

Advanced double-ion-doped mesoporous bioactive glasses for controlled drug delivery and antibacterial protection in the regeneration of hard tissues

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ABSTRACT

Mesoporous bioactive glasses are widely investigated for hard tissue regeneration due to their bioactivity and drug delivery capability. However, systems simultaneously combining multi-ion doping and drug loading remain largely unexplored. In this work, advanced MBGs co-doped with cerium and a second therapeutic inorganic ion (Cu, Ag, Mg, and Sr) were developed and loaded with clinically relevant drugs (ibuprofen, paracetamol and gentamicin), resulting in a multifunctional platform that integrates inorganic and organic therapeutic cues within a single material.

Drug loading and release behaviour in simulated body fluid (SBF) depended on both composition and drug type.

Gentamicin-loaded MBGs exhibited clear and sustained antibacterial activity against *Escherichia coli*, despite limited drug release, suggesting effective local action.

Importantly, all compositions retained their bioactivity, as demonstrated by the formation of hydroxyapatite in simulated body fluid.

Overall, the results demonstrate the feasibility of combining the therapeutic ion doping and drug delivery within a single MBG platform.

This approach provides multifunctional systems with antibacterial activity and bioactive properties that may be beneficial for hard tissue regeneration.

1. Introduction

Bioactive glasses (BGs) have been widely investigated in hard-tissue engineering because they are able to form a hydroxyapatite (HA) layer in physiological environments, a feature that enables them to establish a chemical bond with bone [1–3]. Over the past twenty years, the introduction of mesoporous bioactive glasses (MBGs) has greatly expanded the potential of this class of biomaterials [4]. MBGs exhibit an exceptionally high specific surface area (SSA), tuneable mesoporosity, and a highly ordered pore network [5]. These features not only enhance their intrinsic reactivity toward biomineralization but also make them excellent hosts for drug molecules, enabling controlled loading and

release [1,5,6]. As a result, MBGs have emerged as versatile platforms capable of supporting bone regeneration while simultaneously addressing infection, inflammation, and oxidative stress. The properties of MBGs can be further tailored by incorporating therapeutic inorganic ions (TIIs) into the glass structure. Over the years, our research has focused extensively on cerium-doped compositions (MBGs-Ce) [7–12] and subsequently on systems containing combinations of two different ions [13], with the aim of developing MBGs with enhanced functional performance. Depending on the specific ion introduced, these materials can exhibit additional biological functionalities [7,14,15], such as enhanced angiogenesis (e.g. Cu, Mg), antibacterial activity (e.g. Cu, Ag), promotion of osteogenesis (e.g. Sr), or antioxidant effects (e.g.

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Table 1

LC (%) and LE (%) calculated for MBGs. *Data already published in a previous paper [12,32].

TiIs	MBGs	LC (%) IBU	LE (%) IBU	LC (%) PARA	LE (%) PARA	LC (%) GENTA	LE (%) GENTA
/	MBG	10.7* ± 0.5	53.3* ± 2.5	1.2* ± 0.09	1.2* ± 0.09	4.9* ± 0.3	59.0* ± 3.6
Ce	MBG3.6-Ce	7.0* ± 0.4	35.4* ± 2.0	1.3* ± 0.11	1.3* ± 0.11	5.4* ± 0.3	66.0* ± 3.7
	MBG5.3-Ce	2.3 ± 0.2	11.5 ± 1.0	0.6 ± 0.05	0.6 ± 0.05	4.8* ± 0.3	59.0* ± 3.7
Cu	MBG3.6-Cu	7.0 ± 0.1	35.0 ± 0.5	1.0 ± 0.06	1.0 ± 0.06	4.3 ± 0.2	53.4 ± 2.4
	MBG3.6-Ce/Cu	7.7 ± 0.4	38.1 ± 2.0	1.0 ± 0.07	1.0 ± 0.07	2.4 ± 0.1	29.7 ± 1.2
Ag	MBG2.6-Ag	5.3 ± 0.2	25.8 ± 1.0	0.9 ± 0.09	0.9 ± 0.09	1.4 ± 0.1	18.2 ± 1.3
	MBG2.6-Ce/Ag	8.4 ± 0.5	39.0 ± 2.3	0.5 ± 0.05	0.5 ± 0.05	1.4 ± 0.1	18.2 ± 1.3
Mg	MBG3.6-Mg	9.5 ± 0.5	47.2 ± 2.5	0.8 ± 0.03	0.8 ± 0.03	3.0 ± 0.2	37.4 ± 2.5
	MBG3.6-Ce/Mg	9.4 ± 0.5	47.1 ± 2.5	1.3 ± 0.12	1.3 ± 0.12	3.1 ± 0.2	37.9 ± 2.4
	MBG5.3-Mg	6.0 ± 0.2	30.0 ± 1.0	0.5 ± 0.06	0.5 ± 0.06	3.1 ± 0.2	37.9 ± 2.4
	MBG5.3-Ce/Mg	7.1 ± 0.3	35.3 ± 1.5	0.7 ± 0.04	0.7 ± 0.04	2.8 ± 0.2	35.1 ± 2.5
Sr	MBG3.6-Sr	6.3 ± 0.4	31.5 ± 2.0	0.5 ± 0.05	0.5 ± 0.05	2.4 ± 0.1	30.5 ± 1.3
	MBG3.6-Ce/Sr	6.4 ± 0.3	32.2 ± 1.5	0.3 ± 0.03	0.3 ± 0.03	1.2 ± 0.1	14.9 ± 1.2
	MBG5.3-Sr	3.7 ± 0.2	18.5 ± 1.0	1.0 ± 0.08	1.0 ± 0.08	2.7 ± 0.2	33.4 ± 2.5
	MBG5.3-Ce/Sr	4.1 ± 0.3	20.7 ± 1.5	0.4 ± 0.04	0.4 ± 0.04	2.7 ± 0.2	34.2 ± 2.5

Table 2SSA (m²/g) of MBGs before and after biomolecules loading. Tests were performed in triplicate. Data are presented as averages, with error bars representing the SD. *Data already published in a previous paper [12,13,32].

TiIs	MBGs	UL	IBU	PARA	GENTA
/	MBG	340* ± 26	158* ± 18	255* ± 21	229* ± 15
Ce	MBG3.6-Ce	323* ± 33	151* ± 10	246* ± 28	227* ± 20
	MBG5.3-Ce	354* ± 24	196 ± 19	296 ± 22	230* ± 25
Cu	MBG3.6-Cu	344* ± 38	219 ± 17	320 ± 29	184 ± 12
	MBG3.6-Ce/Cu	330* ± 27	154 ± 18	254 ± 16	199 ± 20
Ag	MBG2.6-Ag	219* ± 15	153 ± 16	177 ± 13	124 ± 14
	MBG2.6-Ce/Ag	248* ± 28	178 ± 12	205 ± 18	161 ± 15
Mg	MBG3.6-Mg	370 ± 31	120 ± 13	343 ± 23	130 ± 15
	MBG3.6-Ce/Mg	362 ± 24	154 ± 15	272 ± 32	184 ± 14
	MBG5.3-Mg	357 ± 36	148 ± 11	283 ± 22	160 ± 18
	MBG5.3-Ce/Mg	346 ± 28	161 ± 11	216 ± 23	155 ± 13
Sr	MBG3.6-Sr	339 ± 23	180 ± 21	190 ± 16	160 ± 15
	MBG3.6-Ce/Sr	295 ± 32	125 ± 9	184 ± 12	165 ± 19
	MBG5.3-Sr	250 ± 19	208 ± 22	201 ± 13	178 ± 21
	MBG5.3-Ce/Sr	248 ± 26	146 ± 11	191 ± 16	185 ± 12

Table 3

Percentage of release of IBU from MBGs as a function of time.

TiIs	MBGs	time (h)						
/	/	1	3	6	24	48	168	336
/	MBG	25	59	58	73	66	64	54
Ce	MBG3.6-Ce	52	72	78	94	100	100	100
	MBG5.3-Ce	100	100	100	100	100	100	100
Cu	MBG3.6-Cu	34	48	65	86	87	93	99
	MBG3.6-Ce/Cu	69	72	72	83	87	95	96
Ag	MBG2.6-Ag	42	43	52	64	64	64	71
	MBG2.6-Ce/Ag	32	39	47	60	65	68	64
Mg	MBG3.6-Mg	35	50	58	71	71	70	65
	MBG3.6-Ce/Mg	55	68	72	71	73	68	63
	MBG5.3-Mg	74	89	93	94	88	84	87
	MBG5.3-Ce/Mg	28	40	55	64	64	66	67
Sr	MBG3.6-Sr	67	63	58	63	63	54	58
	MBG3.6-Ce/Sr	84	83	77	68	69	69	73
	MBG5.3-Sr	50	90	72	76	76	76	76
	MBG5.3-Ce/Sr	79	100	82	81	81	87	81

Ce). Cerium exhibits relevant pharmacological activity and has been used in medical applications for its antiemetic, bacteriostatic, and antitumoral effects. In BGs, cerium confers multifunctional properties, including antioxidant, antibacterial, osteogenic, and angiogenic activities [7,16–18]. Copper is involved in key enzymes such as superoxide dismutase and promotes angiogenesis while exhibiting strong antibacterial activity. The antimicrobial effect of Cu, which is also effective against antibiotic-resistant strains, is mainly due to the release of

Table 4

Percentage of release of PARA from MBGs as a function of time.

