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Effect of SrO incorporation on the morphology of sol-gel derived 58S bioactive glass

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ABSTRACT

In the present study, the structural properties of $\text{SiO}_2\text{-CaO-P}_2\text{O}_5\text{-SrO}$ bioactive glass (BG) were investigated. Bioactive glass powder was synthesized through the sol-gel method and immersed in simulated body fluid (SBF) for a number of days to discover their structure. Precise analysis of the morphological structure of $\text{SiO}_2\text{-CaO-P}_2\text{O}_5\text{-SrO}$ bioactive glass employed scanning electron microscopy (SEM). The results established the formation of hydroxyapatite (HA) on the surface of bioactive glass powder. Additionally, it was found that, in day 14th, the hydroxyapatite surface is entirely covered in BGs and its aggregation is a little greater. It was shown that the apatite on the $\text{SiO}_2\text{-CaO-P}_2\text{O}_5\text{-SrO}$ bioactive glass surfaces had a spherical form. As a result, the microstructural analysis verified the bioactive nature of Sr-BG, supporting its use in bone-related biomaterial research. Evaluation techniques using the alkaline phosphatase (ALP) and MTT assays demonstrated that low strontium concentrations (2% and 5% SrO) stimulated the growth and differentiation of G292 osteoblastic cells. Lastly, the results show that BG-5Sr is a good fit for dental and bone tissue applications.

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1. Introduction

Bone injuries are among the most common health problems affecting the global population [1]. Due to the diversity of available bone grafts, various biodegradable materials are utilized as scaffold implants. Bone's natural structure is an exceptional composite composed of polymers and ceramics, making it essential to develop scaffolds that offer adequate mechanical strength, biocompatibility, biodegradability, and an enhanced rate of new tissue formation [2].

Bioactive glasses (BGs) and glass-ceramics have been extensively studied for over thirty years since their introduction by Hench et al [3]. Bioactive glass and glass ceramic have found numerous uses in the fields of pharmaceuticals, implantology, and tissue engineering [4, 5]. Initially, BGs were produced by melting dried batches of starting materials at high temperatures [6]. Recently, the sol-gel method has gained considerable attention for BG preparation [7]. This low-temperature process offers multiple

advantages, including high purity, ultrahomogeneity, lower processing costs, and ease of handling [8, 9].

Adding elemental additions such as alkali metals [10], alkaline earth metals [11], transition metals [12], and post-transition metals enhances the properties of BGs by imparting osteoconductivity, angiogenicity, and antibacterial activity [13]. In recent years, biologically active ions such as Ag^+ , Mg^{2+} , Ga^{3+} , and so on have been incorporated into silicate, phosphate, and borate BG systems to support bioactivity, osteogenesis, angiogenesis, immunomodulation, antibacterial properties, and uses in cancer treatment, infection prevention, and tissue regeneration [12, 14, 15].

Among these ions, strontium (Sr) is of particular interest as a trace element naturally present in human bone. Sr has therapeutic potential for osteoporosis because it prevents osteoclasts from resorbing bone while promoting bone growth and osteoblast proliferation [16]. Furthermore, Sr can substitute for calcium in tricalcium phosphate, bioactive glasses, calcium silicate, and

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hydroxyapatite, improving them because of their identical ionic radius and charge [17, 18].

Many studies have demonstrated the positive effects of Sr on antibacterial efficiency, bone formation stimulation [19], osteoporosis treatment [20], bone density improvement [21], and fracture risk reduction [22]. However, some reports suggest that Sr may negatively affect biological activity by inhibiting or delaying calcium phosphate formation layers [23].

This research focuses on synthesizing Bioglass-58S nanocomposite using the sol-gel method. The morphology was investigated, and the nanocomposites were analyzed by scanning electron microscopy (SEM). Moreover, their biological performance was evaluated through ALP and MTT assays.

2. Materials and methods

2.1. Materials

BGs were synthesized using strontium nitrate ($\text{Sr}(\text{NO}_3)_2$), tetraethyl orthosilicate (TEOS, $\text{Si}(\text{OCH}_2\text{CH}_3)_4$), calcium nitrate tetrahydrate ($\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$), and triethyl phosphate (TEP, $(\text{C}_2\text{H}_5)_3\text{PO}_4$). The raw materials were purchased from Merck Company.

