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Original article

Strontium Ions Release from Novel Bioactive Glass-Containing Glass Ionomer Cements: A Preliminary Study

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ABSTRACT

This study was conducted to measure the release of strontium ions that leached-out from novel bioactive glass-containing glass ionomer cements and also to evaluate effect of adding bioactive glass particles in various percentages on the strontium rate at different intervals. A series of ionomer glasses were synthesised based on $4.5SiO_2$-$3Al_2O_3$-$0.75P_2O_5$-$3(CaO/SrO)$-$2(CaF_2/SrF_2)$ systems with varying strontium substitution from 0%Sr to 100%Sr. The cement discs were prepared with incorporation of sodium-free bioactive glass via substitutional basis and then were immersed in 10 ml of artificial saliva. After certain periods ranged from 7 days up to 28 days, the discs were collected and solution was analysed using inductively coupled plasma optical emission spectroscopy in order to obtain the cumulative release of strontium ions. Strontium ions release increased with increasing in strontium for calcium substitution, particularly during the first week of immersion. The highest strontium release was obvious from the fully strontium-substituted compositions. However, the strontium rate decreased with increasing in addition of bioactive glass at all time points. A substantial variation in strontium concentrations in the surrounding media was clearly observed with increasing both strontium and bioactive glass amounts in the parent glasses/cements. An extended work should be done to identify the optimal concentrations of strontium and bioactive glass that could combine together to manufacture an ideal bioactive material for dental applications.

Keywords: Strontium; Ion Release; Bioactive Glass; Glass Ionomer Cements.

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أجريت هذه الدراسة لقياس إطلاق أيونات السترونتيم التي تتسرب من الإسمنت الأيوني الزجاجي الحديث التصنيع وأيضا لتقييم تأثير إضافة الزجاج النشط بيولوجيا بنسب مختلفة وعلى فترات مختلفة. تم تصنيع سلسة من الزجاج الأيوني مع استبدال السترونتيم بنسب متفاوتة من 0 إلى 100. تم تحضير أقراص الإسمنت مع دمج الزجاج النشط بيولوجيا الخالي من الصوديوم وغمرها في 10 مل من محلول اللعاب الصناعي؛ لفترات زمنية مختلفة من 7 أيام إلى 28 يوم. بعد ذلك، تم جمع الأقراص وتحليل المحلول بواسطة جهاز التحليل الطيفي للبلازما للحصول على التسريب التراكمي لأيونات السترونتيم. زاد إطلاق أيونات السترونتيم مع زيادة نسبة السترونتيم المستبدل للكالسيوم خاصة خلال الأسبوع الأول من الغمر. تم الحصول على أعلى إطلاق للسترونتيم من التركيبات المستبدلة بالكامل بالسترونتيم. مع ذلك، انخفض معدل إطلاق أيونات السترونتيم مع زيادة نسب الزجاج النشط بيولوجيا. لوحظ وجود تباين كبير في تراكيز السترونتيم في الوسائط المحيطة مع زيادة كل من السترونتيم والزجاج النشط بيولوجيا في الزجاج/الإسمنت الأم. ينبغي القيام بتجارب موسعة لتحديد التراكيز المثلى من السترونتيم والزجاج النشط؛ مما يُسهم في تصنيع مادة نشطة مثالية لتطبيقات طب الأسنان.

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INTRODUCTION

Strontium is an ''alkaline earth metal'' which acts as a network modifier, it's usually added to alumina-silicate glasses in order to replace calcium and thus to achieve the radio-opacity character (aesthetic) for the glass ionomer cements (GICs) [1-2]. The strontium being the element of choice for this substitution, as both strontium (Sr^{2+}) and calcium (Ca^{2+}) ions have the same charge and they are in group II in the periodic table [3]. Mainly, Sr^{2+} is used to replace Ca^{2+} without disrupting the backbone of the original glass [3].

