Synthesis, characterization and evaluation of bioactivity and antibacterial activity of quinary glass system (SiO₂–CaO–P₂O₅–MgO–ZnO): *In vitro* study

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Abstract. Bioactive glasses in the systems SiO₂–CaO–P₂O₅–MgO (BGZn0) and SiO₂–CaO–P₂O₅–MgO–ZnO (BGZn5), were prepared by sol–gel method and then characterized. Surface reactivity was studied in simulated body fluid (SBF) to determine the effect of zinc (Zn) addition as a trace element. The effect of Zn addition to the glass matrix on the formation of apatite layer on the glass surface was investigated through X-ray diffraction (XRD), Fourier transform infrared spectroscopy (FT-IR) and scanning electron microscopy (SEM). Also, inductively coupled plasma–optical emission spectroscopy (ICP–OES) was used to determine the concentrations of released ions in SBF solution after different time intervals in SBF solution. The antibacterial activity of Zn containing glass against *Pseudomonas aeruginosa* was measured by the halo zone test. The presence of Zn in glass composition improved chemical durability, slowed down the formation rate of Ca–P layer and decreased the size of crystalline apatite particles. Zn containing glass exhibited an excellent antibacterial activity against *P. aeruginosa* which could demonstrate its ability to treat bone infection.

Keywords. Bioactive glass; zinc; bioactivity; antibacterial activity; tissue engineering.

1. Introduction

Since the invention of Bioglass[®] by Hench and his colleagues in 1971 (Hench *et al* 1971), different kinds of bioactive materials have been used in a wide range of hard tissue engineering and regenerative medicine (Hench 1998; Livingston *et al* 2002) due to their excellent bioactivity, osteoconductivity and biodegradability (Wilson and Low 1992; Hench 2000; Vallet-Regi *et al* 2003). It has been more than ten years since bioactive materials have been used in clinical applications (Hench *et al* 2004).

The most important disadvantage of bioactive glass is its high solubility in biological environments. Therefore, almost all of the released ions are transported away from the environment of the implantation site by body fluid before the formation of new bones. In addition, because of the poor mechanical properties of bioactive glass, it cannot be used in significant load-bearing sites (Hench *et al* 1971). The incorporation of different inorganic elements can induce several

effects on the surface reactivity of bioactive glass to customize the bioactivity and biodegradability (Li and Zhang 1990; Vallet-Regi 2001; Aina 2009).

Magnesium (Mg) and zinc (Zn) are two elements that have high physiological interests in the biomedical field. These elements are similar with respect to charge and ionic radius, 0.72 and 0.74 Å respectively, and both are expected to have similar effects on glass systems (Watts *et al* 2010).

Mg is an essential minor element in human metabolism that is necessary for the incorporation of calcium (Ca) into bony tissues. Also, the simultaneous release of Mg and Ca ions might be beneficial for bone regeneration (Serre *et al* 1998; Oudadesse *et al* 2004; Li *et al* 2008). In addition, Mg is one of the main substitutes for Ca in biological apatite. Bone, enamel and dentin contain 0.72, 0.44 and 1.23 wt% of Mg, respectively (Gutowska *et al* 2005), therefore, it is expected that Mg-substituted hydroxyapatite (denoted hereafter as Mg–HAp) have excellent bioactivity and biocompatibility. Substitution of Mg in the silica glass matrix would modify their stability and improve their mechanical properties (Vallet-Regi *et al* 1999). Mg is closely connected to the mineralization of calcified tissues (Gutowska *et al* 2005) and has an indirect effect on mineral metabolism (Althoff *et al* 1982). However, clear role of this ion has not been

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discovered yet. It seems that Mg directly stimulates the proliferation of osteoblasts with an effect comparable to that of insulin, a wellknown growth factor for osteoblasts. On the contrary, Mg depletion affects all stages of skeletal metabolism, results in cessation of bone growth, decrement of osteoblast and osteoclast proliferation and osteopenia (Liu *et al* 1988).