2.2. Bioactive glass production

Strontium-doped bioactive glass (BG-Sr) was synthesized using the sol-gel method. Firstly, a 0.1 M nitric acid solution was prepared to serve as the catalyst. Then, TEOS was added to the nitric acid solution and magnetically stirred at 25 °C for 60 minutes. Next, TEP, calcium nitrate tetrahydrate, and strontium nitrate was sequentially added to the mixture under continuous stirring. The mixture was stirred for an additional 60 minutes to ensure complete reaction, followed by aging for 1 hour.

All stoichiometric calculations were based on producing 25 g of bioactive glass. The samples were placed in a beaker covered with aluminum foil and kept at under room-temperature conditions for 8 days to allow complete gel formation. The gels were dried at 80 °C for 1 day to evaporate water. Finally, the dried samples were calcined at 800 °C for 5 hours to remove residual nitrates from the glassy phase. The calcined samples were subsequently ground into

powder for other tests. The process of synthesis is shown in Fig. 1. The compositions of BG-Sr synthesized are also illustrated in Table 1.

2.3. Preparation of SBF

The formation of hydroxyapatite on the BG nanocomposit was studied by immersing them in simulated body fluid for different periods. All samples were ground and pressed to prepare disks weighing approximately 0.6 g, with 3*4 mm, by compacting the glass powder at 10 MPa using an automatic press. A volume of 13.2 ml of SBF was used per BG disk to investigate HA formation. To ensure accuracy, each measurement was made three times. In order to create the SBF by dissolving reagent-grade KH_2PO_4 , $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$, NaHCO_3 , CaCl_2 , NaCl , KCl and into distilled water, then buffered to pH 7.4 with tris(hydroxymethyl)aminomethane and 1 N HCl at 37 °C. Table 2 provides the SBF compositions.

2.4. Bioactive glass evaluation

2.4.1. SEM analysis

The microstructure of the synthesized BG-Sr was characterized utilizing SEM (AIS 2100, Seron Tech) at an accelerating voltage of 20 kV. The hydroxyapatite formation and development on the glass surface were further analyzed through SEM observations.

2.4.2. MTT assay

Following exposure to different bioactive glass specimens, the proliferation of G292 osteoblastic cells was evaluated using the 3-(4, 5dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide) (MTT) assay. The National Cell Bank of Iran (Pasteur Institute of Iran) presented the bioactive glasses' cytotoxic results against the G292 osteoblastic cell line. Cells were cultivated and kept in 90% moisture at 37 °C for 24 hours. After being planted at a density of 6×10^3 cells/well in 96-well culture plates, the cells were left to adhere for a day. The tests were conducted under standard culture conditions. A multi-well microplate reader (EL 312e Biokinetics reader, Biotek Instruments) was used to detect absorbance at 570 nm following reactions. Three readings of each were made.

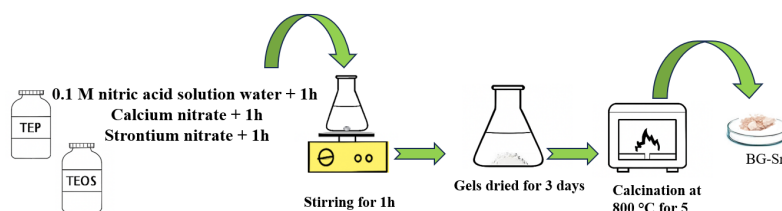


Fig. 1. The schematic of synthesis BG-Sr via Sol-gel method.

Table 1

The chemical compositions of BG-Sr synthesized in the present study.

Sample Identification	SiO_2 (mol. %)	CaO (mol. %)	P_2O_5 (mol. %)	SrO (mol. %)
BG-2Sr	60	34	4	2
BG-5Sr	60	31	4	5
BG-15Sr	60	21	4	15

Table 2

Composition of inorganic part of the SBF (mM) [24].