Previously, it indicated that the bactericidal effect was significantly enhanced against anaerobic Streptococcus and Actinomyces bacteria in strontium-containing cements, and that was such good evidence for controlling the post-operative complications, resulting from the action of the residual bacteria [4]. Further, Sr^{2+} has been incorporated into bone cements to prevent implant-related infections [5]. The authors in this research used injectable bone cement that made of strontium-substituted bioactive glass (BG) and poly-acrylic acid (PAA). The results revealed that an obvious bactericidal effect of strontium-releasing bone cement on Enterococcus Faecalis and Streptococcus Aureus was detected. In addition, stimulation of osteoblast and inhibition of osteoclast mechanisms were noticed. These kinds of cements have promising results for the treatment of osteoporosis via promoting bone formation and minimising implant-related infections, which making them favourable materials for use as injectable bone cements [5-6]. Accordingly, there is increasing interest in the production of strontium-containing cements for medical/dental uses. Moreover, the presence of strontium (Sr^{2+}) and fluoride (F^-) ions together has a combination effect on prevention of dental caries; which is called a synergistic effect [7-8]. During apatite development

stages, addition of Sr^{2+} and F^- ions can create structural changes in the crystallinity of enamel/dentine in terms of forming different apatite crystals [8]. It was also concluded that decrease in the dissolution of synthetic hydroxyapatite (HA) due to the acid production of Streptococcus Mutans occurred as a result of synergistic effect of these ions [9]. Many companies now focus on manufacturing a novel composition of ionomer cements in order to enhance the apatite formation and growth during the setting mechanism of these materials [10]. Therefore, the main aim of the current study was to measure Sr^{2+} ions release that leached-out from the novel bioactive glass-containing GICs and also to assess the impact of incorporating BG on the release of Sr^{2+} ions after immersion in laboratory-made artificial saliva (AS) solution.

MATERIALS AND METHODS

Preparation of Glasses (Ionomer Glasses & Bioactive Glass)

Five glass ionomer compositions that based on Glass Formula = $4.5SiO_2$-$3Al_2O_3$-$0.75P_2O_5$-3(CaO/SrO)-2(CaF_2/SrF_2) with varying strontium substitution on molar basis were synthesised using melt-quench route at a high temperature of 1500°C; as described previously [11-12]. The original glasses with fully, partially, half and no strontium-substituted for calcium are coded as seen in Table 1.

Table 1: Strontium for calcium substitution of studied glasses.

ID	Sr:Ca	% Sr Substitution
Glass I	0Sr:5Ca = 3CaO:2CaF_2	0%
Glass II	2Sr:3Ca = 3CaO:2SrF_2	40%
Glass III	2.5Sr:2.5Ca = 1.5CaO + 1.5SrO:1CaF_2 + 1SrF_2	50%
Glass IV	3Sr:2Ca = 3SrO:2CaF_2	60%
Glass V	5Sr:0Ca = 3SrO:2SrF_2	100%

Subsequently, each glass melt was rapidly quenched by pouring the melt into water to avoid the glass crystallisation. The glass frit was then dried and ground into powder form using a vibrating Gyro mill (Glen Creston, Gy-Ro mill, London, UK) for two cycles of 7 min. The resulting glass powders were sieved to fine (< 45 μm) particles.

The same method was used to synthesise the sodium-free bioactive glass (QMMM7) that based on Glass Formula = SiO_2-P_2O_5-CaO-CaF_2, which was incorporated into ionomer cements powder as a coarse form (45-90 μm).

Preparation of Glass Ionomer Cements

The GIC discs were made by mixing fine glass powder with poly-acrylic acid at specific P:L ratio of 3:1 to obtain a high viscous mixture of GICs. The BG was added on substitutional basis for original ionomer glass powders by weight at a percentage of 5, 10% and 15% respectively.

Afterwards, each mixture was individually mixed using a stainless-steel spatula on a glass slab for about 40-60 sec at room temperature. The cement paste was transferred into a Teflon disc-shape mould; separated with acetate sheets and then clamped between two metal plates using G-clamp.

The assemblies were then left in a laboratory oven (Carbolite®, USA) at 37°C for 1 hour (from starting of mixing) to allow for setting. Subsequently, the set cement discs were removed from the mould and immersed immediately into 10 ml of AS solution at pH of 6.5. The immersed samples were kept in shaking incubator (IKA®, KS 4000 i control, Staufen, Germany) at 37°C. After a certain period, ranged as 7, 14 and 28 days, the cement discs were taken-off and the obtained solution was analysed to measure Sr^{2+} ions release.