Zn is an essential trace element that stimulates bone healing, reduces postmenopausal bone loss and improves bone mineralization and skeletal system (Yamaguchi 1998; Towler *et al* 2009; Hanzi *et al* 2010) and activates bone formation (Yamaguchi *et al* 1987) by promoting the proliferation of osteoblasts (Kishi and Yamaguchi 1994). It also improves mechanical and thermal properties of silica glass. In the case of phosphate glass, it improves the chemical durability (Oki *et al* 2004). Therefore, bioactive glass containing Mg and Zn seems to have a great potential for orthopedic and dental applications.

In general, the synthesis of bioactive glass is performed by the traditional melting method, which is regarded as simple and suitable for mass production (Zhang and Santos 2000). However, the evaporation of the volatile component, P_2O_5 , during high-temperature processing has limited this method. In recent years, the sol-gel technique, an alternative approach to the synthesis of bioactive glass has been widely studied (Sepulveda *et al* 2001). This technique has several advantages such as high purity, ultra homogeneity, taking place at low temperatures and most significantly the possibility of development of new glass compositions (Jeon *et al* 2003).

The bioactivity of sol-gel derived bioactive glass (as represented by the induction time of apatite) and their degradability (as represented by the amount of residual glass) are higher than bioactive glass made by the conventional melting method in both *in vitro* studies (Li *et al* 1992) and *in vivo* tests in animal models (Wheeler *et al* 2000; Hamadouche *et al* 2001).

The aim of this study is focused on the investigation of surface reactivity of glasses containing Zn and Mg to evaluate effects of the modifier elements on the bioactivity, chemical durability and antibacterial properties. Also, in this paper, the effect of Zn and Mg on the lattice structure of the synthesized bioactive glass and newly formed apatite on its surface was completely given and discussed.

2. Materials and method

2.1 Synthesis of samples

Bioactive glass samples based on SiO_2 - P_2O_5 -CaO-MgO system were prepared by the sol-gel method. According to Brauer *et al* (2010), with further addition of zinc to the glass composition, the network connectivity (NC) could remain constant. Herein, ZnO was added to the glass matrix while NC and the ratio of all other components were kept constant. The mol% of each element in both samples are given in table 1.

Table 1. Glass composition (in mol%).

Glass	SiO ₂	P ₂ O ₅	CaO	MgO	ZnO
BGZn0	61.00	4.00	31.00	5.00	0.00
BGZn5	57.00	3.80	29.45	4.75	5.00

The samples were prepared as follows: briefly, tetraethyl orthosilicate (TEOS: $C_8H_{20}O_4Si$) and distilled water were mixed and stirred at room temperature. Then, 2M nitric acid (HNO_3) solution was added as a hydrolysis catalyst. The mixtures were allowed to react for 60 min in the acid hydrolysis of TEOS to proceed almost to completion. The following reagents were added in sequence allowing 30 min for each reagent to react completely: BGZn0: 4.45 cc, BGZn5: 4.15 cc of triethyl phosphate (TEP), BGZn0: 23.94 g, BGZn5: 22.39 g of calcium nitrate tetrahydrate ($Ca(NO_3)_2 \cdot 4H_2O$), BGZn0: 4.19 g, BGZn5: 3.91 g of magnesium nitrate hexahydrate ($Mg(NO_3)_2 \cdot 6H_2O$) and B:4.79 g of zinc nitrate hexahydrate ($Zn(NO_3)_2 \cdot 6H_2O$). All materials in this study were purchased from Merck Inc.

After the final addition, mixing continued for 30 min to allow completion of hydrolysis reaction. Finally, 1M ammonium hydroxide was added dropwise to the mixture which led to polycondensation reactions and the formation of the final gels (Bigi *et al* 1995). The samples were dried at 120 °C for 24 h. A small hole was inserted in the lid to allow the leakage of gases during thermal treatment of the gels to remove all the residual water. Then the dried gels were milled by planetary milling (SVD15IG5-1, LG Company) at 400 rpm for 1 h. After grinding and sieving, the dry powders were heated at 700 °C for 2 h to stabilize the glass and eliminate residual nitrates. The heating rate was 10°C/min.

2.2 Characterization

2.2a X-ray diffraction: The sample powders were analysed by XRD with Siemens-Brucker D5000 diffractometer. This instrument works with voltage and current settings of 40 kV and 40 mA, respectively and uses $CuK\alpha$ radiation ($1.540510 \text{ \AA}$). For qualitative analysis, XRD diagrams were recorded in the interval of $10^\circ \leq 2\theta \leq 100^\circ$ at a scan speed of $2^\circ/\text{min}$ with a step size of 0.02° and step time of 1 s.

