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Promising trends of bioceramics in the biomaterials field

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Abstract Biomedical scientific community is currently demanding new advances in the designing of 3rd generation bioceramics, which promote bone tissue regeneration. In the last years, the development of supramolecular chemistry and the application of organic-inorganic hybrid materials in the biomedical field have resulted in a new generation of advanced bioceramics, which exhibit fascinating properties for regenerative purposes together with the possibility of being used as carriers of biologically active molecules. This communication overviews the evolution occurred from the first silica based bioceramics to the last advances in the synthesis of bioceramics for bone tissue regeneration. A critical review concerning the first bioactive glasses as well as the newest hybrid bioactive materials and templated mesoporous bioactive systems, will be performed from the point of view of their potential applications as replacement materials in bone repair and regeneration.

1 Introduction

The progress regarding bioceramics for bone and dental tissue has experienced an outstanding development from the very first inert ceramics to the regenerative compounds currently developed. This progress responds to the scientific efforts for improving the tissue-material response after implantation, evolving from inert to bioactive behaviour and, finally to regenerative functions [1–4].

The first generation of bioceramics, named inert ceramics and represented by alumina (Al_2O_3) and zirconia (ZrO_2) played an important role for substitution purposes due to their low reactivity. By that time, the main goal was substitution with the lowest tissue response, perhaps because the only expected tissue response was inflammation and material rejection. However, the discovery of Bioglass by Prof. Hench in 1969 led to a shift in the perspectives regarding the reactivity at the tissue implant interface [5].

The scientific efforts made so far have resulted in a deep knowledge about silica derived bioactive materials, especially those synthesised through soft-chemistry routes such as the sol-gel process[6, 7] in ternary (SiO_2–CaO–P_2O_5) and binary (SiO_2–CaO) systems [8].

Finally we must highlight the topics concerning mechanical properties, the actual Achille's heel of bioactive glasses. In this sense, important advances have been made by means of the synthesis of organic–inorganic hybrids [9].

All these advances and experience contributed to the achievement of 3rd generation bioactive materials for regenerative purposes, as well as to their shaping into scaffolds for tissue engineering. At present, the scaffolds fabrication with appropriate meso and macroporosity, the control on the ionic exchange with the environment, the achievement of suitable mechanical resistance for surgery handling and, of course, the osteogenesis induction are attainable aims, thanks to the efforts made in past decades. This manuscript is an overview of some of the achievements in this field that contributed to this aim.

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2 Bioactive glasses: The ionic exchange significance

The ionic exchange was postulated as the first stage of the bioactive process. The dissolution of Ca^{2+} and Na^{+} cations from the glass to the surrounding fluid results in the H^{+} incorporation and the silanol formation at the glass surface. In 2000, Xynos [10, 11] proposed the ionic products of Bioglass dissolution as agents that increased the expression of an osteoblast mitogenic growth factor (IGF-II), suggesting that the ionic products leached during Bioglass dissolution exhibited a stimulatory effect on the osteoblast proliferation mediated by IGF-II. Thereafter, the same research group carried out a larger-scale genomic screening revealing that 45S5 dissolution increased the levels of 60 transcripts, many of them related with the bone tissue formation [12].

Whereas the significance of Ca and P in the process of bone mineralization was well established, a cellular receptor for Si had not been identified. However, these results agreed with those previously reported by Carlisle [13, 14] regarding the role of silicon during the first stages of bone maturation, as well as the bioactive enhancement of calcium phosphate bioceramics when Si is incorporated into the crystalline structure [15–18]. Therefore, the significance of ion exchange achieves another dimension beyond the initial stage of the bioactive process. The Bioglass ionic product promotes the gene up-regulation that results in an osteoblast proliferation, differentiation and, consequently leading to bone regenerative properties.

The silicon release as silicic acid ($Si(OH)_4$) involves not only the implant degradation but also an osteoproductive stimulus, and calculations of the activation energy for silica dissolution and its relationship with the bioactivity were considered [19, 20].

Figure 1 plots the activation energy (Ea) for the SiO_2 dissolution when soaking different melt-derived and sol-gel glasses into tris-buffer solution for 1 week. The Ea values for SiO_2 degradation closely correlates with the bioactivity rate of these glasses. Actually, the induction time for an apatite growth in these glasses decreases in the order 77S > 68S > 58S > 45S5. Those glasses with Ea for SiO_2 degradation higher than 0.35 eV (melt-derived 60S and sol-gel 91S) do not show bioactivity after 1 week in tris-buffer and/or simulated body fluid (SBF).

