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## Magnesium-doped 58S bioglass: Synthesis, characterization, and biomedical applications

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### ABSTRACT

In the current study, bioactive glasses (BGs) in  $\text{SiO}_2$ ,  $\text{CaO}$ ,  $\text{P}_2\text{O}_5$ ,  $X\text{MgO}$  systems ( $X = 1, 3, 6, 10\text{ mol\%}$ ) were synthesized through the sol-gel method and immersed in simulated body fluid (SBF) for a few days to investigate their biocompatibility. The impact of magnesium concentrations on cell viability, antibacterial properties, and the *in vitro* production of hydroxyapatite (HA) was investigated. Scanning electron microscopy (SEM) was utilized to examine the HA formation and its microstructure. The techniques of the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay and alkaline phosphatase (ALP) were used to assess cell differentiation and proliferation MC3T3-E1 osteoblast cells. The highest rate of HA formation occurred in magnesium-doped 58S bioglass BG containing 6 mol%  $\text{MgO}$ . However, bioactivity decreased when the substitution reached 10 mol%. MTT assay and ALP data indicated that the proliferation and differentiation of MC3T3-E1 osteoblast cells improved with  $\text{MgO}$  substitution up to 6 mol%. In contrast, the 10 mol% substitution negatively affected cell proliferation and differentiation. Therefore, the results revealed that the Mg-doped 58S BG demonstrates significant bioactivity, antibacterial properties, and strong cell survival, making it a suitable choice for bone tissue and dental applications.

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### 1. Introduction

Bioactive glasses (BGs) are the third generation of biomaterials. They have gained considerable research attention because of their unique ability to bond with bone and soft tissues. They also have potential uses in tissue engineering and regenerative medicine [1].

The use of BGs for bone replacement and repair has been common since L.L. Hench discovered them in 1971 [2]. 58S [3], 77S [4], and 68S [5] are examples of changed chemical compositions that were used to create it. Recently, these have attracted interest for applications in soft tissue and bone engineering [6, 7].

The main components of BGs are  $\text{P}_2\text{O}_5$ ,  $\text{CaO}$ , and  $\text{SiO}_2$ . These materials help form a HA layer on their surface in living organisms. This process facilitates their binding with bones [8].  $\text{SiO}_2$  is essential for forming networks in glass structures.  $\text{P}_2\text{O}_5$  also helps with the nucleation of the calcium phosphate phase on the glass surface [9, 10].

BGs have been made using several methods, including sol-gel foaming, melt processing, electrospinning, fast prototyping, and foam replication [11, 12].

The most popular techniques are sol-gel and melting. The sol-gel method creates products with higher purity and uniformity because it happens at room temperature. This prevents volatile starting materials like  $\text{P}_2\text{O}_5$  from evaporating. It also allows for the easy and uniform incorporation of different inorganic ions into the BGs structure [13].

Recent studies have examined the impact of dopant ions on the therapeutic qualities of BGs, including silver (Ag) [14], copper (Cu) [15], samarium (Sm) [16], boron (B) [17], zinc (Zn) [18], magnesium (Mg) [19], fluorine (F) [20], and other ions.

One essential trace element found in the human body is magnesium. Magnesium contents in enamel, dentin, and bone are 0.44, 0.72, and weight 1.23 percent, respectively [21]. Furthermore, magnesium inhibits osteoclasts, increases osteoblast cell activity, and plays a significant role in bone growth [22]. A low level of magnesium has also been related to osteoporosis [23].

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Although several studies have been conducted on magnesium-substituted BG, two problems remain unresolved in earlier investigations. The first is how the Mg content of BG composition affects the pace at which HA forms on the MBG surface in vitro, and the second is the ideal ratio of MgO to CaO in BG composition, which promotes cell activity and proliferation.

In the system CaO–MgO–P<sub>2</sub>O<sub>5</sub>–SiO<sub>2</sub>, sol–gel derived glasses were synthesized by Kargozar et al. [24] and J. Ma et al [19]. The potential of glasses to generate apatite was verified by soaking them in simulated body fluid (SBF). Additionally, in vitro tests using human cells revealed that bioactive glasses with magnesium promoted the growth and differentiation of cells. In this study, we synthesized Magnesium-Doped 58S Bioglass using a sol–gel technique to determine the impact of Mg substitution on the generated nanoparticles' bioactivity and biocompatibility.