Preparation of Artificial Saliva (AS)

Laboratory-made AS was prepared and used as a testing medium in order to mimic the oral environment. The ingredients of AS (Sigma-Aldrich, UK) were weight-out one by one and then dissolved very slowly in 800 ml de-ionised H_2O (400 ml cold water & 400 ml boiled water; helping in dispersion of mucin later on) using a magnetic stirrer. The pH of AS was adjusted at room temperature. This step was comprised of adding 0.2 g of sodium azide (NaN3) and then adjusting pH to 6.5 by addition of 0.5 M potassium hydroxide (KOH) solution one drop at time. The solution was transferred into one litre volumetric flask and filled-up to the mark by adding de-ionised H_2O. The solution was first left in a shaking incubator for couple of hours and then was kept in the fridge with storage life not more than a week to avoid ions precipitation.

Inductively Coupled Plasma Optical Emission (ICP-OES) Spectroscopy

The ICP-OES machine (Varian Vista-PROTM CCD, ICP-OES spectrometer) was used to measure the ions concentrations of Sr^{2+}. The standard solutions at different concentrations of 1 ppm (25 μl), 5 ppm (125 μl), 10 ppm (250 μl), 20 ppm (500 μl), 50 ppm (1250 μl), 75 ppm (1875 μl) and 100 ppm (2500 μl) were prepared in 25 ml volumetric flasks and started with adding small amount of AS, and 2.5 ml of 69% analytical grade nitric acid (NHO_3) was added as well. After that, strontium element was pipetted at a specific amount, every flask was filled up to the scale (25 ml) using a freshly-made AS.

For samples preparation, 4.5 ml of total solution volumes without dilution were pipetted into specific plastic tubes and following with acidified each sample by addition 0.5 ml of NHO_3 acid to make a concentration of 10% w/w.

RESULTS

Figure 1 (a-d) shows the cumulative Sr^{2+} ions release for fully, partially, half and no strontium-substituted GICs with and without addition of BG, plotted against the square root time ($t^{1/2}$) at 7, 14 and 28 days respectively. All data exhibited a significant increase in Sr^{2+} ions associated with increasing in strontium for calcium substitution, especially at 7 days of immersion in AS. Afterwards, the Sr^{2+} ions release did not increase dramatically with increasing the exposure time of the cement specimens to the storage solution up to 28 days.

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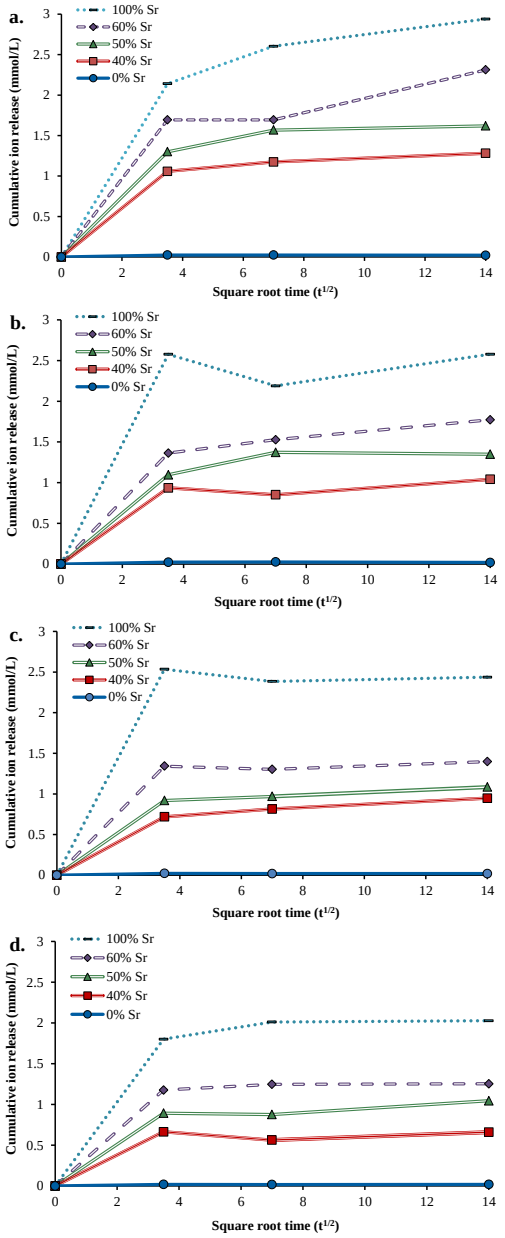