2.2b Fourier transform infrared spectroscopy: IR analysis was performed using a FTIR spectrometer with a Bomem MB 100 spectrometer (Bruker IFS 28, equipped with both MCT and DTGS detectors) in $3500\text{--}400 \text{ cm}^{-1}$ spectral range. KBr pellets were prepared by mixing 1 mg of sample powder with 300 mg of KBr (infrared grade) and pelletizing under vacuum. Transmission spectra of KBr pellets were normally recorded using a DTGS detector in order to reach lower wavenumbers at a scanning speed of 120 scan/min with 4 cm^{-1} resolution.

2.2c Scanning electron microscope: SEM was used to observe the surface morphology of sample disks. For this purpose, BG disks were first coated with a thin film of Au by the sputtering method (EMITECH K450X, England) and then the surface morphology of BG disks were observed by SEM (Philips XL30) that operated at an acceleration voltage of 15 kV.

2.2d ICP–OES measurements: Elemental analysis of SBF solution at different times of reaction with BG disks was performed to identify the releasing patterns of different elements. The solutions were analysed with a Perkin–Elmer Optima 2000 DV spectrometer to determine the following elements: Ca (317.933 nm analytical line), Si (251.611 nm), P (213.617 nm) and Zn (206.876 nm).

2.2e pH meter: The changes in the pH of SBF solutions, isolated at different times of immersion and filtration were measured with a scientific AB15 pH meter by Fisher.

2.3 Antibacterial test

Antibacterial activity of the sample containing Zn against *Pseudomonas aeruginosa* (ATCC 27853) was investigated by the halo zone test. *P. aeruginosa* is one of the most commonly considered gram-negative aerobic bacilli in the differential diagnosis of a number of probable gram-negative infections. This organism is frequently feared because, it causes severe hospital-acquired infections, especially in immune compromised hosts and is often antibiotic resistant, complicating the choice of therapy (Hilf *et al* 1989).

In the halo zone test, antibacterial activity is determined by the ratio (w/d) of width of antibacterial halo (w) and diameter of the sample (d) (Liu *et al* 2008). BGZn0.5 glass powder was ground and sieved to obtain uniform-sized particles. McFarland 0.5 standard was used in the preparation of bacterial inocula for performing antibacterial susceptibility testing. The bacteria were cultured in defibrinated sheep blood agar (DSBA) medium (Russell *et al* 2006). All apparatus were sterilized prior to use. Assay containing BGZn5 in concentration of 0.001 mg/mL was prepared and 50 mL of the assay was poured in the centre of culture plate and the culture was incubated at 37 °C for 24 h.

2.4 In vitro studies in SBF

HAp-forming ability of the bioactive glass disks was analysed by immersing the samples in simulated body fluid (SBF) for various periods of time. Each sample was immersed in SBF solution at 37 °C. The surface area to volume ratio for all the samples was 0.1 cm^{−1} as proposed by Kokubo *et al* (1990) and SBF solutions were not exchanged during the experiments (Balamurugan *et al* 2007). SBF solution was prepared according to the method proposed by Kokubo and Takadama (2006) as follows: reagent-grade NaCl, NaHCO₃, KCl, K₂HPO₄·3H₂O, MgCl₂·6H₂O, CaCl₂ and Na₂SO₄ were dissolved in deionized water.

Then the solution was buffered to a pH of 7.25 with tris–(hydroxymethyl)–aminomethane ((CH₂OH)₃CNH₃) and hydrochloric acid. The ion concentrations and pH of SBF solution is nearly equal to that of human blood plasma and the data are shown in table 2. After the immersion periods were terminated, samples were removed from the incubator, rinsed gently with deionized water and left to dry at ambient temperature. Finally, all the samples were analysed for evaluation of elemental composition and morphology of newly formed bioactive materials on the surface of the samples.

3. Results and discussion

3.1 XRD analysis

XRD patterns of BGZn0 and BGZn5 before and after 1, 7 and 21 days of immersion in SBF are presented in figure 1. Formation of an apatite phase was confirmed by the observation of HAp-characteristic peaks, which developed with the length of immersion time. SEM micrographs also confirmed the presence of an apatite layer on the surface of all samples.