## 2. Materials and methods

### 2.1. Materials

Calcium nitrate terahydrate (Ca (NO<sub>3</sub>)<sub>2</sub>·4 H<sub>2</sub>O), magnesium nitrate hexahydrate (Mg (NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O), tetraethyl orthosilicate (TEOS, Si (OCH<sub>2</sub>CH<sub>3</sub>)<sub>4</sub>), and triethyl phosphate (TEP, (C<sub>2</sub>H<sub>5</sub>)<sub>3</sub>PO<sub>4</sub>) were the compounds used to produce BGs. Every material was acquired from Merck Company at the best grade available.

### 2.2. Preparation of glass powders

The sol–gel technique was used to create four Mg-doped 58S-BGs of the series 60SiO<sub>2</sub>–4P<sub>2</sub>O<sub>5</sub>–(31–x) CaO–xMgO, where x = 0; 1; 3; 6 and 10 on a molar basis.

In Table 1, The detailed compositions of the obtained BGs-M are reported. First, a magnetic stirring bar was used to combine distilled water, 0.1 M nitric acid, and TEOS for an hour. After that, TEP, Ca (NO<sub>3</sub>)<sub>2</sub>·4H<sub>2</sub>O, and Mg (NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O were added, respectively, at intervals of 45 minutes to ensure that each reagent was completely homogenized.

To ensure that the hydrolysis was completed, the final mixture was agitated for a further hour. After the produced solution was transferred to a Teflon container, it was sealed and maintained at 37°C for three days before being dried for twenty-four hours at 75°C. After that, the dried gel was calcined for three hours at 700°C in a furnace to get rid of the organic impurities and nitrates. After being calcined, the resulting nanocomposites were put into a zirconia planetary ball mill and processed into a fine powder with a final particle size of less than 50 µm. Fig. 1 illustrates schematic diagram of the Mg-doped bioactive glasses' Sol–gel synthesis method.

**Table 1**

Elemental compositions of samples (mol%) in the current study.

| Glass Label | SiO <sub>2</sub> | CaO | P <sub>2</sub> O <sub>5</sub> | MgO |
|-------------|------------------|-----|-------------------------------|-----|
| BG-1M       | 60               | 35  | 4                             | 1   |
| BG-3M       | 60               | 33  | 4                             | 3   |
| BG-6M       | 60               | 30  | 4                             | 6   |
| BG-10 M     | 60               | 26  | 4                             | 10  |

Biological evaluations were carried out by submerging specimens in the SBF solution because of its remarkable compositional similarity to human blood plasma.

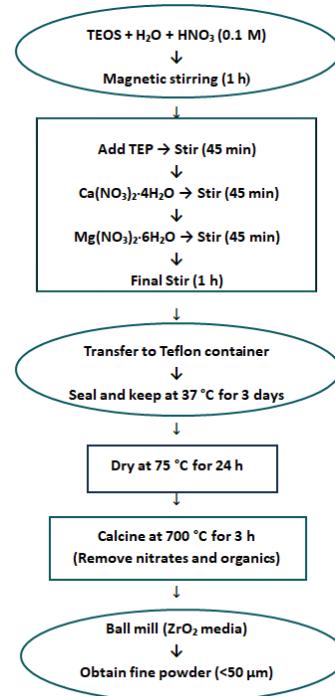
The samples were preserved for 21 days at 25 °C in a sterile bottle after being dipped in the SBF.

In order to prevent additional reactions, the treated BGs were filtered and cleaned with acetone at the end of this time. The table 2 displays the composition of SBF.

**Table 2**

Composition of the SBF (mmol/l).

| Ion                            | SBF   |
|--------------------------------|-------|
| Na <sup>+</sup>                | 142   |
| K <sup>+</sup>                 | 5     |
| Cl <sup>-</sup>                | 147.8 |
| Ca <sup>2+</sup>               | 2.5   |
| Mg <sup>2+</sup>               | 1.5   |
| HCO <sub>3</sub> <sup>-2</sup> | 4.2   |
| SO <sub>4</sub> <sup>-2</sup>  | 0.5   |
| HPO <sub>4</sub> <sup>-2</sup> | 1.0   |



**Fig. 1.** Schematic of synthesis bioactive glasses nanocomposites via sol–gel method.

### 2.3. Bioactive glass characterization and biological evaluation

#### 2.3.1. Scanning electron microscopy

A SEM operating voltage of 20 kV was used to evaluate the microstructure of the produced bioactive glass (SEM-AIS 2100-seron Tech). The tool looked into the growth and formation of hydroxyapatite itself.

