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Tailoring the structure of bioactive glasses: from the nanoscale to macroporous scaffolds

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Abstract

Bioactive glasses are going to play an essential role in the manufacture of 3D scaffolds for bone tissue engineering. Mimicking natural bone, synthetic scaffolds must be tailored at a hierarchy of scales. First, the glasses composition must be carefully designed at the atomic–molecular level to ensure bioactivity and beneficial effects including capabilities for enhance osteogenesis and vascularization or to exert bactericide action. Moreover, the glasses structure need to be designed at the nanometric scale. With this purpose, mesoporous bioactive glasses, exhibiting ordered arrangements of nanometric pores, are optimum candidates. The microstructure of glasses must also be designed to achieve suitable interactions with living cells. Finally, the scaffolds obtained with bioactive glasses must display interconnected pores over 100 μm to made possible bone cell ingrowths and angiogenesis. In this article, the advances in the field of bioactive glasses through the control of the chemical, nanometer scale, microstructural properties and architectural features are presented and discussed. A detailed control of these four levels of matter organization will allow optimizing the biological response of bioactive glasses when used in bone tissue regeneration.

Keywords: Bioactive glasses, bone tissue engineering, composition, mesostructure, microstructure, macrostructure.

Introduction

The discovering of bioactive glasses at the end of the 1960s meant one of the most important achievements in the field of bioceramics [1]. Prof. Larry L. Hench wrote a brilliant page in the History of Biomaterials, when he revealed the capability of certain SiO_2 based glasses to bond to the bone through a chemically stable and mechanically strong linkage. Since then, the development and clinical applications of bioactive glasses have growth during the last 45 years. These glasses have a composition based on SiO_2-P_2O_5-Na_2O-CaO, where SiO_2 and P_2O_5 are network formers, whereas CaO and Na_2O are network modifiers and play a fundamental role in the bioactive behavior of this material [2,3]. We can say that Prof. Hench evidenced the bone regeneration capability of silica based compounds by controlling the chemical composition, i.e. by tailoring the matter at the atomic scale. Thereafter the incorporation of the sol-gel chemistry [4] to the preparation of bioceramics resulted in new bioactive glasses, usually called sol-gel glasses (SGGs), which exhibited a very high potential to develop better implants with osteogenic capabilities. This potential is supported by the enhanced textural properties inherent to the sol-gel method, i.e. surface area, porosity and other microstructural features respect to the conventional melt derived bioglasses (MDGs) [5].

Recently, a new generation of mesoporous bioactive glasses (MBGs) has been developed [6]. MBGs are the result of tailoring bioactive glasses at the nanometer scale through the incorporation of structure directing agents to the sol-gel synthesis. The result is the preparation of highly ordered mesoporous materials with surface and porosity up to three times higher than obtained for the conventional sol-gel bioglasses [7]. MBGs exhibit the fastest *in vitro* bioactivity observed up to date. However, the real clinical significance is still unknown, as the ordered mesoporous structure could allow

incorporating osteogenic agents, osteoclasts inhibitors, antitumoral drugs, etc. thus providing an excellent potential for the treatment of bone diseases [8].

Finally, the regeneration of critical bone defects is one of the most challenging and difficult issue to be tackled by biomaterials science. The regeneration in critical defects requires pieces that must fit to the defect size and morphology. Moreover, the implants must have pores large enough to let the bone cells colonization and blood vessels formation [9]. In this sense, rapid prototyping techniques and additive preparation methods allow the control of the implants macro-architecture and are called to play a very important role in regenerative therapies [10].

Herein, we review and discuss the advances in the field of bioactive glasses through the control of the chemical, nanometer scale, microstructural properties and architectural features (Figure 1). Through the control of these four levels of matter organization, bioactive glasses can optimize their response in the essential biological features involved in the bone regeneration processes.

2.- Design of the composition of bioactive glasses

The three basic components of bioactive glasses are SiO_2, CaO and P_2O_5. The maximum content SiO_2 for a positive bioactive response is 60 mol-% in MDGs and 90 mol-% in SGGs and MBGs. CaO, is also essential and greatly influences the porosity in SGGs and MBGs. P_2O_5 is not essential but beneficial when present in relatively low concentrations [11]. Si, Ca and P participate also in angiogenesis and bone tissue growth.