Ion	Cl^-	HCO_3^{2-}	HPO_4^{2-}	SO_4^{2-}	Na^+	K^+	Mg^+	Ca^{2+}
SBF (mM)	147.8	4.2	1.0	0.5	142.0	5.0	1.5	2.5

2.4.3. ALP activity

The presence of the enzyme alkaline phosphatase (ALP) indicates osteoblast separation and proliferation. Following the manufacturer's recommendations, three samples of each bioactive glass were taken for measurement, and each test was conducted three times [25, 26]. After counting, G292 osteoblastic cell lines were plated at a density of 1×10^4 cells/cm² in 24-well cell plates. For one, three, and seven days, all plates were incubated at 37 °C in a humidified environment of 95% air with 5% CO₂. The cells were then homogenized with 1 ml of Tris buffer, sonicated for 10 minutes on ice, and rinsed 3 times in phosphate buffered saline after the supernatant liquid was removed from each well.

A p-nitrophenyl phosphate solution was incubated for a brief time at 32 °C in 20 ml aliquots of 1 ml. The cells' ALP activity was demonstrated by the conversion of p-nitrophenyl phosphate to p-nitrophenol.

3. Results and discussion

Fig. 2 presents SEM images of the glass samples before and after immersion in SBF for 14 days. The SEM micrographs of Sr-substituted bioglass samples prior to soaking in SBF (Fig. 2 A–C) reveal distinct differences in surface morphology depending on the SrO content. The BG-2Sr sample (A) exhibited a relatively smooth surface with minor irregularities, while the BG-5Sr sample (B) displayed a more homogeneous and compact morphology. In contrast, the BG-15Sr sample (C) showed a rougher surface with noticeable porosity. Following 14 days of immersion in SBF, hydroxyapatite precipitation was observed on all samples (Fig. 2 D–F); however, the degree of apatite formation diminished as the SrO content increased.

The BG-2Sr sample (D) showed the presence of scattered spherical hydroxyapatite particles, whereas the BG-5Sr sample (E) revealed a dense and continuous layer of spherical apatite crystals, indicating superior bioactivity. In the case of the BG-15Sr sample (F), only limited apatite nucleation was detected, and the coverage was less uniform compared to 5Sr-BG. Overall, these results suggest that 5 mol% Sr substitution promotes the most favorable hydroxyapatite formation, while higher Sr contents tend to suppress apatite growth. According to Wu et al. [27], low Sr content (2.5%) had no discernible effect on the mesopore structure such as mesopore size, pore volume, and surface area. The addition of Sr²⁺ may induce structural defects in the atomic array and alter the mesopore structure by disrupting the preferred orientation of SiO₄⁴⁻ during the self-assembly process. Additionally, at high Sr concentrations, a-SrSiO₃ crystals can form within the mesopore BG scaffolds.

In line with earlier findings, investigations have demonstrated that the Sr incorporation 15% significantly decrease the apatite phase's crystal size and overall crystallinity. These results imply that excessive Sr substitution might alter the apatite lattice's structural order, which would affect how well it functions biologically. In order to determine the balance between the positive and negative effects of Sr in biomaterials, more thorough research is necessary to understand the effects of Sr incorporation at the bone crystal level [28].

SrO substitution in 45S5 Bioglass®, according to Fujikura et al. [29], lowered the glass transition and crystallization temperatures, suggesting a more open glass network. With a rise in ring-type Q² between 25 and 50 percent SrO, NMR revealed a mostly Q² silicate structure that most likely improved solubility and bioactivity. High SrO concentrations ($\geq 75\%$), on the other hand, encouraged crystallization, which decreased the amorphous percentage and might have limited regulated ion release. Therefore, it seems that

moderate Sr substitution is optimal for striking a balance between structural alteration and bioactivity.