TiIs	MBGs	time (h)						
/	/	1	3	6	24	48	168	336
/Ce	MBG	100	92	97	100	100	88	88
	MBG3.6-Ce	42	47	58	44	100	100	100
	MBG5.3-Ce	72	76	67	92	100	100	100
Cu	MBG3.6-Cu	36	68	100	100	100	100	100
	MBG3.6-Ce/Cu	26	41	65	100	100	100	100
Ag	MBG2.6-Ag	3	3	7	10	14	14	14
	MBG2.6-Ce/Ag	2	2	6	15	16	24	26
Mg	MBG3.6-Mg	33	34	36	37	40	45	46
	MBG3.6-Ce/Mg	4	6	7	10	9	11	12
	MBG5.3-Mg	40	42	38	38	38	38	37
	MBG5.3-Ce/Mg	3	3	7	14	13	15	19
Sr	MBG3.6-Sr	49	49	50	41	46	46	40
	MBG3.6-Ce/Sr	26	34	57	47	84	84	76
	MBG5.3-Sr	37	37	37	42	39	97	97
	MBG5.3-Ce/Sr	59	63	67	80	76	76	86

Cu⁺/Cu²⁺ ions, which damage microbial membranes, induce oxidative stress, and interfere with enzymatic processes [19–21]. Silver exhibits strong antimicrobial properties by disrupting bacterial membranes and impairing vital cellular functions, including metabolism and DNA activity. Its effectiveness against a wide range of microorganisms, together with a low risk of resistance development, has supported its extensive use in biomedical applications [17,18,22]. Magnesium is an essential element involved in key enzymatic and cellular processes through its role in ATP–Mg²⁺ complexes. In bone tissue, it promotes bone formation and remodelling by enhancing osteoblast activity and inhibiting osteoclasts, contributing to improved bone health [23–25]. Strontium is effective in preventing and treating osteoporosis due to its pro-osteogenic activity. Sr²⁺ ions inhibit osteoclast-mediated bone resorption and stimulate osteoblast-driven formation of new bone. The incorporation of Sr²⁺ into BGs enhances cell proliferation and alkaline phosphatase activity. In MBGs, Sr enables prolonged ion release, also promoting angiogenesis and supporting tissue regeneration [26–28].

Beyond inorganic doping, MBGs can also host biomolecules, such as drugs, within their mesoporous channels [1,5,6,29]. This dual strategy, combining inorganic and organic therapeutic agents, enables the design of composite drug delivery systems (DDSs) with finely tuned and localized release profiles. Gentamicin (GENTA), a widely used aminoglycoside antibiotic with strong bactericidal activity and high local efficacy for preventing postoperative bone infections [30,31], has already been successfully loaded into MBGs–Ce [32], demonstrating sustained release and long-lasting antibacterial activity. Anti-inflammatory drugs such as ibuprofen (IBU) [33,34], which exhibit potent anti-inflammatory effects and inhibit prostaglandin synthesis, and analgesics such as paracetamol (PARA) [35,36], known for their central

Table 5

Inhibition halo diameters (mm) measured against *Escherichia coli* ATCC 8695 for gentamicin-loaded undoped, single-ion-doped, and double-ion-doped MBGs, as a function of pre-soaking time in simulated body fluid (0–10 days). Disks containing 10 µg of gentamicin were used as positive controls. Values are reported as mean diameters ± standard deviation. Different letters indicate statistically significant differences among different MBG preparations, as determined by one-way ANOVA followed by Tukey's post-hoc test ($p < 0.05$). Asterisks indicate statistically significant differences compared with the corresponding day 0 value, as determined by one-way ANOVA followed by Dunnett's post-hoc test ($p < 0.05$). The persistence of measurable inhibition halos demonstrates that the MBGs retained residual antibacterial activity under simulated physiological conditions, whereas the reduction in halo diameter after SBF pre-soaking indicates a decrease in the amount of available gentamicin retained by the materials.[#] Data already published in a previous paper [32].

TiIs	MBGs	Time (days)					
/	/	0	1	2	3	7	10
Ce	Control	17.0 ± 0.3	/	/	/	/	/
	MBG [#]	18.0 ± 0.5 ^a	16.0 ± 0.6*	15.0 ± 0.8*	15.0 ± 0.5*	13.0 ± 0.8*	13.0 ± 0.5*
	MBG3.6-Ce	17.0 ± 0.6 ^a	16.0 ± 0.3*	16.0 ± 1.0	15.0 ± 0.5*	14.0 ± 0.8*	13.0 ± 0.3*
Cu	MBG5.3-Ce [#]	17.0 ± 1.3 ^a	15.0 ± 0.6*	16.0 ± 1.0	15.0 ± 0.8*	14.0 ± 0.6*	13.0 ± 0.3*
	MBG3.6-Cu	17.8 ± 0.3 ^a	10.0 ± 0.0*	9.5 ± 0.6*	9.5 ± 0.0*	10.0 ± 0.0*	9.3 ± 0.3*
	MBG3.6-Ce/Cu	11.3 ± 0.9 ^{d,e,f}	10.5 ± 1.7	9.5 ± 0.6*	9.0 ± 0.0*	9.0 ± 1.2*	9.5 ± 1.7*
Ag	MBG2.6-Ag	14.3 ± 0.9 ^b	8.0 ± 1.2*	8.8 ± 0.9*	8.0 ± 0.6*	6.8 ± 1.4*	8.0 ± 0.0*
	MBG2.6-Ce/Ag	13.8 ± 0.3 ^{b,c}	9.5 ± 0.0*	9.3 ± 0.3*	9.8 ± 0.9*	8.5 ± 0.6*	9.3 ± 0.9*
	MBG3.6-Mg	11.0 ± 0.0 ^{e,f}	7.3 ± 0.3*	8.5 ± 0.6*	7.3 ± 0.3*	7.5 ± 0.6*	7.3 ± 0.3*
Mg	MBG3.6-Ce/Mg	13.0 ± 0.6 ^{b,c}	12.8 ± 2.6	11.0 ± 1.7	9.3 ± 0.3*	9.0 ± 0.0*	8.3 ± 0.3*
	MBG5.3-Mg	10.5 ± 0.6 ^f	8.3 ± 0.3*	8.5 ± 0.6*	7.3 ± 0.9*	8.0 ± 0.0*	8.5 ± 0.6*
	MBG5.3-Ce/Mg	12.3 ± 0.9 ^{c,d,e}	9.8 ± 1.4	8.3 ± 0.3*	4.8 ± 2.6*	5.8 ± 2.6*	5.0 ± 2.3*
Sr	MBG3.6-Sr	12.8 ± 0.3 ^{b,c,d}	11.5 ± 0.9	11.3 ± 1.2	9.3 ± 0.6*	9.7 ± 0.6*	9.3 ± 0.3*
	MBG3.6-Ce/Sr	16.2 ± 0.5 ^a	11.5 ± 0.6*	11.7 ± 0.6*	9.7 ± 0.3*	11.2 ± 1.0*	10.2 ± 0.6*
	MBG5.3-Sr	6.5 ± 0.8 ^g	5.7 ± 0.9	5.7 ± 1.0	4.8 ± 0.3	5.0 ± 0.8	5.3 ± 0.3
	MBG5.3-Ce/Sr	17.8 ± 0.8 ^a	10.8 ± 0.8*	11.5 ± 0.9*	10.2 ± 0.8*	10.0 ± 1.0*	9.8 ± 1.0*

pain-modulating and antipyretic properties also hold significant interest, particularly for the management of pain and inflammation following surgery [12]. In previous studies [12,37], dual-loaded MBGs-Ce were obtained by separately loading the above-mentioned drugs (GENTA, IBU and PARA) and polyphenols (quercetin, 3-hydroxyflavone, morin hydrate and a natural mixture) into MBGs, followed by their combination in a 1:1 wt ratio to exploit their complementary therapeutic functionalities.

As recently discussed by Zhu et al., [38] mesoporous silica BGs have been widely explored as platforms for the co-delivery of therapeutic ions and biomolecules, owing to their high surface area and tuneable porosity. Although these co-delivery strategies have demonstrated promising synergistic effects, their application has been predominantly investigated in oncological contexts. Within MBGs, most reported systems rely on the combination of a single TII with a single biomolecule or drug, typically following a dual-functional design aimed at coupling bioactivity with antimicrobial, osteogenic, or anti-inflammatory effects. In contrast, systems integrating multiple TIIs together with drug delivery functionalities within the same MBG platform remain far less explored. These limitations highlight the need for more systematic studies addressing the combined use of multiple therapeutic ions and drug-loaded MBG platforms, to better understand their mutual interactions and their impact on loading and release behaviour as well as on the resulting biological performance.

However, no comprehensive study has yet explored MBGs that combine double-ion doping with the loading of drugs, such as GENTA, IBU and PARA. A system of this kind would provide a multifunctional therapeutic approach, integrating antibacterial protection, modulation of inflammation, pain relief, mitigation of oxidative stress, and support for bone integration within a single biomaterial.

In this context, the aim of the present work is to synthesize MBGs doped with two TIIs and load them with one of the three clinically relevant drugs mentioned above.

The specific objectives of this study are to:

- investigate the drug-loading capacity and release kinetics for each drug;
- verify that the materials preserve their bioactivity and ability to induce HA formation.

Overall, these investigations aim to evaluate the feasibility and

potential of double-ion-doped, drug-loaded MBGs as multifunctional drug delivery platforms for orthopaedic and regenerative medicine applications.