Figure 1: Cumulative strontium ions release of cements containing 0%, 40%, 50%, 60% & 100% strontium, with (a) 0%, (b) 5%, (c) 10% & (d) 15% bioactive glass at different time points (7, 14 & 28 days).

Figure 2 displays the highest Sr^{2+} ions release which were detected from the fully strontium-substituted GIC (2.939mmol/L). This value was nearly twice the amount of Sr^{2+} ions that released by the half strontium-substituted GIC (1.618mmol/L) with no additives. Additionally, the Sr^{2+} level was negligible for all compositions with no strontium-substituted (< 0.03mmol/L).

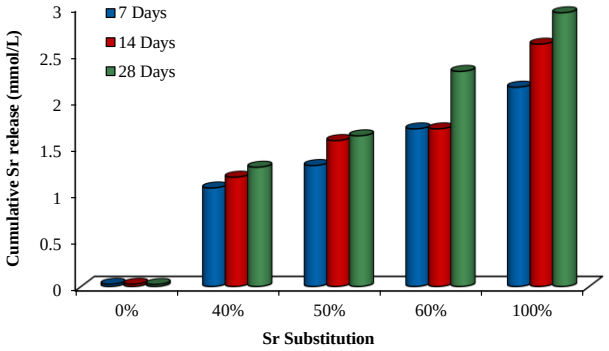
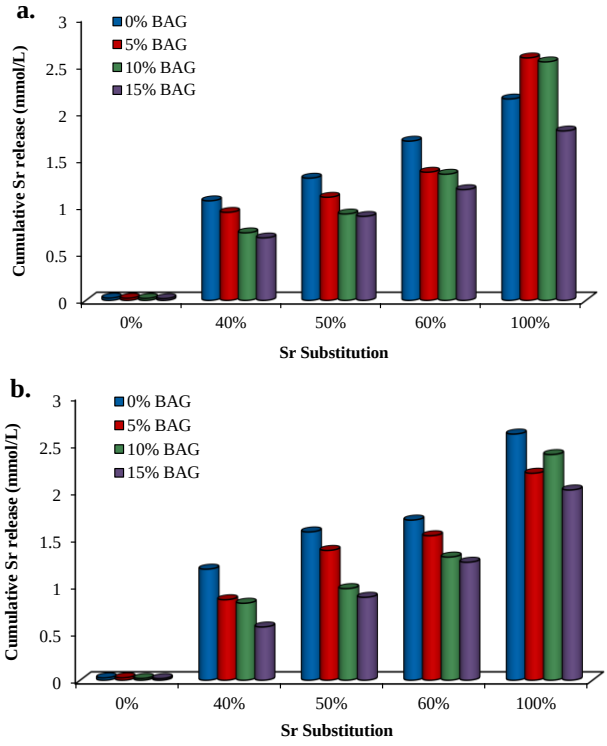


Figure 2: Cumulative strontium ions release of cements containing 0%, 40%, 50%, 60% & 100% strontium versus strontium substitution in original glasses, without bioactive glass addition at 7, 14 & 28 days.

Figure 3 (a-c) presents the Sr^{2+} ions release in correlation with increasing BG amount on weight base at different time points. The elemental concentration of Sr^{2+} decreased with increasing in BG substitution in the parent compositions.



