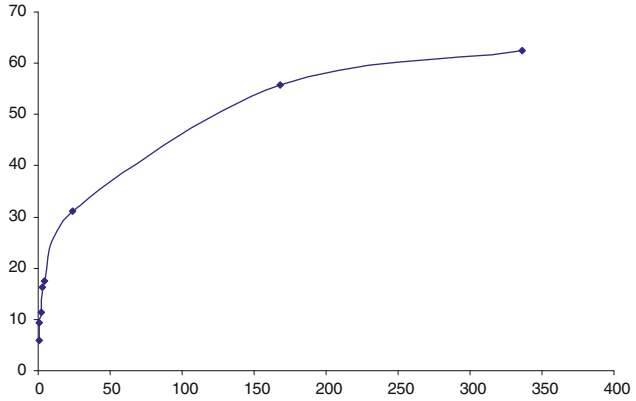

Fig. 2 Release profile for 1% loading of sodium fusidate (y-axis = release concentration (μg/l); x-axis = time (h))

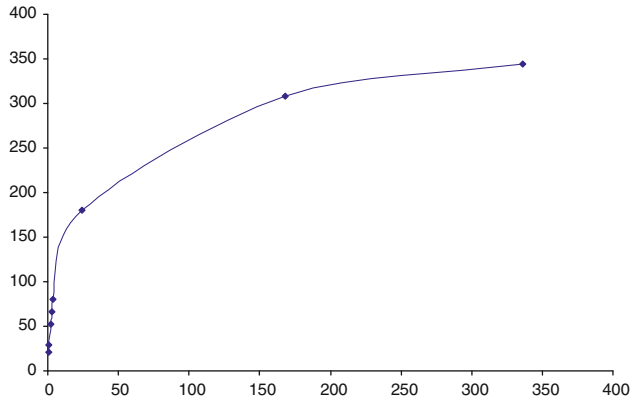

Fig. 3 Release profile for 5% loading of sodium fusidate (y-axis = release concentration (μg/l); x-axis = time (h))

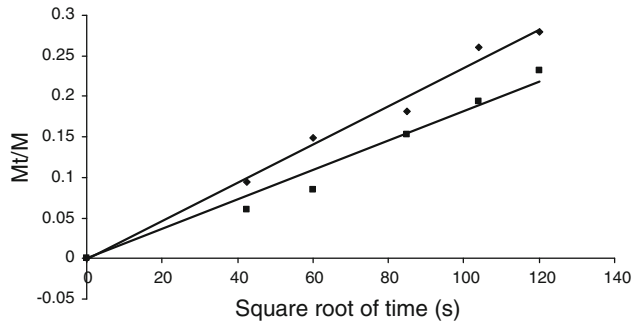

Fig. 4 Plot of M_t/M_∞ versus $\sqrt{}$time for 1 and 5% sodium fusidate addition (*filled triangle* 1%, *filled square* 5%)

Table 1 Summary of release data and water uptake

Property	1% sodium fusidate	5% sodium fusidate
Mass gain (at 2 weeks) (%)	5.1 (SD 2.5)	6.7 (SD 1.6)
Proportion released (%)	20.4 (SD 2.8)	22.8 (SD 2.7)
Diffusion coefficient ($cm^2\ s^{-1}$)	4.4×10^{-8}	3.0×10^{-8}

4 Discussion

In the present study, glass-ionomer cement has been shown to be capable of acting as a controlled release material for sodium fusidate at room temperature. Sampling was carried out from 5 ml volumes, and totalled only 80 μl (i.e. 8 × 10 μl) of each storage solution. This represents only 1.6% of the volume, which means that the volume of the storage solution can be considered approximately constant, despite the sampling

As has been found for previous substances studied, release of sodium fusidate was shown to occur by a diffusion mechanism [14, 15]. In the case of the 5% loading, the system had more or less equilibrated after 2 weeks, and the M_∞ value could be determined with confidence. For the 1% loading, the system had not fully equilibrated, and the two week value was only an approximation for M_∞. Nonetheless, it allowed an estimate to be made of the diffusion coefficient for release from this system.

No previous diffusion coefficients have been reported, so it is not possible to compare rates of diffusion of sodium fusidate with those of chlorhexidine, benzalkonium chloride or cetyl pyridinium chloride. However, it is possible to compare total amounts released at the two week point. Thus sodium fusidate was found to be released to a greater extent than, for example, benzalkonium chloride. Both 1 and 5% concentrations of sodium fusidate gave total release of just over 20% in two weeks, compared with only 4% for benzalkonium chloride [15]. This shows that it is more readily released than the quaternary ammonium salt.

Data were examined using the Stefan approximation i.e.

$$M_t/M_\infty = 2\sqrt{(Dt/\pi l^2)}$$

This neglects edge effects, and has been found to give acceptable results for the release of other species from glass-ionomers [20]. However, edge effects become significant for specimens other than continuous sheets, and these have the effect of reducing the rate of uptake, even though the process is still one of diffusion [19]. In the present experiments, the plot based on the Stefan approximation ceased to be linear after 4 h for the 1% loading and 24 h for the 5% loading. However, this does not mean that the process ceased to be diffusion controlled at these times, and may simply mean that edge effects can no longer be neglected with the particular specimen geometry employed.