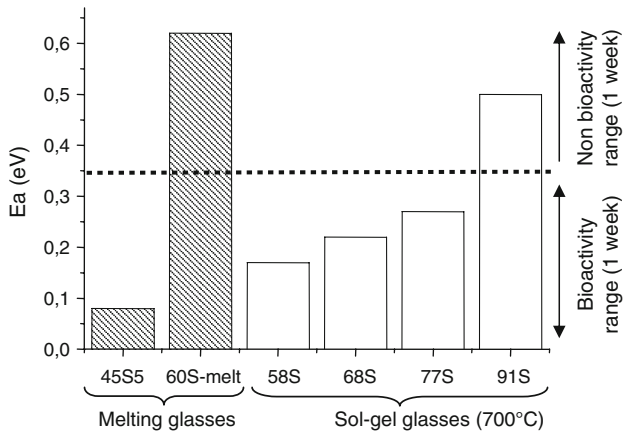

Fig. 1 Activation energy for SiO_2 network degradation in different glasses

3 Bioglass monoliths and scaffolds

Bioactive glasses have limited applications due to their brittleness, which reduce their clinical use within non-bearing sites such as periodontal defects, middle ear surgery and small bone filling in general. This fact results in a loss of their potential as bone regeneration material, since their implantation is not appropriate in those locations where a high amount of bone has been lost.

Some efforts have been aimed to obtain sol-gel bioactive glasses (with high surface area and porosity) with monolithic structure but suitable to be degraded under physiological conditions. Zhong and Greenspan [21, 22] reported on the use of high relative-humidity during the drying stage of sol-gel glasses to obtain crack-free structures. The moisture of the near-equilibrium drying step facilitates the reaction among the gel particles, resulting in strengthened gel structures.

One of the most interesting approaches toward the development of artificial bone is the synthesis of organic–inorganic hybrid materials [9, 23–27]. These materials have the unique feature of combining the properties of traditional materials, such as ceramics and organic polymers, on the nanoscopic scale. The synthesis of organic–inorganic hybrid materials appeared in the eighties with the expansion of soft inorganic chemistry processes. An interesting approach is synthesizing class I hybrids (materials showing weak interactions between both phases) based on bioactive gel glasses and a biocompatible hydrophilic organic polymer. For instance, poly(vinyl alcohol) (PVAL) would tailor the hybrid degradation, i.e. the rate at which the hybrid material is dissolved by the physiological fluids, being replaced by biological new formed bone. Our research group has reported on this system obtained as monoliths and characterized before and after being soaked in simulated body fluid (SBF) [28, 29]. These compounds have been proposed as potential bone defects filler in non-load bearing applications or as matrices for controlled release systems. Much more attention has been paid on silicate-containing class II hybrids, commonly referred as ormosils. These hybrids shows chemical links between the components (covalent or ion-covalent bonds) and several systems have been proposed aimed to obtain

bioactive structures with high mechanical performance. In this sense PEG–SiO_2 ormosils [30], PDMS–CaO–SiO_2–TiO_2 [24, 31], CaO–SiO_2–PDMS [32–34], PTMO–CaO–SiO_2–TiO_2 [35], MPS-HEMA ormosils [36], Gelatine–SiO_2 systems [37], Poly(ε-caprolactone)/silica ormosils [38] and bioactive star gels [39] have been fabricated. Star gels are a type of organic-inorganic hybrids that present a singular structure of an organic core surrounded by flexible arms which are terminated in alcoxysilane groups. Similarly to the ormosils described above, star gels can be upgraded with bioactive properties by Ca^{2+} cations incorporation. Bioactive star gels can be obtained as monoliths of any shape and size and are able to develop an apatite phase on their surface when soaked in SBF. These bioactive star gels are homogeneous and substantially better than conventional bioactive glasses from a mechanical point of view as can be seen in Fig. 2.