#### 2.3.2. MTT assay

The proliferation of MC3T3-E1 osteoblast cells was assessed using a light-sensitive dye (3-(4, 5dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide) MTT test following exposure to various BG samples. The reaction of BG samples with the Iran National Cell Bank (Pasteur Institute of Iran) MC3T3-E1 osteoblast cells line produced the cytotoxic findings. The cultivated cells were maintained in 90% moisture at room temperature for one day. The cells were cultured in 96-well plates at a density of  $6 \times 10^2$  cells per well and allowed to attach for 1, 3, and 7 days. For the experiments, standard culture conditions were employed. A multi-well microplate reader (EL 312e Biokinetics reader and Biotek Instruments) at 570 nm wavelength was used to measure absorbance as the reactions proceeded. Every reading was done five times.

### 2.3.3. Alkaline phosphatase activity

The ALP enzyme was used to indicate the growth and division of osteoblasts. We took measurements on three different specimens and replicated each one three times, following the guidelines provided by the manufacturer. The cellular lines (MC3T3-E1 osteoblast cells) were placed at a concentration of  $1 \times 10^4$  cells/cm $^2$  in 24-well culture plates. For 1, 3, and 7 days, the plates were maintained at room temperature in an incubator with a humidified environment consisting of 5% CO $_2$  and 95% air. The liquid that had developed on each plate's surface was eliminated in the next step. The cells were treated three times with phosphate buffered saline (PBS), homogenized with one milliliter of Tris buffer, and then sonicated for 15 minutes in an ice container. Then, the liquid that had developed on each plate's surface was eliminated in the next step. Cells were treated three times with PBS, homogenized with one milliliter of Tris buffer, and then sonicated for fifteen minutes in an ice container.

For about five minutes, 20 ml aliquots containing one milliliter of a p-nitrophenyl phosphate solution were incubated at 30 degrees Celsius. The ratio of pnitrophenylphosphate to p-nitrophenol revealed the ALP activity of the cells.

### 2.3.4. Analyses of statistics

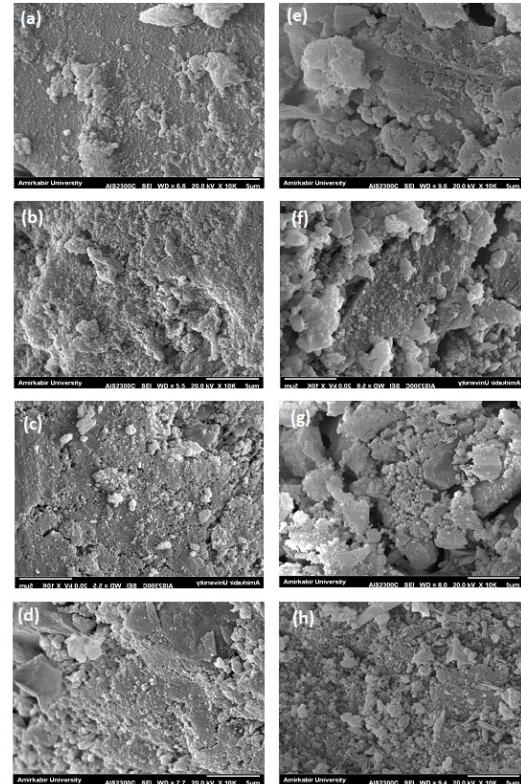
The mean  $\pm$  standard deviation (SD) of at least three repetitions was used to report the quantitative data from the studies. GraphPad Prism (GraphPad Software, USA) was used to assess the test groups' statistical significance. Statistical significance was defined as a *p*-value below 0.05.

