



Featured Letter

Novel multifunctional strontium-copper co-substituted mesoporous bioactive particles



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ABSTRACT

Sr-Cu co-substituted mesoporous bioactive glasses were synthesized by two different sol-gel approaches: an ultrasound-assisted base-catalyzed sol-gel procedure and an aerosol-assisted spray-drying method. The produced spherical shaped particles showed high specific surface area values and tunable pore size. The two different routes allowed obtaining samples with different morphology and size, characterized by the ability to induce hydroxyapatite deposition, to incorporate a specific amount of therapeutic ions (strontium with the aim to improve bone formation and copper for its antibacterial and pro-angiogenic properties) and to release them. The obtained multifunctional biomaterials synergistically combine the ability to promote bone formation and angiogenesis and to impart an antibacterial effect.

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1. Introduction

Mesoporous bioactive glasses (MBGs) have been extensively studied for bone repair [1] and, more recently, for soft tissue applications [2]. The incorporation of metal ions has gained increasing interest to impart different biological functions and enhance their therapeutic potential [3,4].

Among these ions, strontium is one of the most attractive for its role in enhancing bone cell activity and inhibiting osteoclast differentiation [5]. An essential and complementary role in tissue regeneration could be performed by copper due to its capability to provide antibacterial properties [6] and to promote angiogenesis [7]. In the literature, the therapeutic effect associated to the single ion substitution is well established [5–7], and with the aim to combine different biological effects, the joint presence of two different therapeutic ions (i.e. Sr/Co and Cu/Zn) have been investigated for hydroxyapatites [8,9] and bioactive glasses [10,11]. Huang and co-workers [9] fabricated a Sr-Cu co-substituted hydroxyapatite coating and demonstrated the potential to combine in a single formulation the antimicrobial property and the osteogenic differentiation stimulus. In this contribution, for the first time to the best of authors' knowledge, novel multifunctional Sr-Cu-containing MBGs, with binary SiO₂-CaO composition, have been synthesized by two different approaches: an ultra-sound assisted sol-gel technique (US) [6] and an aerosol-assisted spray-drying method (SD) [12].

These two routes allow to obtain MBG particles with adjustable features (i.e. size, surface area, pore size), able to co-release different therapeutic ions and to potentially incorporate and delivery drugs and/or biomolecules.

2. Materials and methods

2.1. SrCu_MBG_2%_US and SrCu_MBG_2%_SD synthesis

Sr-Cu-containing MBGs (molar ratio Sr/Cu/Ca/Si = 1/1/13/85) were produced by modifying an ultra-sound assisted base catalyzed sol-gel procedure previously reported by the authors [6]. First, CTAB was dissolved by stirring in absolute methanol, whose pH was adjusted to 12.5 through addition of NH₄OH. Into this solution, Ca(NO₃)₂·4H₂O, CuCl₂ and SrCl₂ were dissolved. Then TEOS, firstly dissolved in absolute methanol, was added to the first solution with the application of ultrasounds (150 W in a 10 s on/10 s off cycle for 20 min). After 24 h of stirring, the precipitate was washed by centrifugation and dried at 70 °C for 12 h and the final precipitate (named hereafter SrCu_MBG_2%_US) was calcined at 600 °C in air (5 h, 1 °C/min).

The spray-drying Sr-Cu substituted MBGs (molar ratio Sr/Cu/Ca/Si = 1/1/13/85) were produced following the procedure reported by Molino et al. [12]. Briefly, Pluronic P123 was dissolved in bidistilled water by stirring. A solution of TEOS, pre-hydrolyzed for 1 h in diluted HCl (pH 2), was poured in the previous one and stirred for 20 min. SrCl₂ and CuCl₂ were simultaneously added to this batch. Ca(NO₃)₂·4H₂O was added to the solution 15 min before

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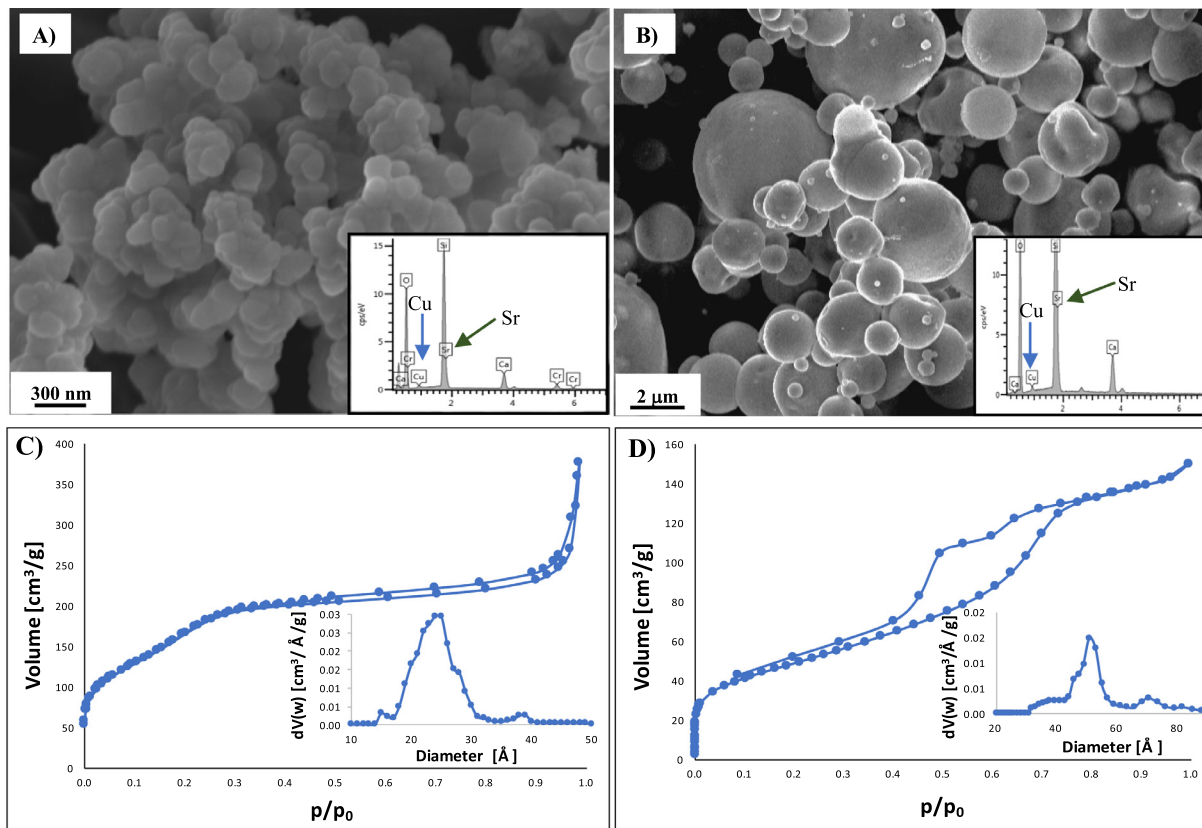