2. Materials and methods

2.1. MBGs preparation, drug loading

MBGs were synthesized by the sol-gel EISA method as reported in our previous studies [8,10,12,13]. The investigated compositions included: the reference $\text{SiO}_2\text{-CaO-P}_2\text{O}_5\text{-(CeO}_2\text{)}_x$ ($x = 0, 3.6$ and 5.3 mol%) with Ce (NO_3)₃, as the precursor, and the double-ion compositions $\text{SiO}_2\text{-CaO-P}_2\text{O}_5\text{-CeO}_2\text{-(Y)}$ ($Y = \text{CuO, Ag}_2\text{O, MgO, SrO}$) with $\text{Cu(NO}_3)_2$, AgNO_3 , $\text{Mg(NO}_3)_2$ and SrCl_2 as precursors. Tetraethyl orthosilicate (TEOS), triethyl phosphate (TEP) and $\text{Ca(NO}_3)_2 \cdot 4\text{H}_2\text{O}$ were used as Si, P and Ca precursors, while Pluronic P123 served as the structure directing agent. The mixture was magnetically stirred for 24 h, then poured into Petri dishes and left to undergo solvent evaporation and gelation. The obtained dried gels were calcined in air at 700 °C for 3 h. All MBGs were sieved to obtain powders in the range 212–355 µm. Table S1 reports the nominal compositions of the studied MBGs.

A 2 mg/mL IBU solution was prepared by dissolving the drug in heptane under magnetic stirring for 30 min, followed by immersion of 0.1 g of MBGs in 10 mL of the solution at 25 °C for 6 h.

A 5 mg/mL PARA solution was prepared in ethanol, and drug loading was performed by soaking 0.1 g of MBGs in 20 mL of the solution at 25 °C for 24 h.

A 0.8 mg/mL GENTA solution was prepared in Milli Q water, and drug loading was performed by soaking 0.1 g of MBGs in 10 mL of the solution at 25 °C for 24 h.

2.2. Characterization techniques

2.2.1. Elemental analyses (AE)

Elemental analysis (EA) was performed using a FLASH 2000 Thermo Fisher analyser to quantify the biomolecules loaded onto the MBGs-Ce by measuring the carbon content (%C). The results for each biomolecule are expressed as loading content (LC, %) and loading efficiency (LE, %), calculated as follows, where m represents mass. All values are based on three replicate experiments.

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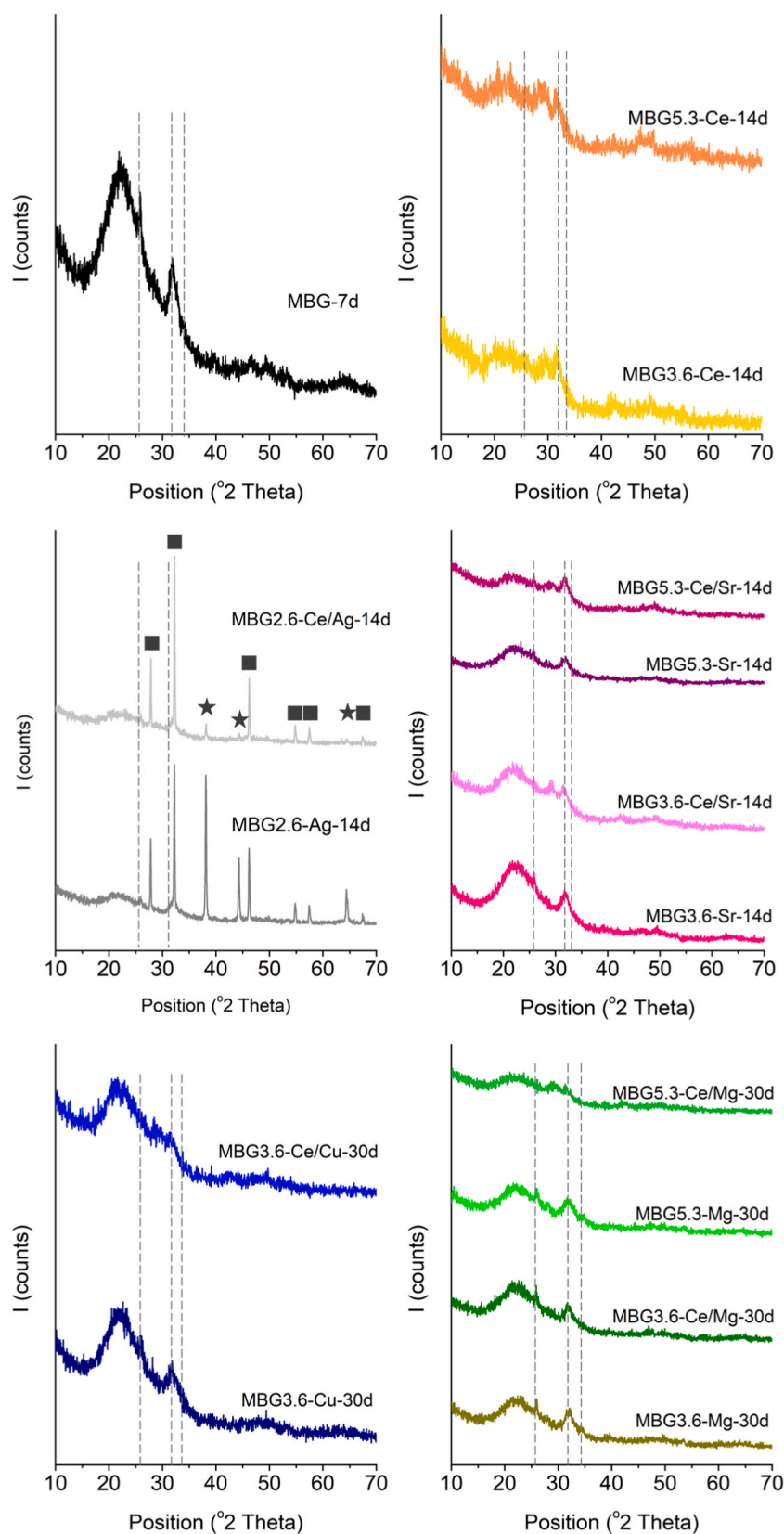


Fig. 1. XRPD patterns of MBG, MBGs-Ce and MBGs-double ions, loaded with IBU, after 7-14-30 days of SBF soaking. Dotted lines: HA; star: metal Ag (JCPDS 00-004-0783); square: AgCl (JCPDS 00-031-1238) [38].

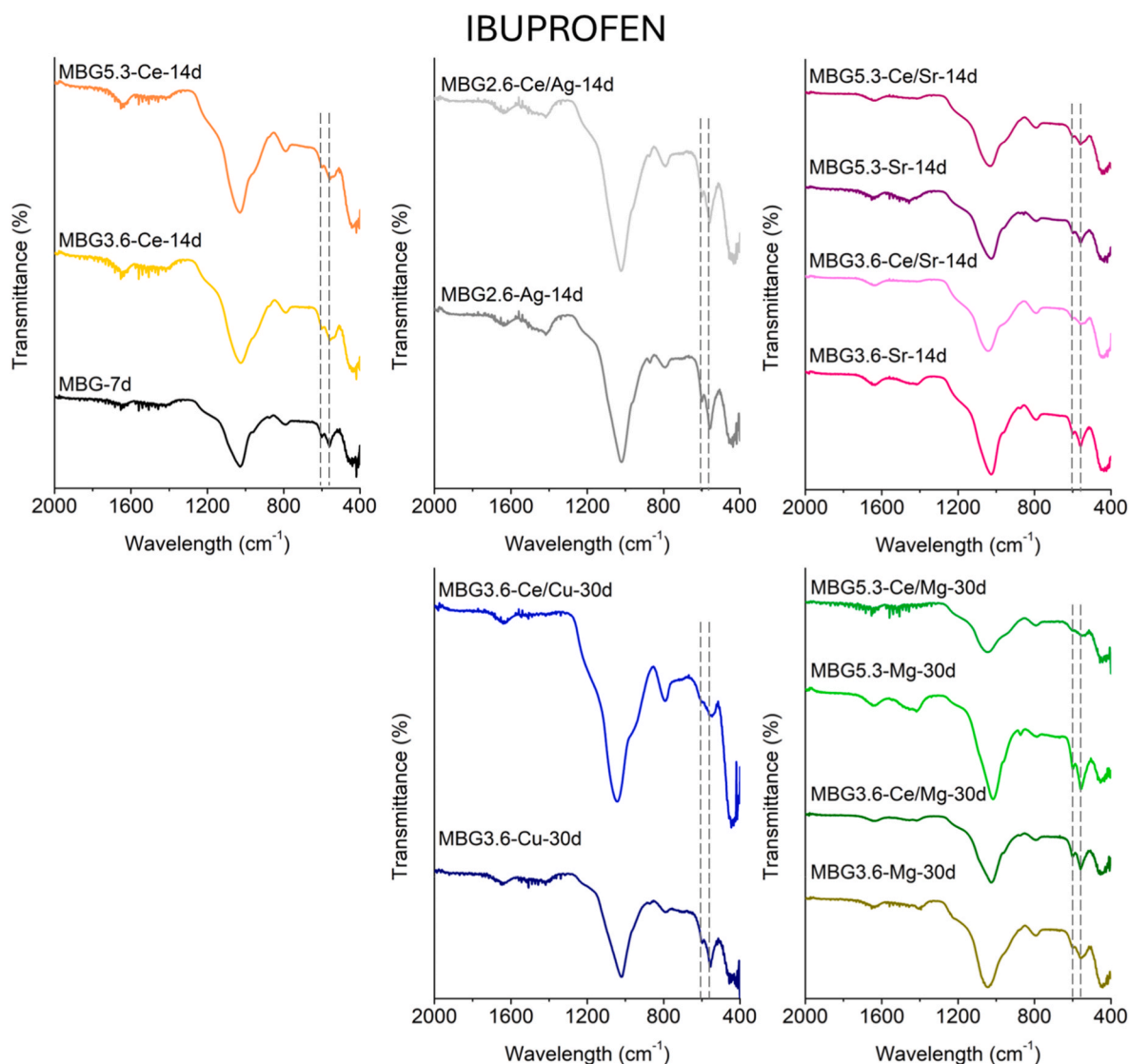


Fig. 2. FT-IR spectra of MBGs, MBGs-Ce and MBGs-double ions, loaded with IBU, after 7–14–30 days of SBF soaking. Dotted lines: HA.

$$LC(\%) = \frac{MM(\text{biomolecule})}{n^{\circ} \text{ of } C \text{ (C into biomolecule)} \times MA(C)} \times C(\%)$$

$$LE(\%)^* = \frac{m(\text{biomolecule loaded})^*}{m(\text{biomolecule loading solution})} \times 100$$

* Derived from LC (%).