## 3. Results and discussion

Fig. 2. illustrates Bioactive glass SEM micrographs prior to immersion in SBF and after 14 days. Before soaking, the surfaces are heterogeneous, with sharp edges and gaps between particles of different sizes. The strong bioactivity of the glasses was demonstrated by the continuous hydroxy apatite-like layer that covered the full surface of every sample. Fine flake-like particles were evenly scattered throughout the glass to form a dense layer on the surface of the sample with 1 mol% Mg. When the magnesium level was raised to 3 mol%, the surface became somewhat rougher and the flakes were larger and more aggregated. The apatite layer seemed thicker and more compact at 6 mol% Mg, with densely packed plate-like structures that suggested improved crystal formation. The sample with 10 mol% Mg, on the other hand, had a less homogeneous surface with coarser aggregates and obvious porosity, which may be because greater Mg concentrations impede the nucleation and development of apatite. These findings imply that while a high Mg level may prevent the hydroxycarbonate apatite layer from uniformly crystallizing, a moderate Mg inclusion encourages the layer's development and densification. The outcomes aligned with previous investigations. The SEM morphologies of glass 10% MgO before and after various test times in SBF were examined by J. Ma et al.[25] heterogeneous surface with uneven particles prior to soaking. After 12 hours, a significant amount of the original glass and a freshly discontinuous layer covered the glass surface. A spot of microscopic particle clusters made up of tiny granules appeared after the glass was submerged in SBF for a day. After three days, a dense layer of fine particulate matter was observed uniformly covering the glass surface. Despite a rise in particle size, the glass morphology did not alter further as the soaking period rose. In addition, Moghanian et al. [26] demonstrated that the maximum rate of HA formation was observed in magnesium-doped 58 S BG

with 5 mol% MgO (BG-5M), however the bioactivity was reduced by substitution of 8 mol% and 10 mol% MgO (BG-8M and BG-10M). Other studies revealed that a modest percentage of magnesium oxide (MgO) produced better results, which were attributed to its larger pore size and surface area [27].

According to Muthusamy Prabhu et al. [28] , when compared to base glass, the presence of magnesium in the glass composition promotes the creation of the apatite layer, while the formation of the HAp layer diminishes when the magnesium concentration rises over 10%.



**Fig. 2.** SEM micrographs of (a)BG-1M, (b)BG-3M, (c) BG-6M and (d) BG-10M samples before soaking in SBF and SEM micrographs of (e) BG-1M, (f) BG-3M, (g) BG-6M, and (h) BG-10M immersed in SBF for 21 days.

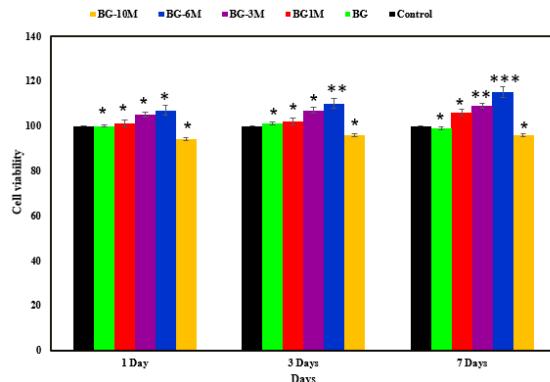
We assessed the growth of MC3T3-E1 osteoblast cells cultivated on synthesized BGs for 1, 3, and 7 days in order to ascertain the BGs' cytocompatibility (Fig. 3).

According to the results, after 1 day of culture, BG-6M significantly increased the MTT activity of the cells compared to the control ( $p < 0.05$ ), while the sample containing the highest magnesium concentration (BG-10M, 10 mol%) exhibited a notable reduction in proliferation ( $p < 0.01$ ).

After 3 days, a statistically significant difference was observed between BG-6M and BG-0M (control) ( $p < 0.001$ ), indicating that moderate Mg substitution enhances osteoblastic proliferation. The BG-10M group showed significantly lower viability than the control ( $p < 0.001$ ). After 7 days, both BG-3M and BG-6M had significantly higher MTT activity than the control ( $p < 0.05$ ), while BG-10M again had the lowest cell proliferation ( $p < 0.001$ ). These results suggest that moderate Mg incorporation (3–6 mol%) into the BG composition greatly improves cytocompatibility and cell growth ( $p < 0.05–0.001$ ). However, high Mg content (10 mol%) reduces osteoblastic proliferation. Kargozar et al. [24] reported a melt-derived magnesium (Mg)-doped bioactive glass (BG) in their work. Its composition is 45SiO $_2$ -3P $_2$ O $_5$ -26CaO-15Na $_2$ O-7MgO-4K $_2$ O (mol%). The Mg-doped BGs were found to be compatible

with human osteosarcoma cells (MG-63 cell line) through in vitro tests. Additionally, the Mg-doped BGs may improve the movement of human umbilical vein endothelial cells (HUVECs) and stimulate bone nodule development in vitro.