Scaffolds for tissue engineering should exhibit an interconnected macroporous structure (with pore sizes above 100 μm). Moreover, the presence of mesopores within the bioceramic skeleton is highly desirable since it facilitates the nutrients permeability and improves the surface area, thus facilitating the subsequent bioresorption. Jones and Hench [40, 41] have proposed a foaming mechanism to fabricate highly macroporous sol-gel glasses with monolithic structures. This strategy relies on the foaming of the gel by means of a surfactant addition and vigorous stirring. Once the sol is foamed, the viscosity is rapidly increased by catalyzing the polycondensation process with HF. The results are SiO_2–CaO–P_2O_5 and SiO_2–Ca foams with hierarchical structure, with interconnected macropores ranging in size between 10 and 500 μm and mesopores of several nanometres.

4 Silica mesoporous materials

The discovery of highly ordered mesoporous silica was quickly recognized as a breakthrough that could lead to a variety of important applications in host-guest systems [42, 43]. Silica-based mesoporous materials have unique structural characteristics, since that an amorphous silica network constitutes the wall of well-ordered arrangement of pore system and cavities [44].

Exploring new applications of these silica based mesoporous materials based in their composition, textural and structural characteristics was a goal to consider them as promising materials with bone regeneration purposes [45]. However, for such desirable application, silica based mesoporous materials must exhibit a "*bioactive response*". In 2004, it was demonstrated that by soaking in a simulated body fluid (SBF), some mesoporous structures could develop biomimetic apatites onto the surface [46]. However, high surface areas and porosities are not enough condition to achieve satisfactory biomimetic behaviour, showing apatite formation layer kinetics too slow by comparing with conventional sol-gel glass. For instance, MCM-41 material is not bioactive after 60 days in SBF and requires be doped with phosphorous or mixed with small amount of conventional bioactive glass to show bioactivity

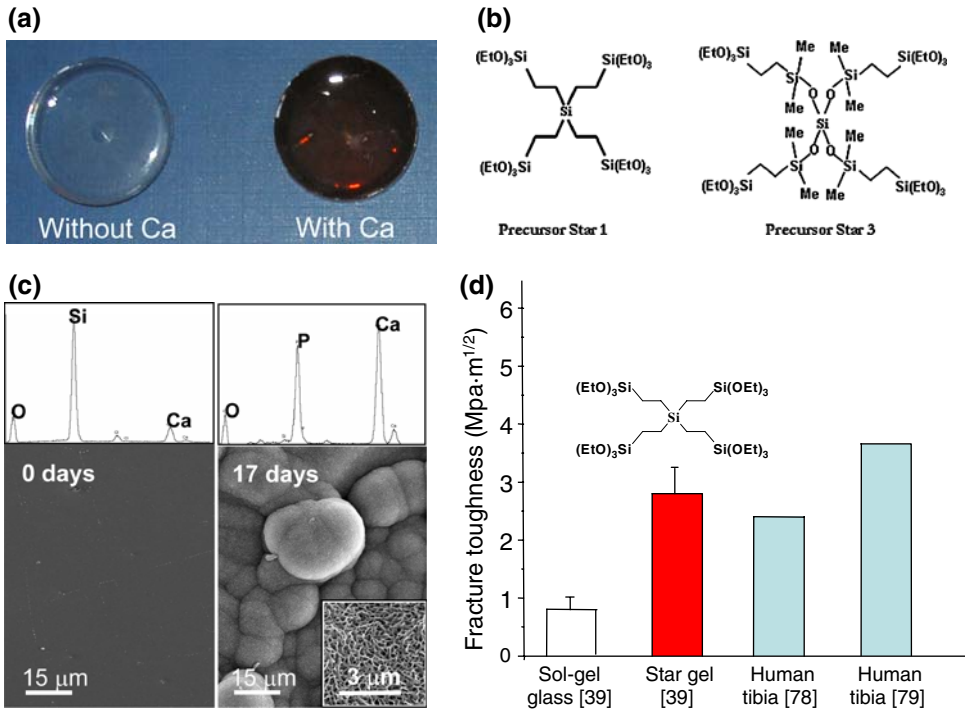

Fig. 2 Bioactive star gels. **a** Crack free star gel monoliths; **b** Two star gels precursors: star 1 and star 3 as denoted in reference [77]; **c** Bioactive behaviour of star gels. After 17 days in SBF an apatite phase covers the star gel surface; **d** Fracture toughness values of conventional sol-gel glasses, star gel [39] and human tibia [78, 79]