First attempts to improve Hench´s Bioglass® tried to increase its bioactivity and mechanical properties by modifying its composition. However, substitutions of MgO or CaF_2 for CaO and of K_2O for Na_2O did not altered significantly the bone bonding behavior. Moreover, Al_2O_3, in contrast with B_2O_3, inhibited bone bonding [12]. On the

other hand, mechanical properties of glasses were substantially improved only when glass-ceramics or composites were synthesized.

In the last few decades, numerous oxides were included in the three families of bioactive glasses looking for favorable biological action when used in bone tissue engineering (BTE) application [13]. That way, Zn, Sr, Cu and Co oxides additions provoked stimulatory effects in osteogenesis and angiogenesis, whereas Ag, Cu or Zn oxides conferred to glasses antimicrobial or anti-inflammatory therapeutic effects [14]. The additions of other elements such as Li, Ce and Ga were also investigated. Thus, a Li-doped MBG has promoted regeneration of osteochondral defects through the release of Li^{+} ions [15]. On the other hand, Ce or Ga additions were investigated because Ce^{3+} favors the osteoblasts growth and reduced enamel mineralization, while Ga^{3+} increases the calcium content in bone and block bone resorption [16,17].

Figure 2 shows the numerous ions investigated to induce beneficial biological properties in bioactive glasses designed for BTE, including osteogenesis, angiogenesis or antibacterial capacity [8]. As it is observed the main role of these elements is to induce osteogenesis. For instance, the release from glasses of Sr^{2+}, Zn^{2+}, Mg^{2+} or Cu^{2+} ions stimulated the osteogenic differentiation of bone marrow stromal cells and periodontal ligament cells. Furthermore, Sr^{2+} stimulated alkaline phosphatase activity and osteogenic-related gene expression of periodontal ligament cells. Boron, released as BO_3^{3-}, enhanced the osteoblasts proliferation. Regarding iron oxide, it was initially included to obtain magnetic scaffolds for hyperthermia treatment, but Fe^{3+} ions release significantly improved the mitochondrial activity and gene expression of bone marrow stromal cells. Finally, the inclusion of tetravalent Zr^{4+} favored osteoblasts proliferation and differentiation because the decrease of the resorption rate of the glass scaffold.

Besides osteogenesis, a bioactive glass designed for BTE needs to stimulate the angiogenesis necessary for the living tissue formation. Actually, a poor vascularization at the injury site is one of the most important concerns in BTE. As is observed in Figure 2, only Cu^{2+} and Co^{2+} ions were investigated with this purpose. The reason is that they induce significant hypoxia (low oxygen pressure) that drives angiogenesis because hypoxic conditions initiate the expression of genes associated with living tissue regeneration (including bone). In this regards, it must be considered that although both ions induce hypoxia in stem cells, the potential toxicity of Co^{2+} is higher than Cu^{2+}.

On the other hand, glasses designed for BTE must exhibit antibacterial capabilities. It must be considered that post-operative bacterial infection is one of the major issues associated with the treatment of bone fractures and diseases with implants. In this regards, the release of Ag^{+}, Cu^{2+}, Zn^{2+} and Ga^{3+} showed antibacterial activity against *Staphylococcus Aureus* and *Escherichia Coli* [18].

In this point is necessary to contemplate that in the design of a bioactive glass intended to exhibit antimicrobial, ostoegenic, angiogenic features or others, is essential to know the amount of ions released from glass to medium and check if this value is inside the therapeutic range and out of ineffective and toxic levels. For instance, in an unpublished study of the authors, a MBG containing 3.5 mol-% of Ga_2O_3 did not exhibit antibacterial properties, because Ga^{3+} ions remained in the glass without be released to medium. In another study, a MBG containing 7 mol-% of ZnO exhibited antibacterial properties, but the amount of Zn^{2+} ions released was so high that converted the glass in non-biocompatible in a cell osteoblasts culture [18]. In such study, the upper limit of ZnO in the MBG to exhibit both biocompatibility and antimicrobial capability was established at 4 mol-%.

Finally, Zn, Ca, or Ce were included in bioactive glasses designed for other applications such as in nerve guidance conduits. Zn and Ca because they are involved in peripheral nerve regeneration and Ce because is a neuroprotective agent. Moreover, the inclusion of Y is investigated for glasses designed for radionuclide therapy.