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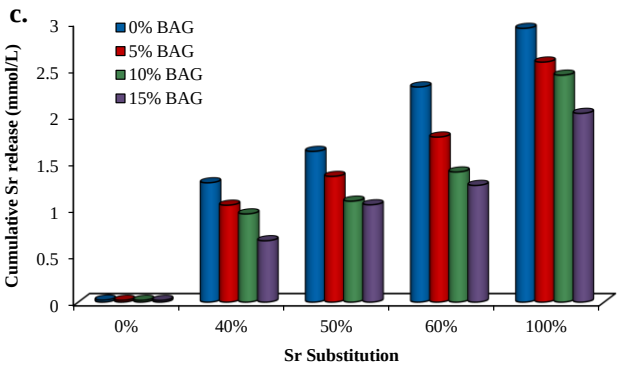

Figure 3: Cumulative strontium ions release of cements containing 0%, 40%, 50%, 60% & 100% strontium versus strontium substitution in original glasses with/without bioactive glass addition, at (a) 7, (b) 14 & (c) 28 days of immersion.

Figure 4 (a-b) shows the relationship between Sr^{2+} ions release and BG concentrations for fully and half strontium-substituted GICs at 7 and 28 days. Generally, a substantial change in Sr^{2+} values in the surrounding media was clearly observed with increasing BG amounts. The obtained trend displayed a clear linear relationship upon the compositions; R-squared values (R^2) were 0.8422 and 0.8442 for half strontium-substituted GICs, 0.7.906 and 0.9262 for fully strontium-substituted GICs at 7 and 28 days respectively.

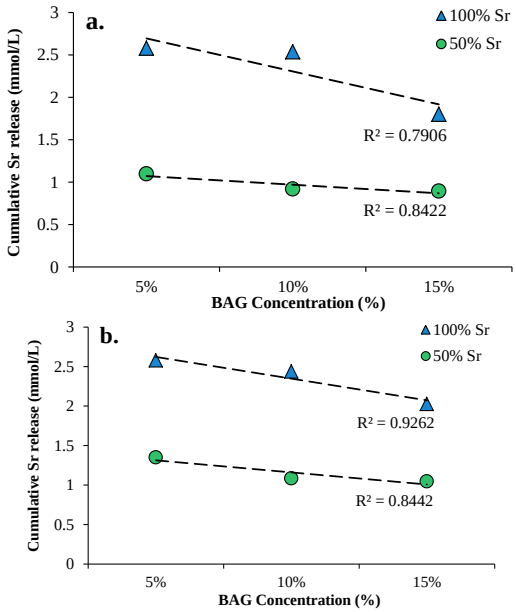

Figure 4: Relationship between cumulative strontium ions release & bioactive glass concentrations for fully & half strontium-substituted GICs at (a) 7 & (b) 28 days.

DISSCUSION

It well known that calcium and strontium are typical network modifiers which owing to similarities in their ionic radius and they can be substituted for each other without a significant altering on the silicate glass network [3-13]. The results of the current study showed that the amount of Sr^{2+} ions release increased with increasing in strontium for calcium substitution, with the majority of Sr^{2+} ions being released during the first week of immersion. Over the remaining time of the exposure (up to 4 weeks = 28 days), concentration of Sr^{2+} ions increased much more slowly. Additionally, the highest Sr^{2+} ions release was noticeable from fully strontium-substituted GICs. This could be explained due to the fact that when substituting the larger ionic radius of Sr^{2+} ions (1.13 Å) for the smaller ionic radius of Ca^{2+} ions (0.99 Å) [14], the original glass network will be expanded, leading to facilitating glass/cement degradation and releasing much more ions [13]. This might also cause a rapid ionic cross-linking of PAA chains of GICs, as a result of larger amounts of cations being available and it explains the shorter mixing/working times of ionomer cements [15-16].

The obtained findings of this study coincide with the results of Osiro et al. work, as their data emphasised that Sr^{2+} ions release from the prepared (fluoro-) aluminosilicate glass-based cements (Glass Formula = $4.5SiO_2$-$3Al_2O_3$-$1.25P_2O_5$-xSrO-ySrF_2-zCaO-yCaF_2) increased proportionally with increasing in strontium amounts [17]. Though, the strontium substitution for calcium had no significant effect on the mechanical/physical properties of GICs [17-18].