Previous studies have determined the diffusion constants for water transport through glass-ionomer cements [20]. For restorative grades of cement, these were found to range from 5.87×10^{-7} to 13.4×10^{-7} $cm^2\ s^{-1}$, whereas in the current study, diffusion coefficients of 4.4×10^{-8} $cm^2\ s^{-1}$ (1%) and 3.0×10^{-8} $cm^2\ s^{-1}$ (5%) were found for sodium

fusidate. Thus water can be seen to diffuse through glass-ionomer cements an order of magnitude faster than sodium fusidate. This may be attributed to the relative sizes of the molecules involved, as water is smaller than sodium fusidate. In both cases, release must involve movement through the matrix of the cement, and escape through the surface. The surface may contain micro-cracks and other imperfections, which could enhance the rate of release.

Sodium fusidate has been shown to be released from glass-ionomer cement, though it is the salt of an acidic organic molecule. This suggests that there is little or no ion-exchange mechanism that would cause the fusidate moiety to be strongly bound within the cement, though further work is necessary before this could be confirmed. Previous reports of glass-ionomer for controlled release have all concerned either quaternary ammonium salts or the nitrogen-containing basic compound chlorhexidine, i.e. chemicals of very different character from sodium fusidate. Our study has thus extended the range of substances shown to be capable of being released by glass-ionomer cements. Release has been found to occur readily and to greater extents than previous substances, so that glass-ionomers can be seen to be versatile controlled release materials.

5 Conclusions

Glass-ionomer cements are capable of acting as controlled release materials for the antibacterial compound sodium fusidate, which is the salt of an acidic organic molecule. Release occurred by a diffusion mechanism for the first 4 h for the 1% level of addition, and for the first 24 h for the 5% level of addition, with calculated diffusion coefficients of 4.4×10^{-8} cm^2 s^{-1} and 3.0×10^{-8} cm^2 s^{-1} respectively.

The two cements released 20.4 and 22.8% respectively of the amount of sodium fusidate added in two weeks; figures which are not significantly different from each other. Diffusion of sodium fusidate occurred at a rate which is an order of magnitude slower than that found previously for water. The slower rate is attributed to the greater size of the sodium fusidate molecule compared to that of water.

This study extends the chemical type of additive that glass-ionomers have been shown to be able to deliver. This work clearly demonstrates their versatility as controlled release materials.

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References

1. Mount GJ. Color Atlas of glass-ionomer cements. 3rd ed. London: Dunitz; 2002.
2. Algera TJ, Kleverlaan CJ, de Gee AJ, Prahl-Andersen B, Feilzer AJ. The influence of accelerating the setting rate by ultrasound or heat on the bond strength of glass ionomers used as orthodontic bracket cements. Eur J Orthodont. 2005;27:472–6.
3. Friedman S, Löst C, Zarrabian M, Trope M. Evaluation of success and failure after endodontic therapy using a glass ionomer cement sealer. J Endodont. 1995;21:384–90.
4. Jonck LM, Grobbelaar CJ. Ionos bone cement (glass ionomer): an experimental and clinical evaluation in joint replacement. Clin Mater. 1990;6:323–59.
5. Babighian G. Use of a glass ionomer cement in otological surgery. A preliminary report. J Laryngol Otol. 1992;106:954–9.
6. Brook IM, Hatton PV. Glass-ionomers: bioactive implant cements. Biomaterials. 1998;19:565–71.
7. Nicholson JW. The chemistry of glass-ionomer cements. Biomaterials. 1998;19:485–94.
8. Boyd D, Towler M. The processing, mechanical properties and bioactivity of zinc based glass ionomer cements. J Mater Sci Mater Med. 2005;16:843–50.
9. Ellis J, Anstice HM, Wilson AD. The glass polyphosphonate cement: a novel glass-ionomer cement based on poly(vinyl phosphonic acid). Clin Mater. 1991;7:341–6.
10. Xie D, Chung I-D, Wu W, Lemons J, Puckett A, Mays J. An amino acid modified and non-HEMA containing glass-ionomer cement. Biomaterials. 2004;25:1825–30.
11. Crisp S, Pringeur M, Wardleworth D, Wilson AD. Reactions in glass ionomer cements: II. An infrared spectroscopic study. J Dent Res. 1974;53:1414–9.
12. Zainuddin N, Karpukhina N, Hill RG, Law RV. A long-term study on the setting reaction of glass ionomer cements by ^{27}Al MAS-NMR spectroscopy. Dent Mater. 2009;25:290–5.
13. Kydonieus A, editor. Treatise on controlled drug delivery. New York: Marcel Dekker; 1991.
14. Palmer G, Jones FH, Billington RW, Pearson GJ. Chlorhexidine release from an experimental glass ionomer cement. Biomaterials. 2004;25:5423–31.
15. Botelho MG. Compressive strength of glass ionomer cements with dental antibacterial agents. J South African Dent Assoc. 2004;59:51–3.
16. Botelho MG. Inhibitory effects on selected oral bacteria of antibacterial agents incorporated in a glass ionomer cement. Caries Res. 2003;37:108–14.
17. Verbist L. The antimicrobial activity of fusidic acid. J Antimicrob Chemother. 1990;25(Supplement B):1–5.
18. Menday AP, Marsh BT. Intravenous fusidic acid ('fucidin') in the management of severe staphylococcal infections: A review of 46 cases. Curr Med Res Opin. 1976;4:132–8.
19. Crank J, Park GS. Diffusion in polymers. London: Academic Press; 1968.
20. Nicholson JW, Czarnecka B. Kinetic studies of water uptake and loss in glass-ionomer cements. J Mater Sci Mater Med. 2008; 19:1723–7.