3.- Mesoporosity design of bioactive glasses

MDGs glasses are dense materials. Thus, their textural properties are negligible. However, SGGs and MBGs exhibit high surface area and porosity. Both families of glasses present cylindrical pores with diameters between 2 and 10 nm, i.e. mesopores, open at both ends, but only MBGs exhibit ordered mesopores arrangements. The design of the bioactive glasses structure at nanometric level can bring enhanced bioactivity and the possibility to load glasses with biomolecules able to drive the living tissues regeneration. In SGGs, the mesopore size and volume can be designed by controlling the synthesis parameters including temperature of thermal treatments and the glass composition, particularly the CaO content [19].

To understand how it is possible to design the MBGs nanostructure it is necessary to know the method of synthesis. Due to MBGs are CaO-containing multicomponent systems, they need to be synthesized by evaporation induced self-assembly method (EISA) [20]. As structure directing agent, a non-ionic surfactant such as Pluronic® 123 is used. A diluted solution of surfactant and precursors is prepared in ethanol/water. The evaporation allows reaching the critical micellar concentration of surfactant when the self-assembly silica-surfactant micelles and further organization into liquid crystalline mesophase take place. After the surfactant removal, MBGs are obtained. This method allows designing textural and structural characteristics that control the bioactive response of MBGs. Ordered mesoporous arrangement depends on type and concentration of surfactant, solvent, additives, pH, temperature but the critical

parameters are calcium and phosphorous contents and solvent evaporation temperature [21,22].

CaO modifies the mesoporosity of the amorphous silica walls and the mesopore structure. Thus, varying the CaO content, 3D-cubic (Ia-3d, space group) or 2D hexagonal (p6mm, plane group) mesopores arrangements can be obtained. These modifications can be explained considering that Ca^{2+} decrease the network connectivity. Consequently, the inorganic/organic volume ratio of micelles increases with the Ca^{2+} content, decreasing the curvature of surfactant micelles and contributing to the formation of hexagonal phases. However, low CaO contents yields to cubic phases. In addition, the textural features of MBGs are ruled by the porosity coming from the surfactant removal, at difference with SGGs where mainly depend on the CaO content.

P_2O_5 content is also critical in mesoporous structure and bioactive behavior of MBGs. The presence of P produced a 3D-cubic structure, while its absence yields to 2D-hexagonal structure. It was demonstrated that P_2O_5 bind to CaO forming amorphous calcium phosphate clusters at the glass surface. Thus, Ca^{2+} is retired from the glass silica network and the effect to include P_2O_5 in MBGs is analogous to decrease the CaO content i.e. to form the cubic structure. Thus, in P-free MBGs hexagonal phases were formed. However, textural parameters in MBGs do not experienced significant changes because of the presence or absence of phosphorus confirming that such main parameters are governed by surfactant removal not being affected by the compositional variations.

Evaporation temperature in the EISA synthesis is also an effective parameter to control the MBGs mesostructure. For identical MBG composition, the structure can change from 3D-cubic to 2D-hexagonal by decreasing the solvent evaporation temperature. Indeed, both structures can coexist for intermediate temperatures. When temperature increases, the micelle size increases by reduced hydrogen interaction

between micelles and water which favor the 3D-cubic structure. However, 2D-hexagonal structure is formed at low evaporation temperatures.

Textural parameters (surface area and porosity) of MBGs are approximately twice than SGGs with similar composition. Thus, for traditional SGGs the typical surface area values obtained by the Brunauer Emmett and Teller method (S_{BET}) are between 100 and 250 m^2/g and the pore volume (V_P) in the 0.2 – 0.4 g/cm^3 interval. On the other hand, for MBGs, typical S_{BET} values are from 200 to 500 m^2/g and V_P usually ranges between 0.5 – 0.7 g/cm^3. Figure 3 shows that MBGs exhibit textural properties intermediate between SGGs and silica mesoporous materials, which often reach and even exceed 1000 m^2/g of S_{BET} and 1 cm^3/g of V_P. However, MBGs exhibit the quickest in vitro bioactive response of all the synthetic materials reported [23,24].