2.2.2. Specific surface area determination (SSA)

SSA was evaluated before and after loading to assess possible textural changes resulting from the process. SSA was determined by nitrogen adsorption using a Micromeritics Chemisorb 2750 porosimeter and the Brunauer–Emmett–Teller (BET) method.

2.2.3. Drugs release profile

The drugs release profiles in simulated body fluid (SBF) were evaluated by UV–Vis spectrophotometry (JASCO V-570, Mettler Toledo, Columbus, Ohio, United States) or HPLC analysis. The measurements were carried out in SBF to simulate the physiological environment in which these materials are intended to be implanted. For UV–Vis analyses, IBU and PARA were monitored at 265 nm and 243.5 nm, respectively. The samples were immersed in SBF for 1, 3, 6, 24, 48, 168 and 336 h to evaluate the release kinetics over time. For each time point,

independent experiments were performed using separate MBG-drug/SBF systems prepared under identical conditions. All samples were prepared using drug-loaded MBGs derived from the same batch, ensuring consistent loading content across experiments.

The percentage of drug release was calculated based on the experimentally determined loading content (LC%) obtained from elemental analysis, according to the following equation:

$$\% \text{ release} = \frac{m_{\text{released}}(t)}{m_{\text{loaded}}} \times 100$$

where m_{loaded} represents the total amount of drug incorporated into the MBG and $m_{\text{released}}(t)$ is the amount of drug quantified in the SBF at each time point and corrected for the total volume of SBF.

For GENTA, HPLC analyses were conducted after soaking in SBF for 1, 3, 6, 24 and 48 h, under the same conditions previously reported [32]. SBF samples (1 mL) were freeze-dried to achieve complete solvent removal and reconstituted in 60 μL of mobile phase. Twenty microliters were injected into an Agilent 1120 Infinity II system (Agilent Technologies, Santa Clara, USA) equipped with an evaporative light scattering detector (ELSD). Chromatographic separation was achieved at 60 $^{\circ}\text{C}$ on a Kinetex® C18 column (5 μm , 100 $\text{\AA}$; Phenomenex S.r.l., Milan, Italy) using water containing 35.4 $\mu\text{g/mL}$ TCA, 0.89 $\mu\text{L/mL}$ of TFA, 0.5%

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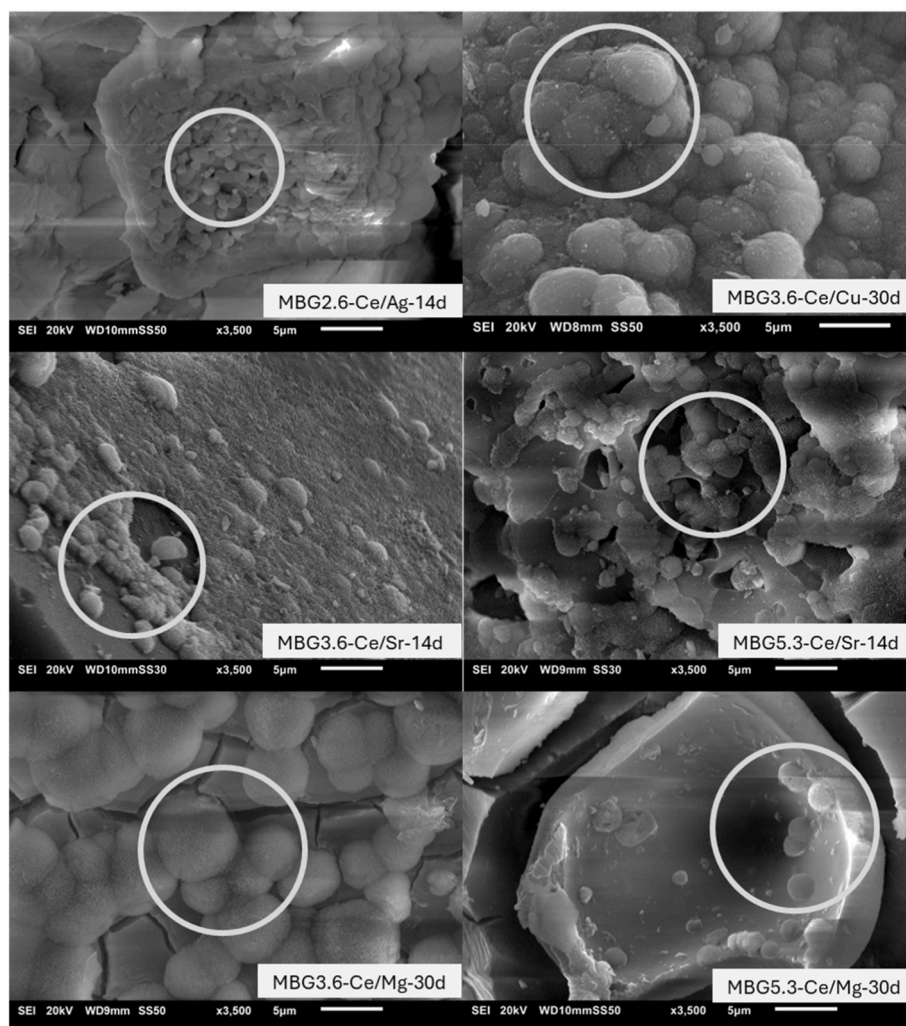


Fig. 3. SEM micrograph of MBGs-double ions, loaded with IBU, after 14 and 30 days of SBF soaking.

methanol, and 0.5% acetonitrile as the mobile phase, at a flow rate of 1.1 mL/min. The ELSD was operated with nitrogen as the carrier gas (1.60 slm); both nebulizer and evaporator temperatures were set at 50 °C, and the detector gain was set to 5. Quantification was performed using an external calibration curve prepared with gentamicin standard solutions in the concentration range of 50–200 µg/mL.

2.2.4. Antibacterial assays of gentamicin-loaded MBGs

The antibacterial activity of double-ion-doped MBGs loaded with GENTA was assessed using a modified Kirby–Bauer agar diffusion assay, which provides a semi-quantitative method to compare the antibacterial performance of the different samples under diffusion-controlled conditions. Briefly, 10 mg of each sample was deposited in a single spot onto Petri dishes containing 15 mL of Tryptic Soy Agar (TSA; 15 g/L tryptone, 10 g/L soy peptone, 5 g/L NaCl, and 15 g/L agar). A disk containing 10 µg of GENTA was placed on each plate as a positive control for bacterial growth inhibition. Subsequently, 10 mL of molten TSA maintained at 45 °C was inoculated with fresh overnight cultures of *Escherichia coli* ATCC 8695, to obtain a final bacterial concentration of approximately 10^6 CFU/mL. The inoculated agar was gently poured over the plates and allowed to solidify. After overnight incubation at 37 °C, antibacterial activity was evaluated by measuring the diameters of the inhibition halos surrounding the samples. The tests were

performed on undoped, Ce-doped, and double-ion-doped MBGs, and on the corresponding drug-loaded MBGs to evaluate the combined effect of ion release and drug delivery. To assess the functional persistence of antibacterial properties under simulated physiological conditions, selected samples were immersed in SBF for periods ranging from 1 to 10 days before testing. Antibacterial assays were then repeated to verify the retention of antimicrobial activity after SBF pre-soaking. Inhibition halo diameters are reported as mean values $\pm$ standard deviation (mm) from at least three independent experiments.

Statistical analysis was carried out using one-way ANOVA followed by Tukey's post-hoc test ($p < 0.05$). Significant differences compared with the corresponding day 0 value, were determined by one-way ANOVA followed by Dunnett's post-hoc test ($p < 0.05$). The persistence of measurable inhibition halos demonstrates that the MBGs retained residual antibacterial activity under simulated physiological conditions, whereas the reduction in halo diameter after SBF pre-soaking indicates a decrease in the amount of available gentamicin retained by the materials.