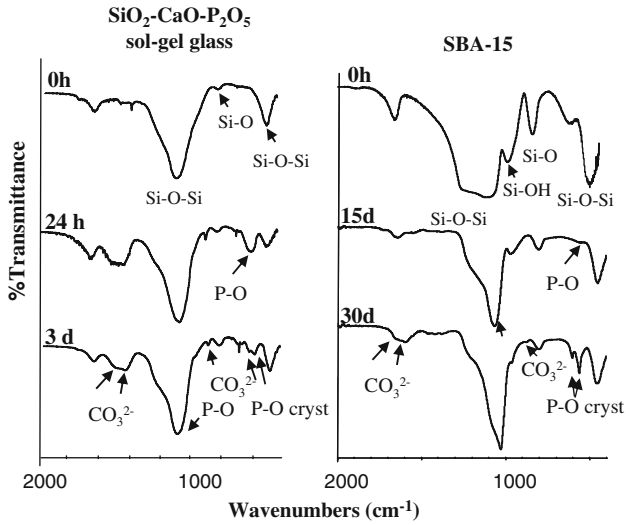

Fig. 3 Comparative in vitro bioactive study by FTIR technique of a conventional sol-gel glass in the SiO_2–CaO–P_2O_5 system and SBA-15 mesoporous materials

[47, 48]. Other phases like MCM-48 or SBA-15 materials develop a nanocrystalline apatite-like phase one their surface after 60 and 30 days. Figure 3 shows a comparative in vitro study in SBF between a conventional sol-gel glass in SiO_2–CaO–P_2O_5 and a silica based mesoporous material (SBA-15), showing very different kinetics of growing of needle-like HCA layer onto their surface of such materials [8, 46]. Although the high ordered porosity means an added value over conventional bioactive sol-gel glasses, none of the silica based mesoporous materials described until now improve the bioactive behaviour of the conventional ones.

5 Templated bioglasses

The real challenge has been to obtain bioactive multicomponent sol-gel glasses, with the textural properties and porous arrangement of the silica based ordered mesoporous materials. The research group of Prof. Zhao carried out the synthesis of SiO_2–CaO–P_2O_5 ordered mesoporous glasses through the evaporation-induced self-assembly (EISA) method in the presence of a non-ionic triblock copolymer ($EO_{20}PO_{70}EO_{20}$), resulting in 2D-hexagonal pore arrangement after calcinations at 700°C [49]. Such materials as consequence of presence of CaO and P_2O_5 in their composition together with extraordinary textural properties showed an enhanced bioactive behaviour with faster apatite phase formation than conventional bioactive sol-gel glasses.

The possibility to obtain different pore arrangement with different geometries and well-defined textural properties in this new family of "*templated bioglasses*" has been a reality when the research group of Prof. Vallet-Regí showed an evolution from 2D-hexagonal to 3D-bicontinuos cubic structures when CaO content decreases (Fig. 4) [50]. These structural modifications can be explained in terms of the influence of the Ca^{2+} ions on the silica condensation due to the Ca^{2+} ions act as network modifiers, decreasing the network connectivity. Consequently, the inorganic/organic volume ratio of the micelle is increased with the Ca^{2+} content, thus increasing the curvature ratio of the surfactant micelles and contributing to the formation of hexagonal phases rather than cubic ones.

By tailoring the structural and textural properties at the nanometric level, a variety of bioactive responses with fascinating properties can be observed. For instance,