High Resolution Transmission Electron Microscopy (HRTEM) images included in Figure 3 shows that SGGs and MBGs are materials with textural properties intermediate between SGGs and mesoporous materials. Indeed the structure of both families of glasses is identic at the atomic scale but differs at the mesoscale. As expected, because they are glasses, high magnification HRTEM images of the SSG and the MBG do not show order. Accordingly, the Electron Diffraction (ED) patterns included as insets are typical of materials exhibiting an amorphous structure at atomic scale.

However, in the HRTEM image of the MBG at lower magnification, mesopores arrangement is clearly visualized and the ED pattern confirms the hexagonal arrangement at the mesoscale. Therefore, although the three families of bioactive glasses exhibit the amorphous structure at atomic scale, MBGs exhibit also mesopores

arrangement, which confers them outstanding properties that make them optimum candidates as raw materials to fabricate scaffolds for tissue engineering applications.

4. Microstructural design of bioactive glasses

Tailoring the bioactive glasses at the micrometrical scale involves controlling the particle size and morphology, as well as the inter-granular porosity when the implant is a solid piece. It is well known that in the range between 1 – 1000 micrometers, the microstructural characteristics condition different processes that take place at the implant-tissue interface. In this way, micro-features (particle size and porosity) about 1 μm determine, among other factors, the newly formed carbonate hydroxyapatite growth onto the surface [25] and the serum proteins adhesion [26]. Besides, those micro-features in the range of 1 – 20 μm are related with the processes of cellular adhesion and proliferation.

Most of the clinical applications of bioactive glasses require their implantation as granulates [27], as this form increases the surface contact between the bone and the graft. Depending on the application method and the anatomical location the particle size varies. For instance, the bioactive glass particles incorporated within toothpastes for dentine regeneration in the treatment of tooth hypersensitivity and commercialized as NovaMin® (GlaxoSmithKline LLC, Wilmington, NC), exhibit particle sizes of about 20 μm. In this case, the friction during brushing favors the adhesion to dentine, blocking the dentinal tubules and relieving the pain. The ions released by the glass trigger the apatite growth that occludes the tubules until the permanent filling of the cavities takes place. The small particles size facilitates their crossing through the enamel and avoids the user to feel them.

In the case of periodontal and orthopedic applications, the bioglass derived products are manufactured with larger particle sizes [28]. This microstructural changes are addressed to match the bone growth with the glass dissolution while fitting with the anatomical volume conditions. In this sense PerioGlas (Novabone Products LLC) is a particulate material for periodontal tissue repair made of particles in the range of 90 – 710 μm. Other commercial products aimed for similar applications are Biogran (Gobal Headquarters, FL) with a particle size distribution ranging in size between 300 – 360 μm. In the case of bioactive glasses manufactured for spinal grafting, the particle sizes found fall in the range of 1 – 2 mm (BonAlive, BoneAlive Biomaterials Ltd., Turku, Finland)

The ionic dissolution products of bioactive glasses lead to other beneficial effects such as osteoinductive behavior and antimicrobial properties. Some studies point out that Bioglass particulates smaller than 100 μm show antimicrobial and antiinflamatory effects [29-32], although the mechanism that explain these properties are still unknown. However, the microstructure determines the kinetic release of the ionic products, which strongly affects this col-lateral behavior. In this sense, Cerruti et al [33] could establish differences by dissolving Bioglass particles of 2, 16 and 90 μm in Tris-Buffer. The smallest particles released the network modifiers cations (Ca^{2+} and Na^{+}) faster, thus leading to a higher pH increase of the surrounding fluid. Besides, the newly formed apatite layer was also thinner compared with that precipitated onto the largest particles. The silica released, presumably as silicic acid, was not affected by the particle size.

Not only the particle size control but also the particle morphology has awakened much interest for designing the microstructure of bioactive glasses. The versatility of

the sol-gel method allows obtaining a variety of morphologies through the addition of different catalysts (Figure 4). In this sense, Chen et al [34] achieved to control the morphology of SiO_2-CaO-P_2O_5 sol-gel bioactive glasses using lactic acid (LA) as catalyst of the TEOS and TEP hydrolysis and, subsequently, adding ammonia to carry out the gelling under basic conditions. The particle morphology changed as a function of the LA/TEOS ratio and the different textures obtained resulted in different in vitro bioactive behavior: those morphologies containing nanoparticles and narrow mono or bi-modal pore size distributions exhibited faster formation of an apatite-like layer in contact with simulated body fluid (SBF).