2.2.5. In vitro bioactivity assessment

All MBGs were soaked in SBF at 37 °C for 7, 14 and 30 days to assess the formation of an apatite layer, primarily composed of $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ (hydroxyapatite, HA) which indicates the bioactivity

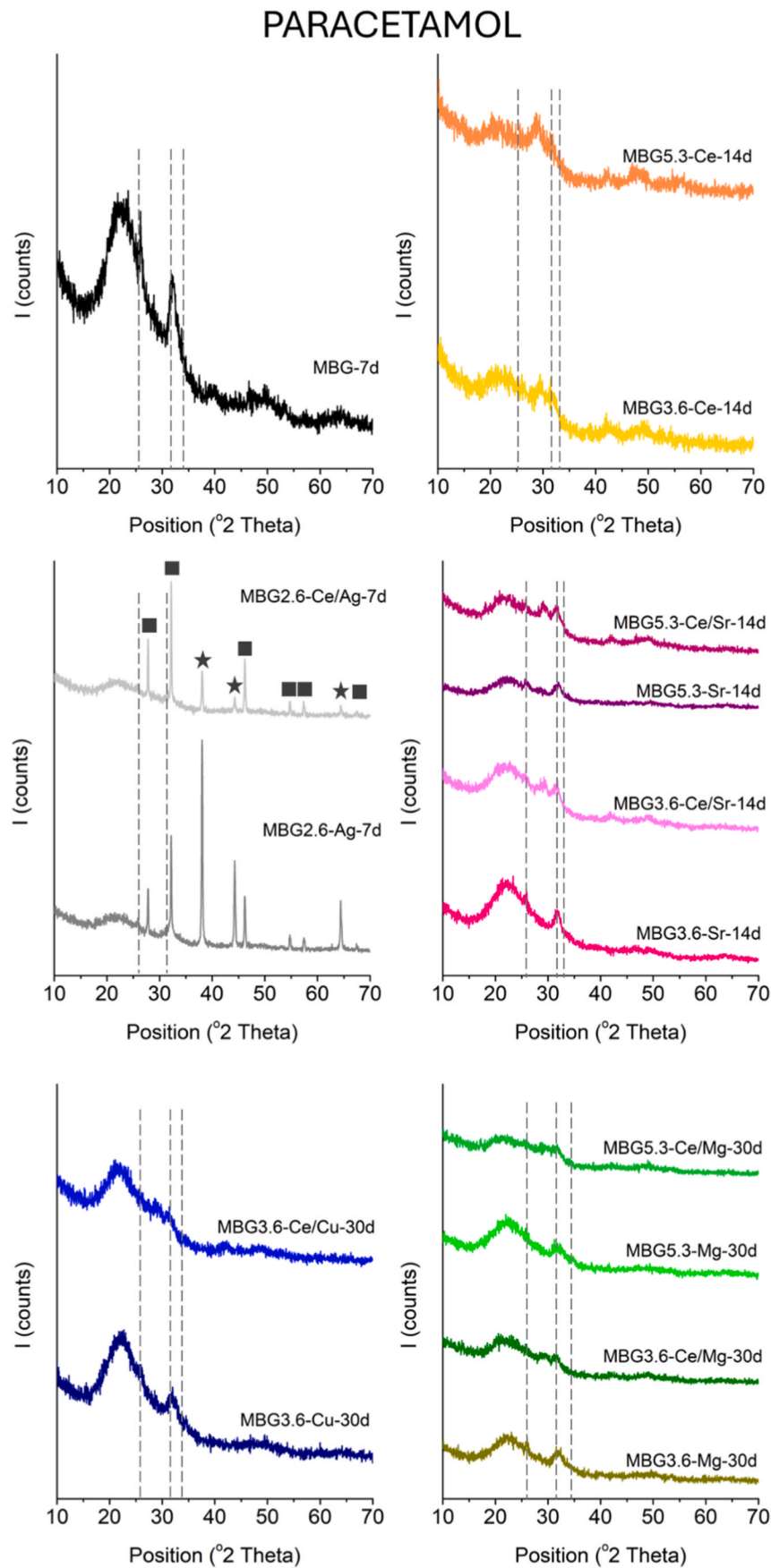


Fig. 4. XRPD patterns of MBG, MBGs-Ce and MBGs-double ions, loaded with PARA, after 7-14-30 days of SBF soaking. Dotted lines: HA; star: metal Ag (JCPDS 00-004-0783); square: AgCl (JCPDS 00-031-1238) [40].

PARACETAMOL

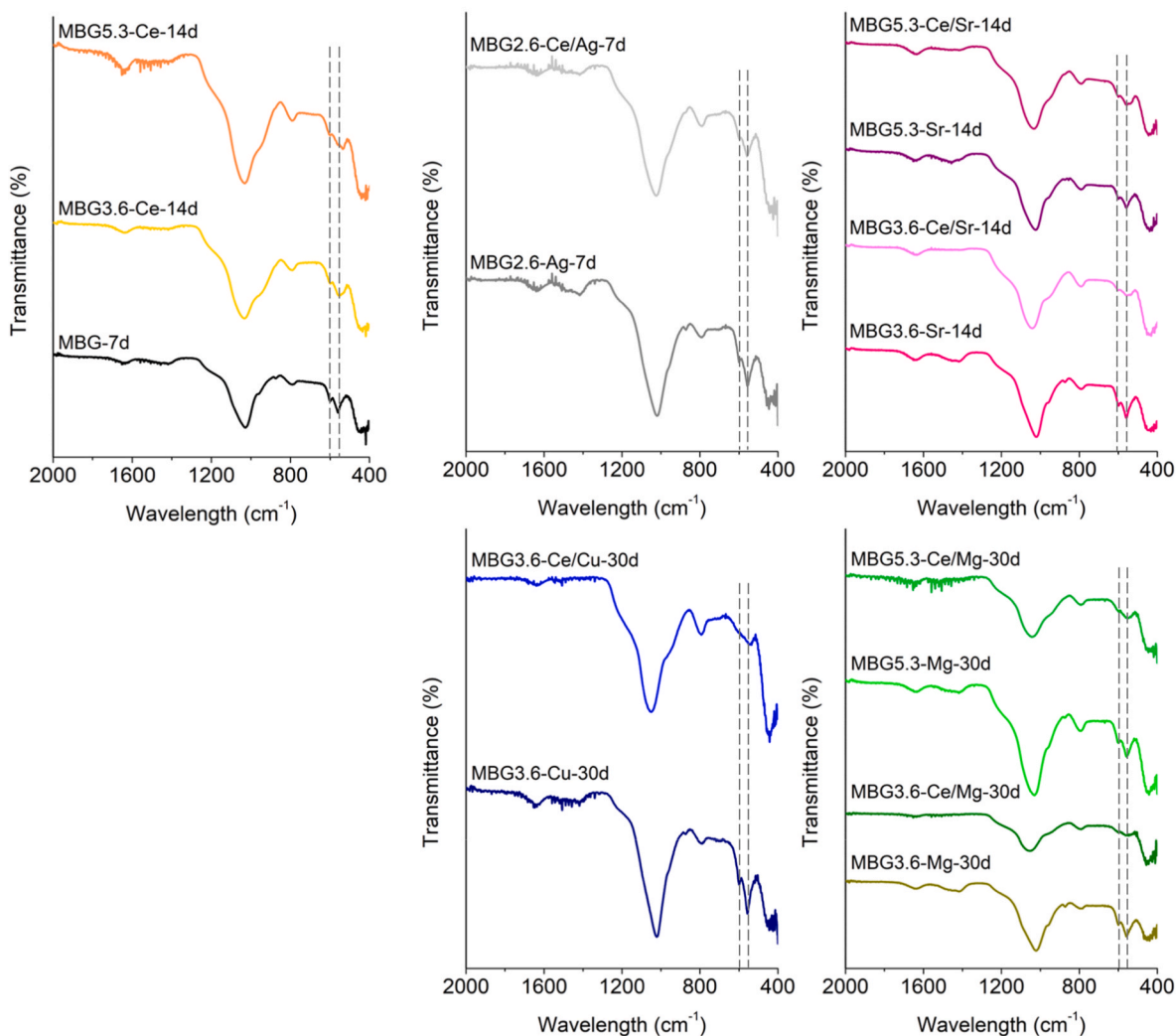


Fig. 5. FT-IR spectra of MBGs. MBGs-Ce and MBGs-double ions. Loaded with PARA. after 7–14–30 days of SBF soaking. Dotted lines: HA.

of the materials even after biomolecule loading.

After soaking, the samples were characterized by:

- X-Ray Powder Diffraction (XRPD), using an Empyrean MultiCore 3rd generation diffractometer (Malvern Panalytical, Malvern, United Kingdom) to verify the presence of crystalline HA;
- Fourier Transform Infrared (FTIR) spectroscopy with a Perkin Elmer FT-IR 160 spectrometer (Waltham, Massachusetts, United States) to identify characteristic bands of HA;
- Scanning Electron Microscopy (SEM) with a JEOL JSM-6010LA microscope (equipped with Electron Dispersive Spectroscopy, EDS, Leica Microsystems Wetzlar, Germany) to evaluate morphological changes on the surface.

3. Results and discussion

3.1. Loading evaluation

The MBGs were loaded with three drugs. Regarding drug loading (Table 1), the values obtained for IBU (LC: 2.3–10.7%, LE: 11.5–53.3%), PARA (LC and LE: 0.3–1.3%), and GENTA (LC: 1.2–5.4%, LE: 14.9–66.0%) agree with previously reported results [12,32]. Overall, IBU shows the highest LC% among the investigated drugs, followed by

GENTA, while PARA exhibits consistently low values across all compositions. Concerning ion doping, for IBU, an increase in the total dopant content generally leads to a decrease in drug loading. In addition, the type of dopant ion affects loading: Sr-double-doped MBGs show markedly lower loading; interestingly, Ce co-doping partially improves IBU loading in some compositions. For GENTA, loading is less affected by composition, although a slight decrease is observed in dual-doped systems, while PARA remains poorly loaded regardless of doping. Overall, no clear linear correlation is observed, but higher dopant content tends to reduce loading, and the nature of the ion plays a key role in modulating drug–MBGs interactions.