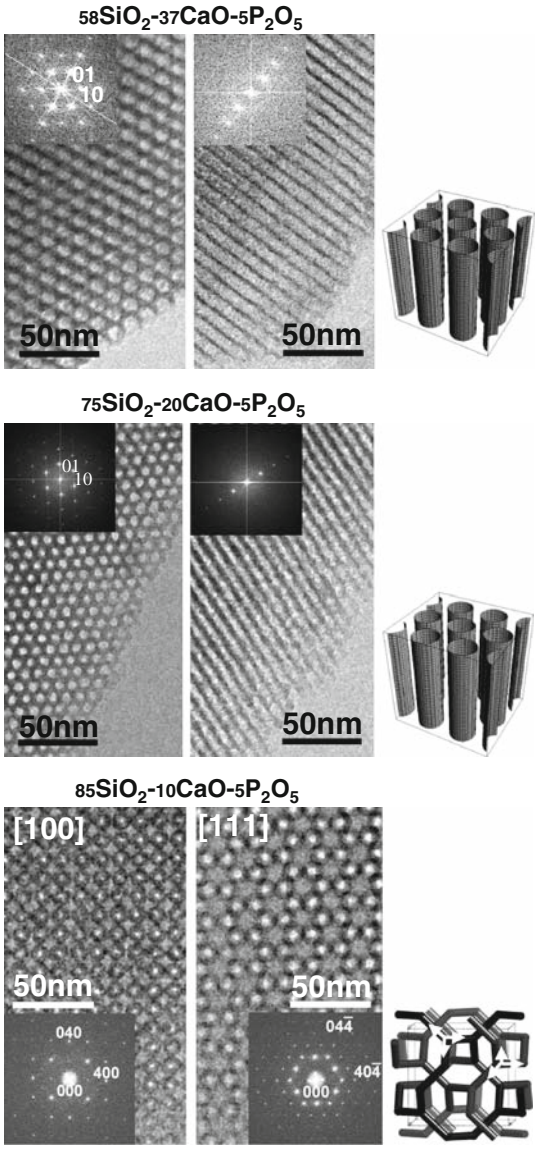

Fig. 4 Evolution of structural characteristics as function of the CaO content in the SiO_2–CaO–P_2O_5 mesoporous glasses by TEM study. Images and FT diffractograms with schematic representing the pore arrangement structure of mesoporous glasses

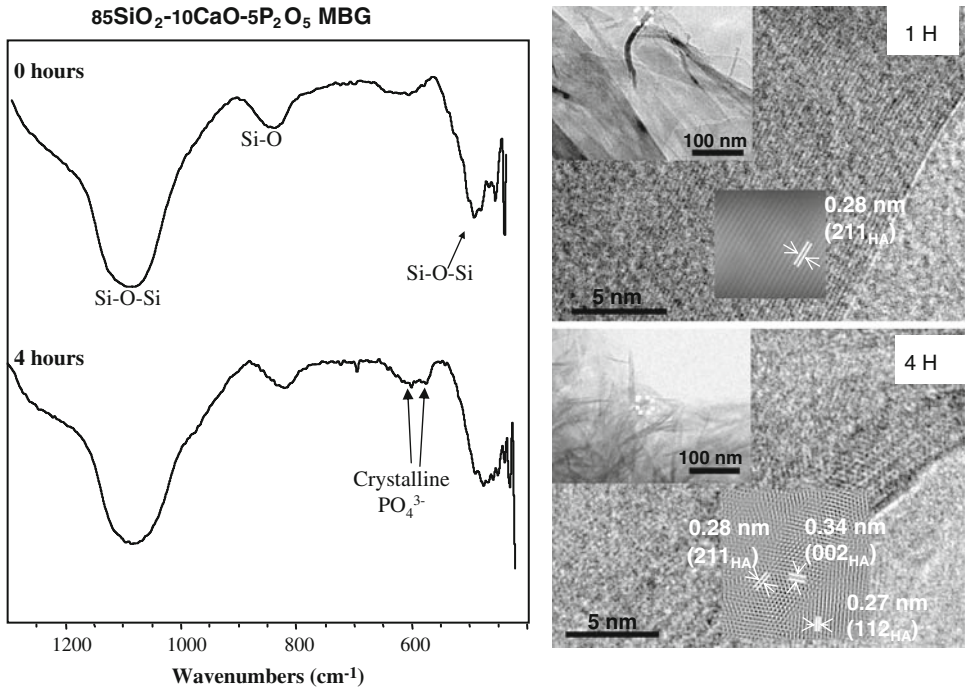

Fig. 5 In vitro bioactive study in SBF of a mesoporous glass with 10% in mol of CaO content and 3D-cubic structure by FTIR and TEM techniques

mesoporous glasses with low CaO content (10% in mol) and 3D-bicontinuos cubic structure has shown an unexpected fast bioactive behaviour compared with conventional sol-gel glasses. In fact, this composition has exhibited the fastest HCA formation observed up to date in a silica based bioactive material. This amazing behaviour could be explained in terms of the mesoporous structure and the textural properties derived from it. In this case, the 3D pore system provides not only high surface area and porosity, but also easier interchange of ions, increasing mass transport and diffusion processes and thus, higher crystallization rate (Fig. 5).

6 Biomimetism in templated bioglasses

Another new property derived from the textural and structural characteristics of "*templated bioglasses*" is their biomimetic mechanism where a sequential transition from amorphous calcium phosphate (ACP)–octacalcium phosphate (OCP)–calcium deficient carbonatehydroxyapatite (CDHA) maturation, similarly to the in vivo biomineralization process, has been for the first time observed [51].