JCPDS pattern of standard HAp (code no. 9-432) was used as the reference for evaluation of the newly formed apatite layer. After immersion in SBF solution, XRD patterns of BGZn0 and BGZn5 showed some differences in crystallization. The obtained results demonstrated the formation of Ca–P layer on the surface of both samples after just 1 day of immersion, two significant reflection peaks of HAp (2 1 1) at 32° and (1 0 2) at about 28° were observed and the intensity of these peaks increased with the length of immersion (Ashok *et al* 2003). Also, other peaks of apatite appeared at 26, 40, and 46° which corresponds to (0 0 2), (2 2 1) and (2 0 3) HAp reflections. The crystalline character of HAp in BGZn5 was decreased due to the lower dissolution rate of the glass. In fact, presence of Zn in glass composition decreases the crystalline character of the newly formed apatite layer (Dietrich *et al* 2008; Erol *et al* 2010; Oudadesse *et al* 2011).

The rate of HAp formation on BGZn5 was slower than that of BGZn0. The main effect of Zn addition to the glass composition is that it slows down the rate of apatite formation (Du and Chang 2006; Aina 2009).

Table 2. Ion concentrations in SBF and human blood plasma.

Ion	SBF (mmol/L)	Plasma (mmol/L)
Na ⁺	142.5	142.5
K ⁺	5.0	5.0
Mg ²⁺	1.5	1.5
Ca ²⁺	2.5	2.5
Cl [−]	147.5	103.0
HCO ₃ [−]	4.2	27
HPO ₄ ^{2−}	1.0	1.0
SO ₄ ^{2−}	0.5	0.5

3.2 FTIR analysis

FTIR has been used to identify the formation of apatite layer over the samples. Figure 2 shows the functional groups and chemical bonds formed on the surface of glass samples during immersion in SBF solution.

FTIR spectra of all the samples exhibited bands located in the range of 450–480, 725–800 and 1000–1200 cm^{-1} corresponding to the bending mode of Si–O–Si, vibrational mode of symmetric stretch of Si–O–Si and vibrational mode of asymmetric stretch of Si–O–Si, respectively.

For all the samples, precipitation of Ca–P layer was confirmed by the presence of the main phosphate band at about 600–650 cm^{-1} , which is the characteristic band of phosphate in its crystalline phase (Carta *et al* 2007). Moreover, presence of the carbonate band at about 880 and 1500 cm^{-1} indicated the formation of a newly formed hydroxycarbonate apatite

(HCAp) on the surface of the samples (Dietrich *et al* 2008; Mami *et al* 2008).

The introduction of Zn as a modifier to the glass composition changed the position and intensity of the reflection bands. The intensity of Si–O–[NBO] band and Si–O–Si asymmetric stretch (1100 cm^{-1}) generally decreased. The decrease of the intensity of Si–O–[NBO] suggested that more bridging oxygens were formed in the glass network. An increase in bridging oxygens with Zn substitution led to an increase in the glass density as a result of decrease in discontinuity of the vitreous network. In fact, a higher concentration of Zn in the glass matrix leads to a lower degree of depolymerization in the structure and a lower concentration of Si–O–[NBO] groups. These functional groups control the dissolution rate of the silica glass through the formation of silanol groups in SBF. Therefore, chemical durability of bioactive glasses in SBF solution increases with the

Figure 1. XRD patterns of (a) BGZn0 after 1, 7 and 21 days immersion in SBF solution and (b) BGZn5 after 1, 7 and 21 days immersion in SBF solution.

Figure 2. FTIR spectra of (a) BGZn0 after 1, 7 and 21 days immersion in SBF solution and (b) BGZn5 after 1, 7 and 21 days immersion in SBF solution.

Figure 3. SEM micrograph of BGZn0, (a) before immersion in SBF; (b) after 7 days immersion in SBF; SEM micrograph of BGZn5 (c) before immersion in SBF and (d) after 7 days immersion in SBF.

increase of Zn content. The chemical durability of bioactive glass plays an important role in the biological response at the interface of bioactive materials when exposed to body fluids and therefore, study of the bonding configuration is a key step in the development of new glasses and their biomedical applications (Hwa *et al* 1998).