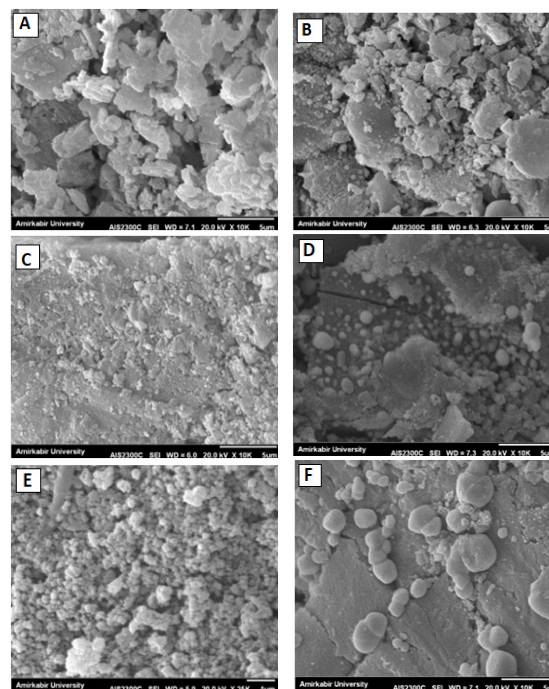


Fig. 2. SEM images of different samples: (A) BG-2Sr, (B) BG-5Sr, and (C) BG-15Sr before to immersion in SBF, and (D) BG-2Sr, (E) BG-5Sr, and (F) BG-15Sr samples after 14 days of immersion in SBF.

Bioactive glasses with different Sr percentages have been examined for their in vitro cytotoxicity against G292 osteoblastic cells (Fig. 3). The cell viability of five groups Control, BG, BG-2Sr, BG-5Sr, and BG-15Sr was assessed using the MTT assay at three different time points, 1, 3 and 7 days. With viability percentages higher than those of the Control, BG, and other Sr-doped groups, the BG-5Sr sample demonstrated the maximum cell viability at all time points analyzed, according to the data. At moderate Sr doping levels, this implies improved biocompatibility and a stimulatory effect on cell proliferation. Although their viability was lower than that of BG-5Sr, both the BG-2Sr and BG-15Sr samples had enhanced viability when compared to the Control and pure BG group.

This suggests a dose-dependent response in which the ideal concentration of Sr maximizes cell viability. The lowest viability percentages were shown by the pure BG and Control groups, indicating that the Sr ions in the doped glasses favorably influence cell growth and survival. Long-term material compatibility and possible stimulation of cellular metabolic activity are reflected in the viability increase over time, which is especially noticeable for BG-5Sr. These results are consistent with research showing that adding strontium to bioactive glasses improves overall cellular response and lessens cytotoxic effects by increasing osteoblast activity, inhibiting osteoclasts, and promoting bone regeneration. In the research reported by Eileen Gentleman et al., Saos-2 cells treated with dissolution products from strontium-substituted BG exhibited significantly higher MTT activity after two weeks of culture compared to cells exposed to BG without strontium. This indicates that Sr²⁺ ions further enhance osteoblast proliferation and metabolic activity beyond the effects of conventional BG. The amplified response is likely due to a synergistic interaction between strontium and other ions, particularly silicon, released from the BG matrix. Complementary assays are necessary for a thorough assessment of cytotoxicity since the MTT assay, which assesses metabolic activity representing viable cell population, is

impacted by variables such mitochondrial function and reagent interaction. Fiorilli et al. [30] assessed MBG_Srx-SD ($x=2,4\%$), synthesized via the Sol-Gel method. Their results clearly demonstrated that Sr-containing MBG particles did not noticeably affect cell morphology, which remained comparable to that of cells cultured on the untreated polystyrene plate. MTT assay results further confirmed that both MBG-Sr2%-SG and MBG-Sr4%-SD exhibited excellent biocompatibility, with cell viability exceeding the 70% threshold. Similarly, in our study, the incorporation of 2 mol% Sr did not significantly alter the material's structure, consistent with these findings.

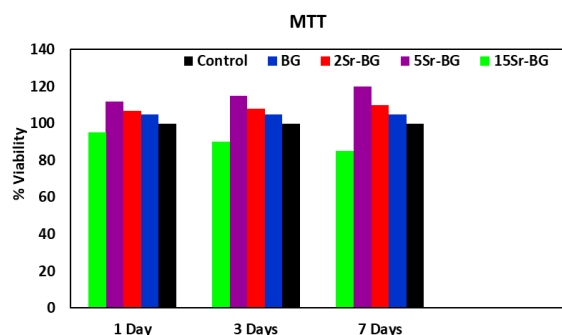


Fig. 3. The viability results of osteoblast G292 culture for control, BG, BG-2Sr, BG-5Sr, and BG-15 Sr samples for 1, 3 and 7 days.