Usually, all bioceramics obtained so far develop a CHDA phase through the direct crystallization of previously precipitated ACP [52], without previously formation of OCP phase which is formed in natural bone biomineralization process [53–55]. OCP is a metastable phase and will appear only if the pH in the crystallization system is below 7.

"*Templated bioglasses*" with 2D-hexagonal mesoporous arrangement and high CaO content (37% in mol) allow an intense Ca^{2+}–H_3O^+ exchange as a consequence of the open channel array, the high textural parameters and the relatively high CaO content. The resulting surface silanol groups eventually condense into and acid hydrated silica layer with local pH values of 6.5 during the first stage, which favour the OCP formation. On the contrary, this local acid pH does not occur in the surface of conventional bioglasses, whose surface exhibit the same basic media (pH 7.4 or higher) than the surrounding fluid from the beginning of the bioactive process and it can explain the reason OCP has never been observed.

The biomimetic bone mineralization can be followed by TEM, as displayed in Fig. 6. After 1 h soaked into the SBF, the "*templated bioglasses*" generates a large amount of newly formed amorphous calcium phosphate with Ca/P ratio of 1.2. This event has been widely observed in many bioactive compositions, and corresponds to the step 4 of the bioactive process described by Hench [56]. Up to date, the accepted mechanism involved the crystallization of an apatite-like phase from the ACP. However, "*templated bioglasses*" evidences a unique phenomenon with the development of nanocrystalline oval biphasic nuclei with 12 nm in width and 18 nm in length constituted by OCP with a small fraction of HA after 4 h in SBF. The Ca/P ratio is 1.3 (Ca/P ratio is 1.33 for OCP). The transformation from oval OCP nuclei to needle shaped apatite nanocrystals is finally evident on "*templated bioglasses*" surfaces after 8 h.