To date, the effects of strontium substitution for calcium in dental materials field are still controversial. Further investigation is essential to elucidate the role of strontium for preventing carious lesion. Various studies showed that the release of Sr^{2+} ions enhance osteoblastic bone formation and reduce osteoclastic bone resorption [6-19-20], as well as improve tooth remineralisation [6-21]. It is generally assumed that strontium substitution for calcium results in formation of complexes of calcium/strontium-hydroxyapatite [$Ca_6Sr_4(PO_4)_6OH_2$] or

calcium/strontium-fluoroapatite [$Ca_6Sr_4(PO_4)_6F_2$]. Previous studies reported that strontium significantly inhibited the dissolution of HA and this is thought to be related to mix formation of surface calcium/strontium apatite crystals [7-22]. Another research demonstrated that the strontium-substituted apatite was substantially more soluble than pure HA [23]. This could be due to the disruption of crystal stability by the larger Sr_{2+} ions and the high carbonated content in the strontium-substituted HA.

Understanding the impact of BG incorporation is of great interest for controlling the behavior of newly-developed GICs, in order to improve the biological properties of the restorative materials in terms of remineralising purposes. Our data for novel bioactive glass-containing GICs exhibited that Sr^{2+} ions release decreased with increasing BG substitution. This is to somewhat surprising, as might be expect the highest degradable behaviors of dental materials for the long-term performance happen on addition of BG. Indeed, we can overcome the surprising results via; (1) BGs should contain strontium oxides to be capable of releasing Sr^{2+} ions and/or (2) BGs would be incorporated on additional basis rather than substitutional basis.

The mechanism of bioactivity occurs when the BGs expose to body fluids which undergo to unique sequences of surface reactions, and then form a layer of hydroxy-carbonate apatite (HCA) [24]. The HCA surface layer is thought to play a critical role for formation of an intimate bond to bone/tooth surfaces [24]. Well known that Hench mechanism provides an adequate explanation as how HCA forms on the hydrated silica-rich layer of the glass, allowing for bone formation [25]. Even though, this mechanism in limited to allow for apatite formation by silicate glasses containing no calcium and/or phosphate, in terms of different compositions [24-25]. Previous research confirmed that bioactive glass-containing GICs (S53P4) are bioactive and able to initiate apatite crystals on dentine surface in-vitro and in-vivo [26-27].

The conventional GICs were developed in 1960s by Wilson and Kent at Laboratory of the London Government Chemist [28]. These ionomer cements are formed by mixing a calcium (fluoro-) aluminosilicate glass powder with an aqueous PAA solution via a neutralisation process [10-28]. The inorganic ions involved in the setting reaction of GICs are derived from the glass components such as; Si^{4+}, Al^{3+}, P^{5+}, Na^{+}, F^{-}, and Ca^{2+} which often replaced in modern GICs with Sr^{2+} [29]. Majority of BGs used in dentistry has high sodium content which quickly reacts during the acid-base reaction releasing Na^{+} cations and then interferes with the GIC matrix formation, negatively impacting the material's physical properties and extending the setting time, leading to dissolution rather than degradation of the final set cements [10]. Accordingly, the sodium-free BG has been introduced as additives into ionomer glasses in the current study. Thus, understanding of glass/cement structure and degradation process is essential for designing novel restorative materials.

CONCLUSION

Within the limitations of this study, it can be concluded that: (1) Sr^{2+} ions release increased with increasing the strontium for calcium substitution; (2) fully strontium-substituted GICs showed the highest release of Sr^{2+} ions; (3) addition of BG via substitutional basis had an adverse effect on Sr^{2+} ions concentrations for all tested samples of AS; (4) it found that the data displayed to somewhat a linear relationship between the Sr^{2+} ions release and BG concentrations for fully and half strontium-substituted GICs at 7 and 28 days. Further experiments are needed to synthesise an ideal bioactive restorative material with high-viscous/anti-cariogenic properties for the potential improvements of Minimally Invasive Dentistry.

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Conflict of Interest

The author declares that there is no conflict of interest.

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