The ALP activity for G292 osteoblastic cells was measured for each sample at various incubation time points, as shown in Fig. 4. Following treatment with glass-conditioned media for 1, 3 and 7 days, G292 cells in the 2Sr and 5Sr groups generated noticeably more ALP activity than the control group. At every time point, the activity of ALP was considerably reduced in the 15 Sr glass conditioned media. Compared to the 0Sr bioactive glass, the 5Sr-substituted bioactive glass enhanced ALP activity between day 1 and day 3 of culture.

Substituting strontium for calcium in BG enhances osteoblast function by promoting proliferation and increasing ALP activity. This stimulatory effect is observed when strontium-containing BG is in direct contact with cells, suggesting that Sr ions released from the glass network act synergistically with other dissolution ions (likely silicon) to boost osteogenic activity. The mechanism may involve cation-sensing receptors, potentially beyond the calcium-sensing receptor, contributing to strontium's role in bone regeneration [31]. According to Juliane Isaac et al. [32], strontium-doped bioactive glasses markedly improved osteoblast differentiation in vitro.

Foetal mouse calvarial osteoblasts cultivated with Sr-doped sol-gel-derived bioactive glass (B75-Sr5) shown high levels of osteocalcin secretion, ALP activity, and up-regulation of osteogenic genes like COL1A1, Osterix, and Runx2, especially at 5 weight percent Sr content. These findings suggest that increased Sr incorporation can promote matrix mineralization and osteogenic differentiation without causing cytotoxicity. Our studies also showed that adding Sr increased ALP activity, which is in line with their findings. This suggests that a modest amount of Sr replacement (about 5%) offers the best compromise between bioactivity and biocompatibility in bioactive glasses. Liu et al. [33] identified that 5% strontium-substituted bioactive glass (5Sr) significantly increased the cell number, ALP activity, type I collagen expression, and mineral nodule formation of MC3T3-E1 cells. These results show the potential of Sr-substituted bioactive glasses for dental and bone regeneration applications while also promoting osteogenic responses of MC3T3-E1 osteoblast-like cells.

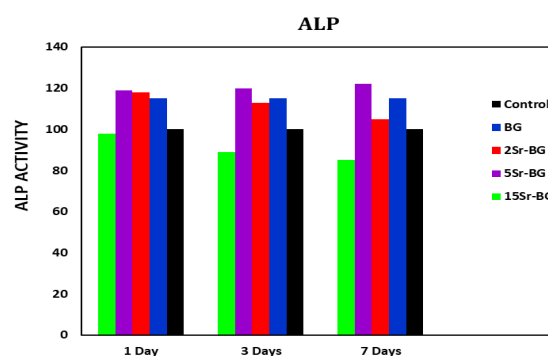


Fig. 4. Analysis of ALP activity for G292 osteoblastic cells grown on bioactive glasses following 1, 3, and 7 days of incubation.

4. Conclusion

This study highlights the impact of Sr^{2+} on the biological performance of bioactive glasses and investigates the optimal Sr^{2+} concentration within BG matrices, identifying 5 mol% as the most effective level. It was also demonstrated the cell viability and ALP activity of G292 osteoblastic cells cultured on various bioglass formulations: BG, BG-2Sr, BG-5Sr, and BG-15Sr. The BG-5Sr sample showed the highest cell viability across all time points, compared to the other groups. Additionally, Sr-containing BGs have been shown to improve osteoblast adhesion, and stimulate the differentiation and proliferation of G292 osteoblastic cells into mature osteoblasts.

Author contributions

Firoyzeh Niazvand: Investigation, Conceptualization, Writing – original draft, Writing –review & editing. **Jalaladdin Hosseinzadeh:** Investigation, Writing – original draft, Writing – review & editing; **Parisa Zahed:** Investigation, Writing –Original Draft Preparation and Writing –Review & Editing. **Negar Azizabadi:** Writing – original draft, Writing –review & editing.

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Conflict of interest

The authors declare no conflict of interest.

Data availability

No data is available.

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