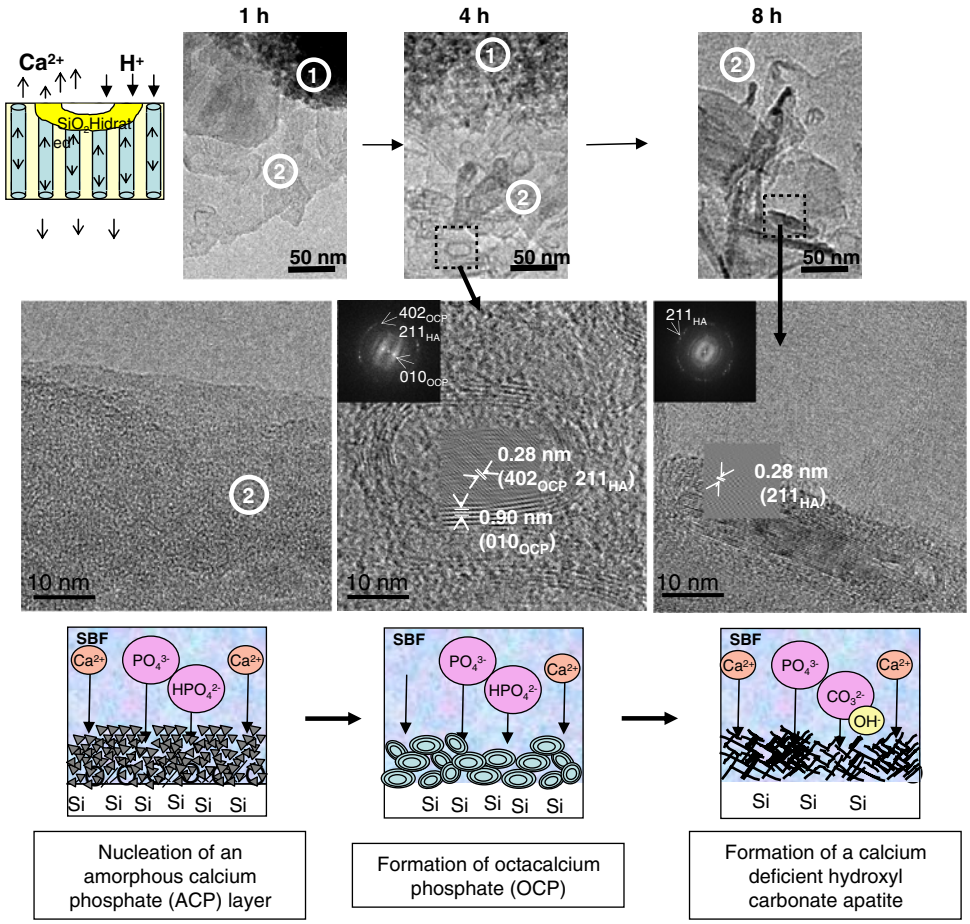

Fig. 6 HRTEM study corresponding to a MBG with composition SiO_2 (58)–CaO(37)–P_2O_5(5) (% in mol) with 2D-hexagonal mesoporous arrangement after different times in simulated body fluid. A sequential transition from ACP, OCP and CDHA phases is observed as biomimetic governing mechanism

7 Nanostructured materials: New trends in controlled delivery of biologically active molecules for bone tissue regeneration

The characteristics of silica-based ordered mesoporous materials such as: (i) biocompatibility, (ii) large surface area and pore volume, (iii) tunable pore size and distribution and (iv) suitability to be functionalized with organic molecules, make them excellent candidates to be employed as delivery systems of biologically active molecules. Especially interesting is the synergic effect of their properties as bone regenerative bioceramics, together with the capacity to host and release osteogenic agents for bone regenerative purposes. It was in 2001, our research group demonstrated for the first time such capability [57]. Ibuprofen, a common anti-inflammatory drug, was confined inside of MCM-41 type mesoporous materials with different pore size and was subsequently released from such matrices in a simulated body fluid. Since then, the interest in this field has exponentially growth as reflected by the number of research works concerning mesoporous materials as drug delivery systems. Revision articles on this topic can be found in references [58–63].

Different factors such as textural parameters (surface area, pore volume and pore size) and the functionalization of the pore surface by organic molecules has shown to highly influence the loading and release rate of biologically active molecules (Fig. 7). In this sense, the pore diameter will determine the size of the guest drug, i.e., size selectivity. One of the most important features of mesoporous matrices is that the mesopore sized can be tuned from 1.5 nm to several tens of nanometers by changing the synthesis procedure. Therefore, the loading capability of mesoporous materials is very large from small molecules to macromolecules such as proteins [64–66]. Moreover, the pore size has been also demonstrated to influence the release rate of molecules since that this parameter affects drugs diffusion to the delivery medium [67–69].

The drug incorporation is commonly carried out by soaking the matrix into a highly concentrated drug solution and subsequent drying. Therefore, the process is mainly based on the adsorptive properties of mesoporous materials and the surface area has been demonstrated as the main factor, which determines the amount of drug molecules adsorbed, i.e., the greater the surface area the higher