The position of bands associated with the phosphate band, PO_4^{3-} antisymmetric bend, ($600\text{--}650\text{ cm}^{-1}$) and Si–O–Si symmetric stretch ($725\text{--}800\text{ cm}^{-1}$) shifted towards higher values ($700\text{--}750\text{ cm}^{-1}$ and $800\text{--}850\text{ cm}^{-1}$, respectively) and their intensity decreased. Also, presence of Mg in glass composition decreases intensity of the phosphate band in its crystalline phases (Dietrich *et al* 2008). Here, intensity of phosphate bands in BGZn5 was very weak because of the simultaneous presence of Mg and Zn. It seems that Mg may be substituted into the newly formed apatite nuclei and inhibit the crystallization of apatite to favour the formation of amorphous calcium phosphate (Oliveira *et al* 2000).

Substitution of Mg ions into the apatite lattice changes its physicochemical properties. Mg substituted apatites result in Ca deficient apatite or amorphous calcium phosphate $(\text{Ca,Mg})_9(\text{PO}_4)_6$ (Gutowska *et al* 2005). In fact, inorganic ions like Mg^{2+} and Zn^{2+} are suppressants for the

crystallization of apatite through the reduction of the crystal size of the apatite, and higher concentrations of Mg and Zn lead to the formation of amorphous calcium phosphate (Bigi *et al* 1993). This phenomenon promotes dissolution rate of the apatite precipitates.

The formation mechanism of HCAp includes some specific steps which highlight the following phenomena: a hydrated silica layer is formed on the surface of bioactive glass before the precipitation of Ca–P species and the silanol groups are specific sites for apatite nucleation (Ohtsuki *et al* 1991). A well-detailed sequence of reactions occurring at the surface of bioactive glasses has been previously described in the literature (Clark *et al* 1976).

Indeed, thanks to the band assignment, it is possible to identify effect of addition of different elements on the surface reactivity of bioactive glasses. The bands located at 470 cm^{-1} (Si–O–Si bend) and $725\text{--}800\text{ cm}^{-1}$ (Si–O–Si symmetric stretch) are related to the amount of silica present in the newly formed layer. The band at $725\text{--}800\text{ cm}^{-1}$ is specially related to the formation of silica-like layer and its intensity becomes low with the addition of Zn to the glass composition. The intensity of the band at about 470 cm^{-1} (Si–O–Si bend) also decreased (Dietrich *et al* 2008). In fact,

Figure 4. Ions released (ppm) from BGZn0 and BGZn5 after 1, 7 and 21 days immersion in SBF solution (mean % dispersion per element, calculated for these ICP-ES data, is 0.5 for Ca, 0.02 for P, 0.5 for Si, 0.05 for Mg and 0.005 for Zn).

if the formation of silanol groups is inhibited, the formation of SiO₂-rich layer will also be inhibited.

The crystallization of Ca-P layer results in the formation HCap. Here, the appearance of band at a range of 600–650 cm⁻¹ in FTIR spectra, characteristic band of phosphate in the crystalline phase, confirmed the crystallization of the newly formed apatite layer. The intensity of phosphate band in BGZn5 was lower than that in BGZn0, which means the addition of Zn to the glass composition suppresses

the crystallization of Ca-P precipitates. It is important to point out that Bigi *et al* (1995) pointed out that Zn inhibits crystallization of precipitated HAp through the reduction of crystal sizes of apatite.

3.3 SEM observations

Figure 3 shows SEM micrographs of sample surfaces before and after 7 days of immersion in SBF. It was observed that

morphology of the newly formed apatite layer changed by adding Zn to the glass composition. Clearly, precipitation of the apatite layer is initiated with the formation of individual granules after the first few hours of immersion, which then gradually grew together to form a dense layer on the glass surface (Saboori *et al* 2009). After 7 days, the newly formed HCAp layer completely covered the surface.