The SSA study (Table 2) allows the evaluation of the effect of drug loading and the presence of dopant ions. In all compositions, drug-loaded MBGs exhibit lower SSA values than their corresponding unloaded (UL) counterparts, consistent with partial pore filling and surface coverage. In general, the order of SSA reduction, from highest to lowest, can be indicated as follows: IBU > GENTA > PARA, apart from some minor differences that fall within the experimental error. These trends are in good agreement with the corresponding LC and LE results. Regarding the incorporation of a second dopant ion, as already discussed previously [13], no significant variations are generally observed compared to the initial SSA value of MBG (340 m²/g). Only Ag-based glasses show lower values, for example 219 m²/g for MBG2.6, which

PARACETAMOL

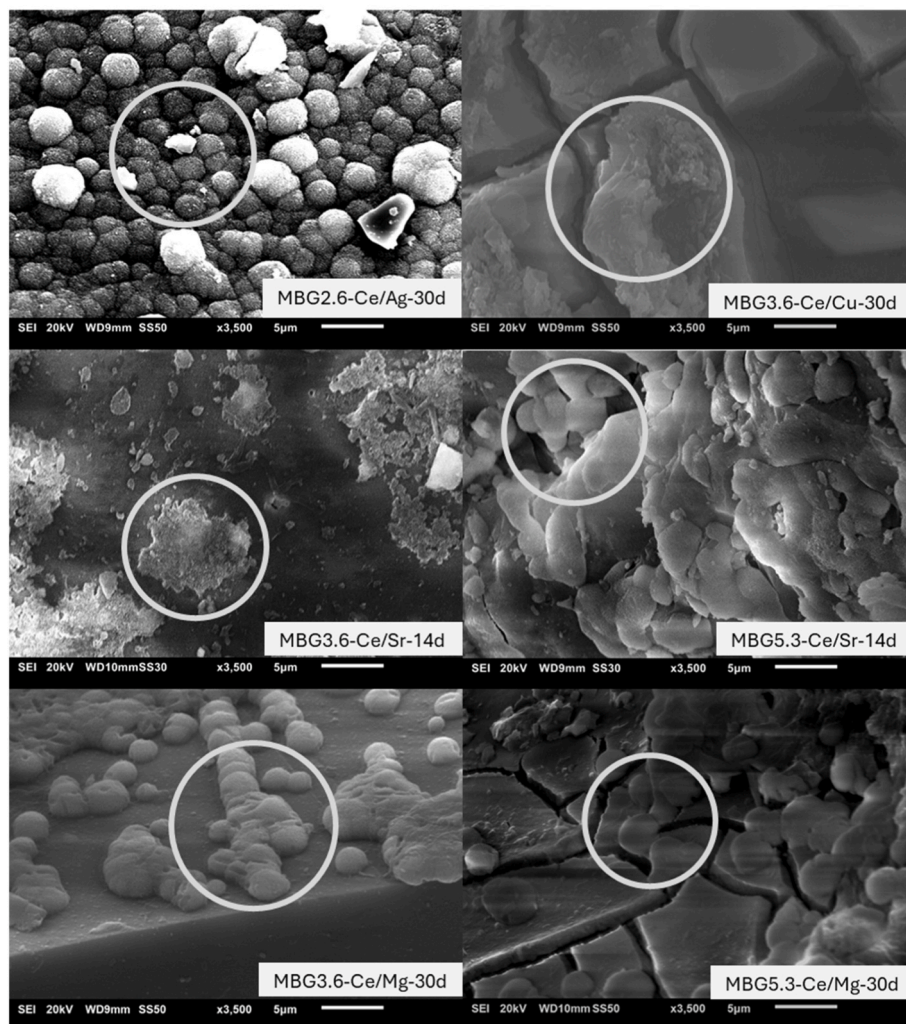


Fig. 6. SEM micrograph of MBGs-double ions, loaded with PARA, after 14 and 30 days of SBF soaking.

nevertheless still ensure a mesoporous structure.

3.2. Evaluation of drug release

The release profiles of IBU and PARA from MBGs, expressed as release percentages as a function of time, show a strong dependence on both glass molar composition and dopant ion chemistry (Tables 3 and 4). In Fig. S1–4, it is possible to observe the $\mu\text{g/mL}$ of drug released from the different samples and the percentage of release over time.

The undoped MBG exhibits a relatively fast initial IBU release, reaching ~ 70 – 75% within 24 h, followed by a plateau at moderate release values (~ 54 – 66%) up to 336 h, indicating partial and weakly sustained release. In contrast, Ce-containing MBGs exhibited higher and more complete IBU release than the corresponding undoped formulation. MBG3.6-Ce reaches 100% release after 48 h, while MBG5.3-Ce achieves complete release already at 1 h and maintains this level throughout the experiment, suggesting that the presence of cerium may influence IBU desorption and diffusion from the mesoporous matrix. Cu-doped MBGs display a gradual and sustained release behaviour, with MBG3.6-Cu reaching $\sim 86\%$ at 24 h and approaching full release ($\sim 99\%$) only at 336 h. Notably, Cu/Ce co-doped MBGs exhibit accelerated release kinetics, with MBG3.6-Ce/Cu showing higher initial release ($\sim 70\%$ at 1 h) and near-complete release ($\sim 96\%$) at prolonged

times, suggesting that the presence of cerium may contribute to the observed increase in enhancing IBU release. Ag-doped systems exhibit reduced and slower IBU release, with MBG2.6-Ag reaching only $\sim 64\%$ at 24 h and remaining below $\sim 75\%$ even at 336 h. This effect is further intensified in the Ce/Ag co-doped composition, which shows consistently lower release values (~ 60 – 68%), supporting the presence of strong drug–matrix interactions that hinder IBU diffusion. Mg-doped MBGs present a composition-dependent behaviour: MBG3.6-Mg reaches $\sim 70\%$ release at 24 h, whereas MBG5.3-Mg shows faster and more extensive release, exceeding 90% within 6 h. Co-doping with cerium results in more moderate profiles, with Ce/Mg systems exhibiting ~ 60 – 70% release at 24 h, suggesting a balance between improved drug loading and controlled release. Sr-doped MBGs show intermediate and relatively stable release kinetics (~ 60 – 75%), while Ce/Sr co-doped samples display higher initial release (up to $\sim 85\%$ at 1 h) and increased overall release, indicating that cerium-containing formulations are associated with higher IBU release even in the presence of strontium.

PARA release is generally faster and more complete than that of IBU across all compositions. The undoped MBG shows very rapid release, reaching $\sim 100\%$ within the first 6 h, indicative of weak drug–matrix interactions and predominantly surface-associated loading. Ce-containing MBGs also achieve complete PARA release, although with a

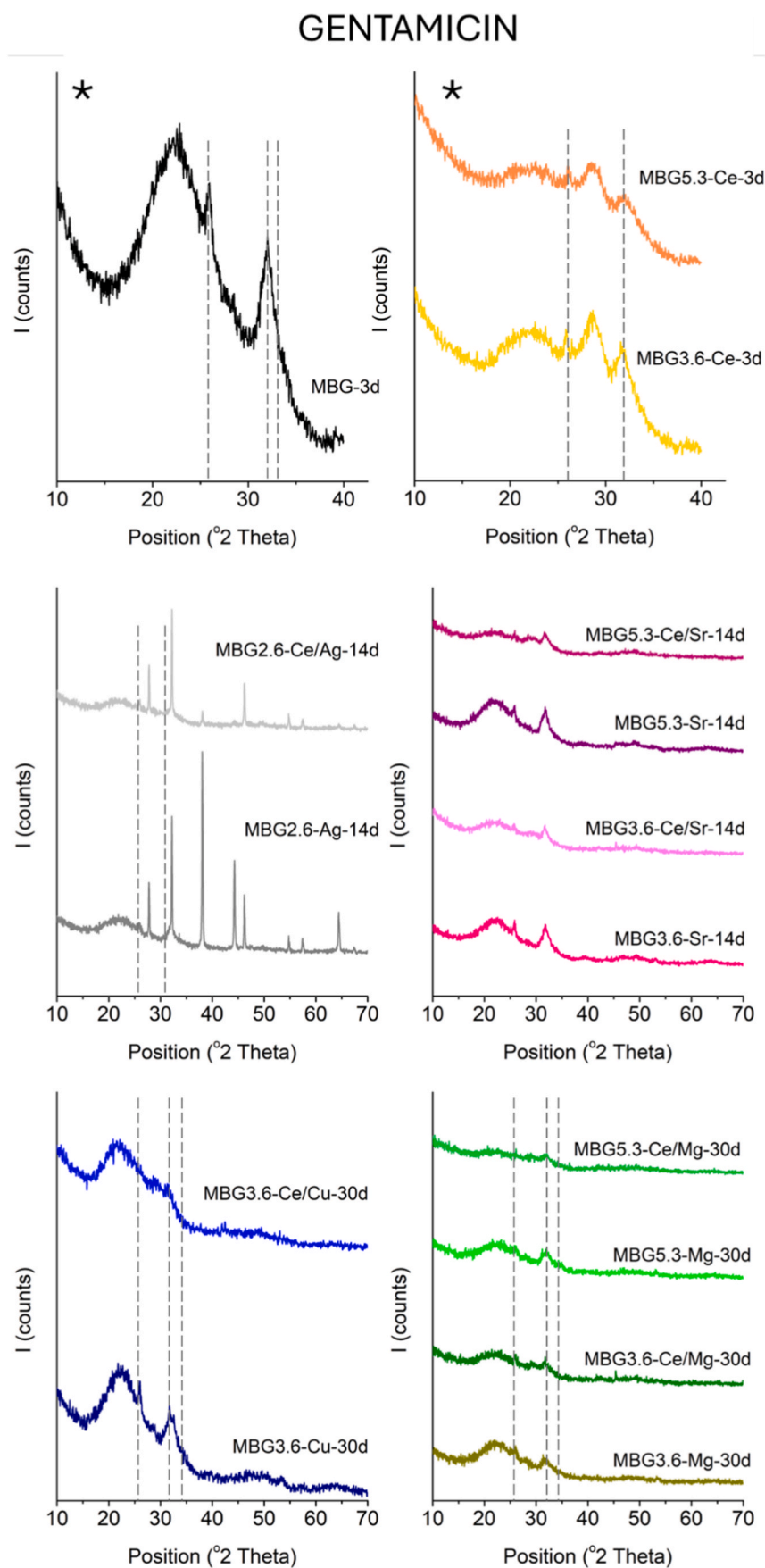


Fig. 7. XRPD patterns of MBG, MBGs-Ce and MBGs-double ions, loaded with GENTA, after 3-14-30 days of SBF soaking. Dotted lines: HA; star: metal Ag (JCPDS 00-004-0783); square: AgCl (JCPDS 00-031-1238) [40]. *Data already published [32].