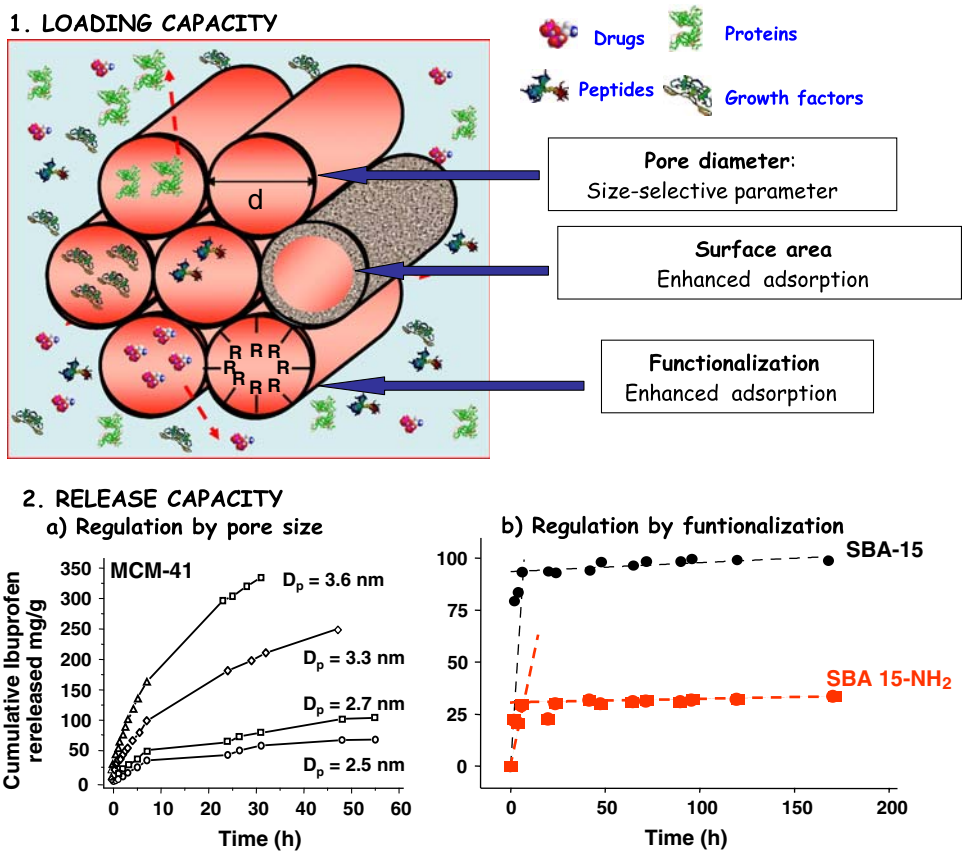

Fig. 7 Parameters governing the loading and release rate of biologically active molecules into the silica-based ordered mesoporous materials

amount of drug can be incorporated within the mesoporous matrix [70, 71].

Finally, it must be highlighted that the keystone in the development of silica mesoporous materials as DDSs has been the organic modification of the surface or functionalization. Functionalization of the surface through organic groups provides numerous possibilities to control drug adsorption and release [71–73]. Silica based mesoporous materials show a high density of silanol groups, which can be used to obtain functionalized surfaces by grafting organic silanes ($(RO)_3SiR'$) [74, 75]. The drug loading and release can be effectively controlled by increasing the drug-surface interaction [76]. For this purpose the surface is functionalized with chemical groups that are able to link to the drug molecules through ionic bonds or through ester groups and thus, to enhance the loading and rate release properties via increasing the guest-matrices affinity.

8 Summary and outlook

The advances in bioceramics field have been closely linked to search materials that promoted optimum implant-tissue interactions. Up to 70s, this interaction was considered to be the inert behaviour at the interface, and bioceramics were synthesised aimed to substitute the bone tissue. This concept changed when bioactive bioceramics came out in 1969. The goal of an inert response shifted towards the synthesis of reactive surfaces able to induce specific responses with the living tissues that, in the case of bioceramics, resulted in a strong chemical link with the bones through the so-called bioactive bond, thus ensuring the implant-tissue integration. The bioactive bond is formed through the nucleation and growth of an apatite like phase on the implant surface. This apatite is quite similar to the mineral part of the bone and sometimes has been referred as biomimetic apatites. In fact, the crystal–chemical features and microstructure closely resemble to those of biological ones and the crystallization process mimics the natural formation, in the sense that apatite nanocrystals are formed from their ions in solution. Finally, the 3rd generation bioceramics came up with a new conceptual shift from osteointegration toward osteoregeneration. As explained in this article, some processes such as ions dissolution acquired a new significance concerning the osteogenic function through gene up-regulation. Since bone must colonize the implant, the porosity has become a fundamental factor. Furthermore, the development of tissue engineering has encourage the materials science researchers to develop meso and macroporous ceramics suitable to be used as scaffolds for bone tissue engineering, as well as carriers of osteogenic agents.

By over-viewing the research on bioceramics along time, we can realize that their development and advances are, in some way, related to the decreasing of our pretensions as materials researchers. The 1st generation of inert ceramics was aimed to substitute natural bone; the 2nd one was aimed just to mimic some biomineralization related-function; finally, with the 3rd generation of bioceramics we only pretend to help the bone cells to make their work, by means of supplying appropriated scaffolding. Insofar we develop more sophisticated systems by controlling the implant-tissue interface, we are moving back in our artificial purposes to give way at the natural agents.

The current aims in bioceramic research must be framed in this field. The development of osteoregenerative ceramics through the control of their chemical composition, meso and macroporosity, or by means of osteogenic agents incorporation should play a main role in biomaterials science. Finally, the tailoring of scaffolds with hierarchical porosity (with different pore size level) and precise architectures to fit into specific bone defects also will have a deep impact in near future. In this sense, rapid prototyping techniques are excellent tools for this purpose and are called to be fundamental instruments for the development of the 3rd bioceramics generation.

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