Fig. 1. FE-SEM image of SrCu_MBG_2%_US (A) and SrCu_MBG_2%_SD (B) with related EDS spectra (inset); isotherm curve of SrCu_MBG_2%_US (C) and SrCu_MBG_2%_SD (D) with related pore size distributions (inset).

spraying using a Mini Spray-Dryer B-290 (Buchi). The collected powder (named hereafter SrCu_MBG_2%_SD) was calcined in air at 600 °C (5 h, 1 °C/min).

2.2. Characterization

The particle morphology was analyzed using a FE-SEM microscope (Philips 525 M) equipped with EDS analyzer (Philips Edax 9100). The crystalline nature of HA deposits was investigated by wide-angle XRD analysis (XRD, X'Pert PRO, PANalytical). N₂ adsorption-desorption analysis was performed on powders outgassed at 423°K for 5 h by using a Quantachrome Autosorb 1. The BET (Brunauer–Emmett–Teller) equation was adopted to calculate the specific surface area (SSA_{BET}) in the relative pressure range of 0.04–0.1. The pore size distribution was studied through DFT (Density Functional Theory) using the NLDFT equilibrium model. To evaluate the sample bioactivity, 30 mg of powder were kept immersed up to 14 days in simulated body fluid (SBF) with a concentration of 1 mg/mL inside an orbital shaker (37 °C, 150 rpm) [13].

Ion release was assessed by soaking powder in SBF with a concentration of 1 mg/mL for 3 h, 1, 3 and 7 days. At each time point, 1 mL of supernatant was collected after centrifugation and analysed by ICP (ICPMS Thermoscientific ICAQ spectrometer).

3. Results and discussion

SrCu_MBG_2%_US particles were spheroidal, slightly aggregated, with a size of about 100 nm (Fig. 1A). SrCu_MBG_2%_SD showed spherical particles ranging between 500 nm and 5 μm. For both samples, EDS analysis (inset in Fig. 1A and B) revealed that the incorporation successfully occurred for both ions.

Table 1
Textural properties of samples.

Samples	SSA_{BET} (m ² /g)	Pore Volume (cm ³ /g)	DFT Pore Size (nm)
SrCu_MBG_2%_US	470	0.23	2.5
SrCu_MBG_2%_SD	176	0.21	5

N₂ adsorption-desorption measurement showed IV type isotherms for both samples (Fig. 1C and D), confirming their mesoporous structure. SrCu_MBG_2%_US curve exhibited a well-defined step between 0.1 and 0.2p/p₀, indicative of the filling of regular mesopores. Pore size distribution in Fig. 1C (inset) revealed an average pore diameter of 2.5 nm. SrCu_MBG_2%_SD isotherm showed a hysteresis loop corresponding to the filling of mesopores and pore size distribution revealed an average pore diameter of 5 nm (Fig. 1D – inset). Although for spray-dried sample the specific surface area is lower (Table 1), the value is still remarkably higher compared to that of not-templated sol-gel glasses [14]. These data highlighted that the ion co-substitution did not significantly affect the textural properties of the final powder that resulted only slightly different from Sr- or Cu-containing MBGs [6,12].

In vitro bioactivity assessment highlighted that partial replacing of Ca with Cu and Sr ions did not significantly hamper the hydroxyapatite nucleation and deposition. After 1 day of soaking, the Ca/P ratios revealed by EDS analysis were 2.89 and 1.63 for SrCu_MBG_2%_US and for SrCu_MBG_2%_SD, respectively. After 7 days of soaking in SBF the samples were fully covered by a layer of needle-like crystals (Fig. 2) and, for both samples, the Ca/P ratio was in good accordance to the stoichiometric value of hydroxyapatite (1.67). The formation of hydroxyapatite layer was confirmed by wide-angle XRD analysis (Fig. S1).

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