GENTAMICIN

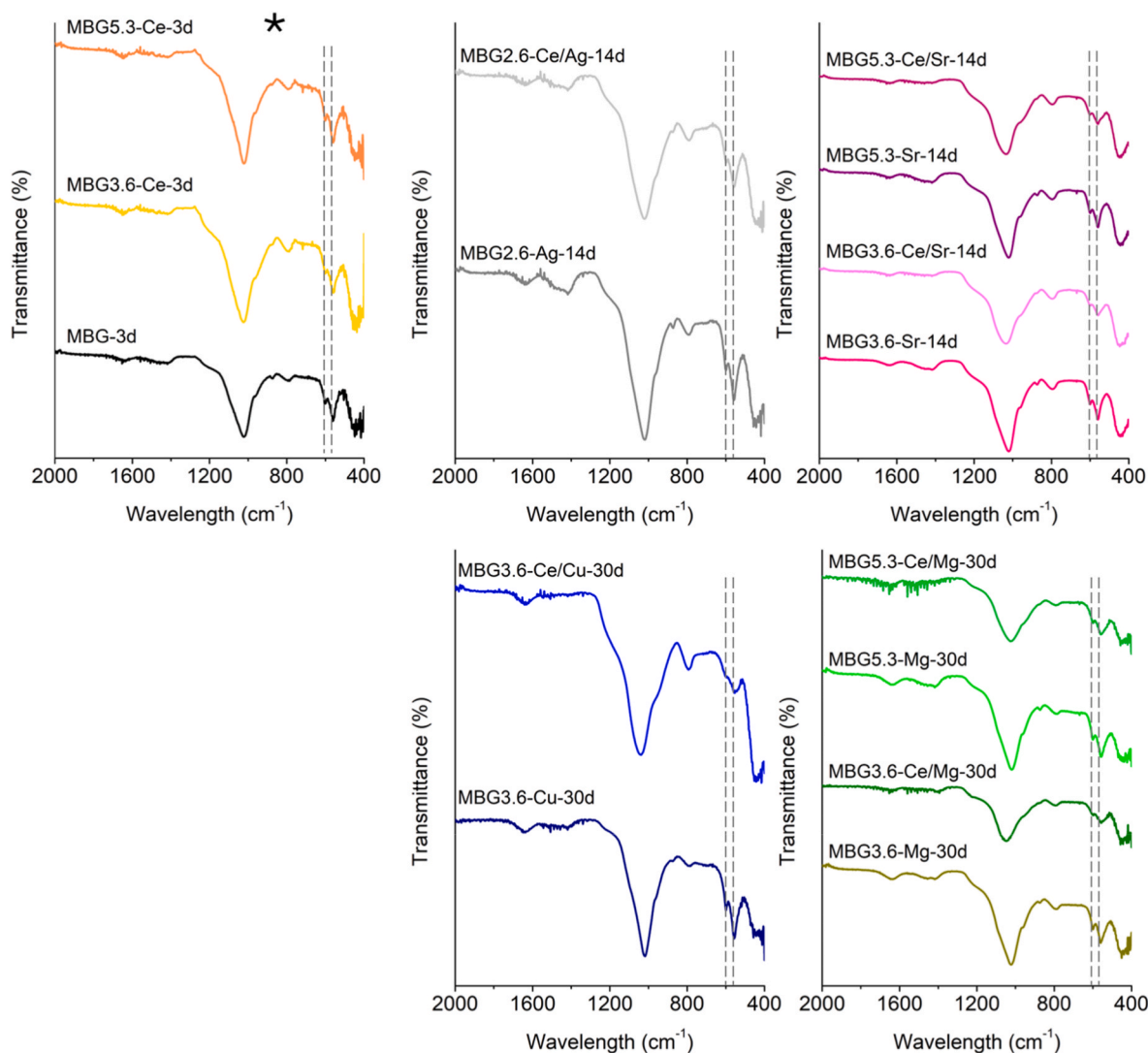


Fig. 8. FT-IR spectra of MBGs. MBGs-Ce and MBGs-double ions. Loaded with GENTA. after 3–14–30 days of SBF soaking. Dotted lines: HA. *Data already published [32].

slight delay: MBG3.6-Ce reaches 100% at 48 h, while MBG5.3-Ce achieves full release by 24 h.

Cu-doped MBGs exhibit similarly rapid release kinetics, with both MBG3.6-Cu and MBG3.6-Ce/Cu reaching 100% PARA release within 6–24 h, indicating that copper does not significantly hinder PARA diffusion from the mesoporous structure. In contrast, Ag-doped systems show markedly slower and incomplete PARA release, with MBG2.6-Ag reaching only ~14% and MBG2.6-Ce/Ag ~26% even after 336 h, highlighting strong interactions between PARA and the Ag-containing matrix.

Mg-doped MBGs display moderate and sustained PARA release, with MBG3.6-Mg reaching ~45% and MBG5.3-Mg ~38% at prolonged times. Co-doping with cerium further suppresses PARA release, with Ce/Mg systems remaining below ~20% at 336 h, indicating enhanced drug retention within the mesoporous network. Sr-doped MBGs show intermediate PARA release (~40–50%), while Ce/Sr co-doped systems exhibit higher and more sustained release, particularly at longer times (up to ~86%); suggesting that the presence of cerium may partially offset the retention effect observed in Sr-containing formulations.

These results indicate that IBU and PARA release kinetics are

influenced by the ionic composition of the MBGs. While PARA generally exhibits faster and more complete release than IBU, dopant ions such as Ag and Mg significantly reduce drug release, whereas the presence of cerium is often associated with higher release values and may influence the effects of other dopants on drug delivery behaviour.

All SBF samples collected after soaking GENTA-loaded MBGs showed gentamicin concentrations below the limit of detection (LOD = 0.050 mg/mL) of the analytical method, indicating minimal release over the 1–10-day period. Assuming an average drug loading of 2%, less than 10% of the GENTA was released during the SBF test. The limited liberation of GENTA prevented the detection of any significant differences in release behaviour among the differently doped MBGs.

Compared with the consistent release of ibuprofen and paracetamol, the markedly lower desorption of GENTA (<10% in 10 days) is most likely associated with strong electrostatic interactions with the negatively charged MBG surface, due to its polycationic nature and the presence of multiple protonable amino groups. These interactions, possibly combined with hydrogen bonding contributions, may enhance drug adsorption and reduce desorption kinetics. In contrast, paracetamol, with a predominantly neutral structure at physiological pH, and

GENTAMICIN

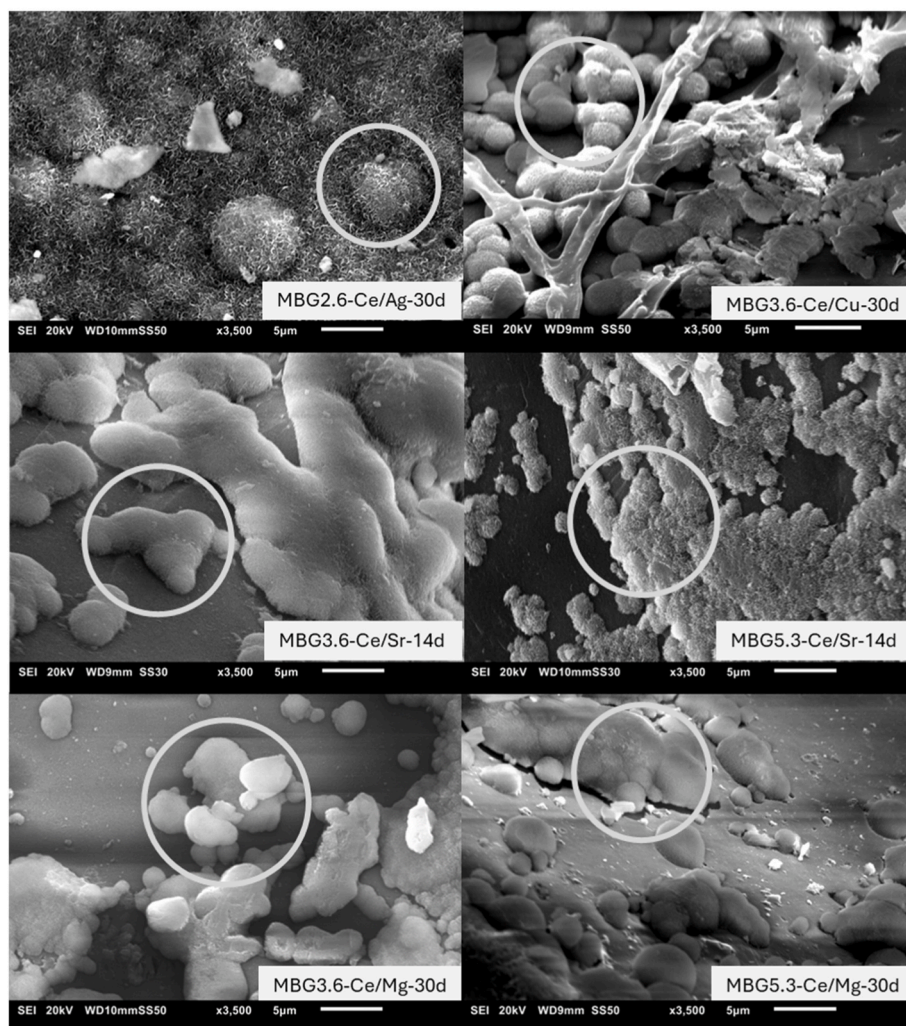


Fig. 9. SEM micrograph of MBGs-double ions, loaded with GENTA, after 14 and 30 days of SBF soaking.

ibuprofen, mainly present in its deprotonated form under the same conditions, exhibit weaker affinity toward the glass matrix, resulting in faster release profiles.