3.4 ICP–OES emission spectroscopy

ICP–OES spectroscopy was used in monitoring the concentration (ppm) of species released from glass disks after immersion in SBF for different periods as shown in figure 4. The obtained results noted the following effects: (i) Phosphate concentration for BGZn0 had a sharp increase followed by a rapid decrease during the first day of immersion. This result confirmed an early precipitation of calcium-phosphate layer on the surface of glass samples which means that BGZn0 containing no Zn has excellent bioactivity. In contrast, the release rate of phosphate ions for BGZn5, containing 5 mol% of Zn, was very slow and a significant decrease of phosphate concentration was initiated after 7 days of immersion. In fact, BGZn5 had higher chemical durability and a lower rate of apatite formation due to the presence of Zn (Aina 2009), (ii) the release of Ca ions for BGZn0 was definitely higher than that for BGZn5 (For example, after 1 week, the figures are: 237 ppm for BGZn0 and 191 ppm for BGZn5). Ca release patterns were in agreement with pH variation during the dissolution process, BGZn0 had higher pH variation, from 7.25 to 8.29, whereas the pH increment of BGZn5 was from 7.25 to 8.16 due to the lower release of Ca ions. Indeed, during the dissolution process, an exchange occurs between Ca ions released from glass and H₃O⁺ ions of SBF solution that leads to a pH increment. The glass sample with higher chemical durability has a lower release of Ca ions. Therefore, the exchange process followed by a pH increment becomes limited (iii) a simultaneous gradual increase in Si and Mg content was observed for all samples with the length of immersion but the release of Si and Mg ions for BGZn0 was faster than the other sample and the (iv) the release of Zn ions from BGZn5 was very rare, lower than the human blood plasma value. In fact, the concentration of Zn in SBF solution was fairly close to the detection limits of ICP instrument used. A significant increase in Zn concentration was observed after 7 days of immersion. The slow release of zinc incorporated into the glass promotes bone formation around the implant and accelerates the patient's recovery (Ito 2002; Yamaguchi *et al* 2004). Therefore, bioactive glass with slow release of Zn ions is an appropriate candidate for orthopedic applications.

SBF solution pH was also monitored throughout this study. pH of SBF measured throughout the testing period indicated a slight increase with immersion time. pH value of BGZn5 was lower than that for BGZn0 during SBF immersion (figure 4f). This is probably due to the release of Zn ions into SBF solution. Migration of Zn ions into SBF solution causes it to become more acidic and explains

Figure 5. Antibacterial “halo” of bioactive glass containing Zn against *Pseudomonas aeruginosa*.

the lower amount of pH for BGZn5 during SBF immersion (Balamurugan *et al* 2007).

3.5 Antibacterial test

The antibacterial activity of the sample containing Zn against *Pseudomonas aeruginosa* (ATCC 27853), a gram-negative bacterium was investigated by the halo zone test. In halo zone test, the antibacterial activity of the material is determined by the ratio (w/d) of width of antibacterial halo (w) and diameter of the sample (d) (Liu *et al* 2008). BGZn0.5 glass powder was ground and sieved to produce homogenized particles. The McFarland 0.5 standard was used in the preparation of bacterial inocula for performing antimicrobial susceptibility testing. The bacteria were cultured in defibrinated sheep blood agar (DSBA) medium (Russell *et al* 2006). All the apparatus were sterilized prior to use. Assay containing BGZn5 with a concentration of 0.001 mg/mL was prepared and 50 mL of the assay was poured at the centre of the culture plate and the culture was incubated at 37 °C for 24 h.

The halo zone test revealed that BGZn0.5 had considerable antibacterial activity against *P. aeruginosa* (figure 5). As it can be seen, inhibitory zone of the bacteria is transparent and the growth zone is opaque and the width of antibacterial halo (w/d) after 24 h is 0.41, similar to the value reported by Hairong *et al* (Liu *et al* 2008) for Ag-doped antibacterial material. According to the obtained results, it can be concluded that Zn also has a great potential as an antibacterial agent.

4. Conclusions

Highly bioactive glasses, composed of SiO₂–CaO–P₂O₅–MgO containing 0 and 5 mol% Zn have been successfully synthesized by sol–gel technique. The addition of Zn to glass composition induced significant modifications of chemical durability, antibacterial activity and bioactivity. Zn reduced the number of non-bridging oxygens in the glass

structure resulting in the lower dissolution rate. Eventually, Zn containing glass sample showed considerable antibacterial activity against *P. aeruginosa* indicating its potential not only as a bioactive material but also as a candidate for the treatment of bone infections.

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