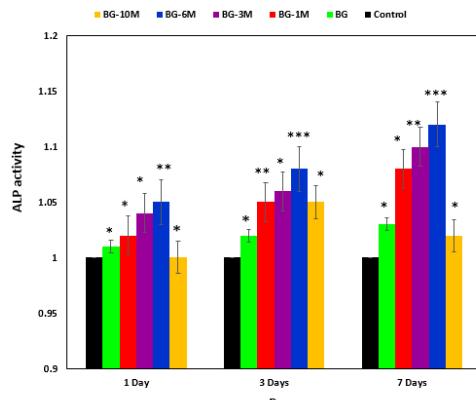
It should be noted that Mg-doped glasses have previously been shown to improve the osteogenic differentiation of mesenchymal stem cells (MSCs) [29].



**Fig. 3.** The MTT assay of MC3T3-E1 osteoblast cells, cultured on synthesized BGs for 1, 3 and 7 days, \*P < 0.05, \*\*P < 0.01 and \*\*\*P < 0.001).

Fig. 4 displays the alkaline phosphatase (ALP) activity of cells that were cultivated on BGs for 1, 3, and 7 days. From the first to the seventh day of culture, all of the BGs showed a notable rise in ALP activity. In contrast, BG-6M had the greatest ALP activity value throughout all culturing times when compared to BG-0M. When the Mg content was raised from 6 to 10 (in mol.%), the ALP activity of BG-10M was much lower than that of BG-6M.

BG-6M demonstrated the highest proliferation and ALP activity of the G292 cells, as indicated by the ALP activity and MTT investigations. On the other hand, the SEM results verified that out of all the synthesized BGs, BG-6M exhibited the best hydroxyapatite production. Devis Bellucci et al. [30] reported that ALP activity was measured to assess MC3T3-E1 differentiation toward the osteoblast phenotype. All tested disks showed enhanced ALP activity compared to the TCPS control (p < 0.001). Differentiation began at day 3 for BGa/TCP-Mg and BGa/TCP-Sr, and at day 7 for BGa/TCP-Mg-Sr. Notably, the bisubstituted TCP sample exhibited the highest ALP levels, indicating a synergistic effect of Sr<sup>2+</sup> and Mg<sup>2+</sup>. Another study demonstrated that in vitro experiments with osteoblasts showed bioglass containing a small amount of magnesium stimulated alkaline phosphatase activity [31].



**Fig. 4.** The ALP activity of MC3T3-E1 osteoblast cells, cultured on synthesized BGs for 1, 3 and 7 days (\*P < 0.05, \*\*P < 0.01 and \*\*\*P < 0.001).

## 4. Conclusion

In conclusion, bioactive glasses (BGs) in the SiO<sub>2</sub>–CaO–P<sub>2</sub>O<sub>5</sub>–MgO system with varying MgO content (1, 3, 6, and 10 mol%) were successfully synthesized via the sol-gel technique and evaluated in SBF. The results demonstrated that MgO substitution up to 6 mol% enhanced hydroxyapatite formation, MC3T3-E1 osteoblast cells proliferation and differentiation, and antibacterial properties. However, higher MgO content (10 mol%) negatively affected these biological activities. Therefore, 58S bioactive glass doped with up to 6 mol% MgO exhibits excellent bioactivity, antibacterial performance, and cell compatibility, making it a promising potential for bone tissue engineering and dental applications.

## Author contributions

**Nazanin Jafari:** Investigation, Conceptualization, Writing – original draft, Writing – review & editing; **Ketevan Mikeladze:** Conceptualization, Writing – original draft, Writing – review & editing.

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No funding was received for this study.

## Conflict of interest

The authors declare no conflict of interest.

## Data availability

No data is available.

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