The preparation of spherical particles is a topic of maximum interest in the field of the microstructural design of bioactive glasses. Certain studies claim that spherical particles exhibits better physic-chemical and biological behavior than bulky irregular bioglass particles. [35,36] Although some interesting results have been obtained in vitro with human marrow mesenchymal stem cells [37,38], up to date there are no *in vivo* evidences supporting this claim. However, the spherical morphology is optimal to tailor drug delivery matrixes made of mesoporous bioactive glasses. The dimensions of the carrier, the volume/surface ratio and, therefore, the kinetic of drug release can be easily tailored if the carriers are spherical and mono-dispersed particles instead of irregular bulky poly-dispersed grains. The synthesis of SiO_2 based mesoporous spherical nanoparticles is commonly carried out through the modified Stöber method.[39] This method basically consists on the precipitation of depolymerized silica in basic media in the presence of a cationic surfactant. The highly negative charge concentrated at the SiO_2 surface under basic conditions force nanoparticles to grow spherically, thus reducing the surface energy. In the case of calcium containing bioactive glasses, several research groups devoted with the obtaining of mesoporous bioactive spheres have

developed different strategies to achieve this aim. For instance, Hu et al [40] achieve to prepare monodispersed mesoporous bioactive spheres in the system SiO_2-CaO-P_2O_5 by means of adding dodecylamine (DDA) as basic catalyst and structure directing agent. DDA is an amphyfilic molecule that templates the mesoporosity while catalyzes the hydrolysis and condensation under basic media, thus leading to spherical morphology as explained above.

The alkaline precipitation method allows the synthesis of mesoporous bioactive spheres in the submicron scale. However, the nanospheres prepared by this route have been prepared with calcium contents below 20% mol or less [38,41]. The main drawback of the alkaline precipitation is the precipitation of calcium hydroxide if the Ca^{2+} concentration is too high. The precipitation as a solid phase impedes the incorporation of Ca^{2+} as network modifier within the silica matrix. For this reason, porous spherical particles with high calcium content have been prepared through confined spaces synthesis methods, such as microemulsions, aerosol assisted methods [42] or with templates that impose spherical morphology such as chitosan microspheres [43]. In these cases the alkaline environment is not needed to form spheres and the acid pH allows higher calcium contents in the reaction media.

5. Macro-architectural design of bioactive glasses.

Manufacturing scaffolds able to stimulate bone regeneration is one of the most exciting challenges in the field of bioactive glasses. Bioactive glasses can be manufactured as 3D macroporous bone grafts that provide a temporary structural support during the bone tissue ingrowth. Eventually, the scaffolds are intended to be resorbed thus achieving the *restitutio ad integrum* of the damaged bone. For this purpose, the ideal bone graft has been described as that able to [10]:

a) Be compatible and reabsorbible while showing a degradation rate that match with the bone tissue ingrowth, thus keeping the mechanical stability during the healing process.

b) Show an appropriated surface for the adhesion, differentiation and proliferation of osteoprogenitor cells

c) Exhibit a three dimensional and highly porous network to allow the newly formed bone tissue all through the graft. In addition, this macroporous arrangement should promote the angiogenesis, nutrients transport and metabolic wastes rinsing.

d) Exhibit mechanical properties similar to those of the host tissue (commonly cancelous bone)

e) Show a manufacturing process scalable to the industrial level

There are many different strategies aimed to prepare bioactive glass based scaffolds.[44-47]. Among them, foaming [48] and electrospinning [49] methods are some of the most important strategies used so far. The preparation of bioactive glass macroporous scaffolds through foaming processes have been widely studied and optimized. The method consists of the preparation of the bioactive glass by the sol-gel method adding a surfactant during the sol stage. By means of vigorous stirring a gas phase (atmospheric air) is interposed within the sol, which remains stable for short time before collapsing. The size and amount of the air bubbles determine the final macroporosity, so that is important to accelerate the gelation for keeping the porosity of the foam. For this purpose HF is incorporated as catalyzer achieving the gelation stage after a few minutes due to the complexation between fluoride and silica. After the calcination treatment, surfactant and nitrates are removed. In this way, scaffolds

exclusively made of bioactive glass are obtained, showing mechanical properties similar to those of cancellous bone.