3.3. Antibacterial activity and persistence of GENTA-loaded MBGs

The antibacterial activity of GENTA-loaded MBGs was evaluated by agar diffusion assays against *Escherichia coli* ATCC 8695, and inhibition halo diameters are reported in Table 5, Fig. S5. All MBGs exhibited a clear inhibition zone, ranging from 6.5 to 18.0 mm, confirming the preservation of GENTA bioactivity after incorporation into the mesoporous structure. These results are consistent with previous reports on GENTA-loaded MBGs-Ce [32,37].

A general correlation between GENTA loading content (LC) and antibacterial efficacy was observed. Undoped MBG and single Ce-doped samples (MBG3.6-Ce and MBG5.3-Ce), which showed the highest LC values (up to 5.4%; Table 1), exhibited the largest inhibition halos (17.0–18.0 mm). Similarly, MBG3.6-Cu, characterized by relatively high LC (4.3%), displayed a pronounced inhibition halo (17.8 mm). Coherently, the incorporation of a second dopant ion generally reduced SSA and drug-loading efficiency (Section 3.1), resulting in smaller inhibition halos in double-doped systems. For example, MBG3.6-Ce/Cu and MBG3.6-Ce/Sr exhibited reduced antibacterial activity compared to

their single-doped counterparts. Although Cu and Ag are intrinsically antibacterial due to membrane damage, oxidative stress induction, and interference with essential cellular processes [19–22], the present results do not allow us to claim a clear synergistic effect between therapeutic ions and gentamicin. Under the experimental conditions used in this study, the antibacterial response appears to be mainly governed by the amount of gentamicin retained by, and released from, the MBG matrix rather than by ionic dissolution. This interpretation is also supported by previous results on the corresponding unloaded ion-doped glasses, which showed absent or very limited inhibition halos against *E. coli* [13]. Moreover, since ion release was not quantified in the present work, any contribution from Ag or Cu ions should be considered secondary and not sufficient to demonstrate synergy. Nevertheless, in Ag-containing samples, a compensatory contribution of silver cannot be excluded: despite their lower GENTA loading (LC ~ 1.4%), MBG2.6-Ag and MBG2.6-Ce/Ag maintained moderate inhibition halos (13.8–14.3 mm). Therefore, while no true synergistic amplification can be demonstrated, a compensatory contribution of silver may be suggested.

The persistence of antibacterial activity was assessed after soaking in SBF. Generally a more pronounced decrease in inhibition halo occurred within the first 24 h, followed by substantial retention of activity. Measurable inhibition halos were still present after 10 days, indicating

prolonged antibacterial functionality. HPLC analyses of the collected SBF solutions showed GENTA concentrations below the detection limit, indicating limited release under the tested conditions (<10% of loaded GENTA over 10 days). This apparent discrepancy can be explained by the different nature of the two assays: agar diffusion detects local antibacterial activity, whereas HPLC quantifies gentamicin released into the bulk SBF solution. Based on the loading values reported in Table 1 and on the 10 mg of GENTA-loaded MBGs used per test, up to 500 µg of gentamicin were present in each spot. Thus, even a small locally available fraction, not quantitatively detectable by HPLC, may be sufficient to diffuse from the MBG particles into the agar and inhibit bacterial growth. Moreover, this behaviour agrees with previous findings for GENTA-loaded MBGs [32] and can be explained by the coexistence of weakly and strongly bound GENTA within the mesoporous network. Weakly adsorbed molecules are likely released during the first hours of soaking, accounting for the initial decrease in activity, whereas strongly bound GENTA, retained through electrostatic interactions between the polycationic drug and negatively charged silanol groups, remains associated with the glass surface.

3.4. In vitro bioactivity assessment

We previously demonstrated [7,10,11] that cerium can be incorporated into the glass composition without completely suppressing its bioactivity; however, cerium tends to delay the formation of an apatite layer due to the precipitation of cerium phosphate. In a previous study, we also optimized the composition of double-ion-doped MBGs [13], demonstrating that an appropriate balance between the dopants allows the materials to retain their bioactivity. Additionally, we have shown that drug loading [12,32,37] can further slowdown apatite formation by reducing the available specific surface area (SSA). This effect may be associated with partial pore occupation and interactions between drug molecules and silanol-rich surfaces, which can temporarily limit ion exchange processes and delay calcium phosphate nucleation [39]. Considering these findings, the present work aims to evaluate the bioactivity of MBGs containing both double ionic doping and drugs, to assess whether the simultaneous presence of these components still allows the glass to maintain its bioactive behaviour.

3.4.1. IBU-loaded MBGs

XRPD patterns (Fig. 1) confirmed the presence of HA through characteristic peaks at 26, 31 and 33 (°2θ), in accordance with JCPDS card No. 00-009-0432 [40]. After 7 days in SBF, MBG-IBU system was bioactive; in contrast, MBGs-Ce systems required up to 14 days to develop detectable HA formation. A similar delay was observed for MBG2.6-Ag, MBG2.6-Ce/Ag, MBGs-Sr, and MBGs-Ce/Sr samples, for which 14 days in SBF were also necessary to detect HA precipitation. Conversely, systems containing Cu and Mg further slowed down the bioactive response, with HA formation becoming detectable only after 30 days of immersion. FT-IR spectra (Fig. 2) revealed characteristic HA bands at 605 and 565 cm⁻¹ [41], however, the MBG3.6-Ce/Cu and MBG5.3-Ce/Mg samples exhibited a more pronounced delay in the appearance of these bands compared to the other systems. SEM analysis of MBGs-double ions surfaces after 14 and 30 days in SBF (Fig. 3) revealed spherical HA aggregates (grey circles) and the corresponding Ca/P molar ratios are reported in Table S3.

3.4.2. PARA-loaded MBGs

PARA-loaded MBGs (XRPD and FT-IR, Figs. 4 and 5) exhibited similar overall trends, with PARA showing a stronger inhibitory effect on bioactivity than IBU in double-ion-doped samples, particularly in Ce/Mg and Ce/Cu systems, as well as in samples containing cerium as the sole dopant. SEM analysis (Fig. 6) revealed the presence of well-defined, spherical HA aggregates in the bioactive systems and the corresponding Ca/P molar ratios are reported in Table S3.

In contrast, for MBG3.6-Ce/Cu and MBG5.3-Ce/Mg samples, where

bioactivity was less evident, the surfaces were mainly characterized by degradation phenomena with only sparse and small HA aggregates.

3.4.3. GENTA-loaded MBGs

In previous studies [32,37], the ability of MBG, MBG3.6-Ce and MBG5.3-Ce samples loaded with gentamicin to maintain good bioactivity after only 3 days of immersion in SBF was already demonstrated. Similarly, in the present study, the behaviour of the double-ion samples, loaded with GENTA (XRPD and FT-IR, Figs. 7 and 8), is consistent with that observed with the two previously tested drugs: the simultaneous presence of both TIIs and the drug slows, but never fully inhibits, bioactivity. In Fig. 9 the formation of HA aggregates on the glass surface can be clearly observed and the corresponding Ca/P molar ratios are reported in Table S3.

4. Conclusions

In this work, advanced MBGs double-doped with cerium and a second TII (Cu, Ag, Mg, or Sr) were successfully synthesized and loaded with clinically relevant drugs, demonstrating the feasibility of integrating multiple therapeutic functionalities within a single platform.

Drug loading was strongly influenced by both composition and drug type. IBU exhibited the highest loading capacity (LC: 2.3–10.7%, LE: 11.5–53.3%), followed by GENTA (LC: 1.2–5.4%, LE: 14.9–66.0%), whereas PARA showed consistently low incorporation (LC ≤ 1.3%). Increasing dopant content generally reduced loading, while the nature of the co-dopant played a key role in modulating drug–matrix interactions.

Release studies in SBF confirmed that delivery behaviour can be effectively tuned through ionic doping. IBU release ranged from moderate to complete (~54–100% over 336 h), with Ce-containing formulations generally exhibiting higher release values (up to 100% within 1–48 h). PARA showed generally rapid release (up to ~100% within 6–24 h), although strong retention was observed in Ag- and Mg-containing systems. In contrast, GENTA exhibited very limited release (≤10% over 10 days), indicating strong interactions with the glass surface. GENTA-loaded MBGs displayed clear antibacterial activity against *Escherichia coli*, with inhibition halos ranging from ~6.5 to 18 mm and persisting after soaking in SBF.

All compositions retained their bioactivity, as demonstrated by hydroxyapatite formation after 7–30 days in SBF, confirming that drug loading and ion incorporation did not compromise the intrinsic bioactive behaviour of the MBG.

Although numerous studies have investigated either ion-doped MBGs or drug-loaded MBGs separately, and a limited number have explored single-ion co-doped systems, the simultaneous integration of double TII doping with the loading of clinically relevant drugs, together with a systematic evaluation of loading, release and post-loading bioactivity, remains largely unexplored. Overall, the combination of double-ion doping and drug loading represents a powerful strategy for designing multifunctional MBGs with tuneable therapeutic performance. These systems show strong potential for tissue regeneration, enabling the simultaneous delivery of antibacterial, anti-inflammatory and regenerative effects.

CRedit authorship contribution statement

Chiara Cavazzoli: Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Stefano Raimondi:** Investigation, Methodology, Resources, Writing – original draft, Writing – review & editing. **Sara Pedroni:** Data curation, Investigation, Methodology. **Alfonso Zambon:** Conceptualization, Data curation, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. **Gigliola Lusvardi:** Conceptualization, Data curation, Investigation, Methodology, Resources, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ceramint.2026.07.292>.

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