Electrostatic spinning or electrospinning is an interesting method for producing nonwoven fibers with diameters in the range of submicrometers down to nanometers. In this process, a continuous filament is drawn from a polymer solution or melts through a spinneret by high electrostatic forces and later deposited on a grounded conductive collector [50]. This technique allows obtaining structures with high surface areas that somehow mimics the bone extracellular matrix. A first approximation is the preparation of composite scaffolds with electrospun polymer fibers and subsequent coating with a sol-gel bioactive glass. [51] However, other routes must be followed to obtain inorganic scaffolds prepared by electrospinning techniques. An interesting strategy has been recently developed with electrospun inorganic sol-gel solutions. This method results in 3D bioactive scaffolds with cotton-wool like structures that exhibit flexible structures without the need for binders. [52] The preparation of MBGs scaffolds by electrospinning techniques have been recently carried out by different authors. The structures prepared of organic/inorganic composite fibers have shown very promising osteoregeneration properties both *in vitro* and *in vivo* [53,54], as well as very interesting capabilities to deliver different growth factor in a sequential manner. [55]

The development of rapid prototyping techniques and additive manufacturing methods has created enough technology to design customized implants that fulfill the morphological requirements of the defect. [56] Ideally, the implant morphology can be tailored from the defect medical imaging. Thereafter, the macroporous structure is built by means of any of the additives manufacturing techniques, which involve the fabrication of the object by building up in layers by depositing material, i.e. the bioactive glass. Yun et al [57] incorporated the free form fabrication of MBGs implants

through computer assisted designs for the preparation of MBGs macroporous scaffolds with ordered macroporous architecture. These scaffolds showed three different porous systems in the nanometer, micrometric and macroscopic levels. The structure directing agent supplied the ordered mesoporous arrangement at the nanometer level, the incorporated methylcellulose left pores of several microns after calcination and the layer by layer robocasting procedure built the macroporous architecture.

MBGs scaffolds have demonstrated to improve their mechanical properties during the bioactive process under *in vitro* conditions. [58] The fast formation of an apatite-like phase that reinforces the grain boundaries result in a significant increasing of compressive strength values. However, even with this mechanical reinforcement, the mechanical properties of MBGs based scaffolds are still clearly insufficient for most of orthopedic applications or for bone regeneration purposes in critical defects. The combinations of MBGs with biocompatible polymers, such as polycaprolactone (PCL) [59], polyvinyl alcohol (PVA)[60], poly(3-hydroxybutyrate-co-3-hydroxyhexanoate) (PHBHH) [61] etc., have been proposed. These composite scaffolds have shown excellent results regarding the mechanical improvement, while keeping their bioactive properties under both *in vitro* and *in vivo* conditions. In this sense, the development of macroporous scaffolds manufactured with MBGs, and combined with antiosteoporotic agents, opens very promising perspectives for the treatment of fractures in osteoporotic patients.[62]

Conclusions

Bioactive glasses are materials with optimum present and future in the design of 3D scaffolds for bone tissue engineering applications. With the appropriate design of composition, mesostructure, microstructure and macrostructure and, after decorate the scaffolds with signals and cells, optimum constructs for bone regeneration will be

obtained. Such constructs will exhibit the required features for this application including mechanical stability and resorption as well as osteogenesis, angiogenesis, cell adhesion and cell proliferation capabilities and good pathological response.

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Figure Captions

Figure 1. The four levels of matter organization at which the bioactive glasses must be designed and the essential biological features exerted for each level.

Figure 2. Inorganic ions with its biological activity investigated to upgrade SiO_2-CaO-P_2O_5 bioactive glasses designed as scaffolds for bone BTE applications.

Figure 3. HRTEM images and ED patterns of typical examples of a SGG, a MBG and a mesoporous material. Average values of textural properties and time required to be coated by an apatite layer after be soaked in SBF are also included.

Figure 4. Different microstructures of MBGs particles prepared by different strategies. (a) Evaporation induced self-assembly (EISA) method. (b) Aerosol assisted EISA method. (c) Modified Stöber method. (d) Hydrothermal SBA-15 synthesis.

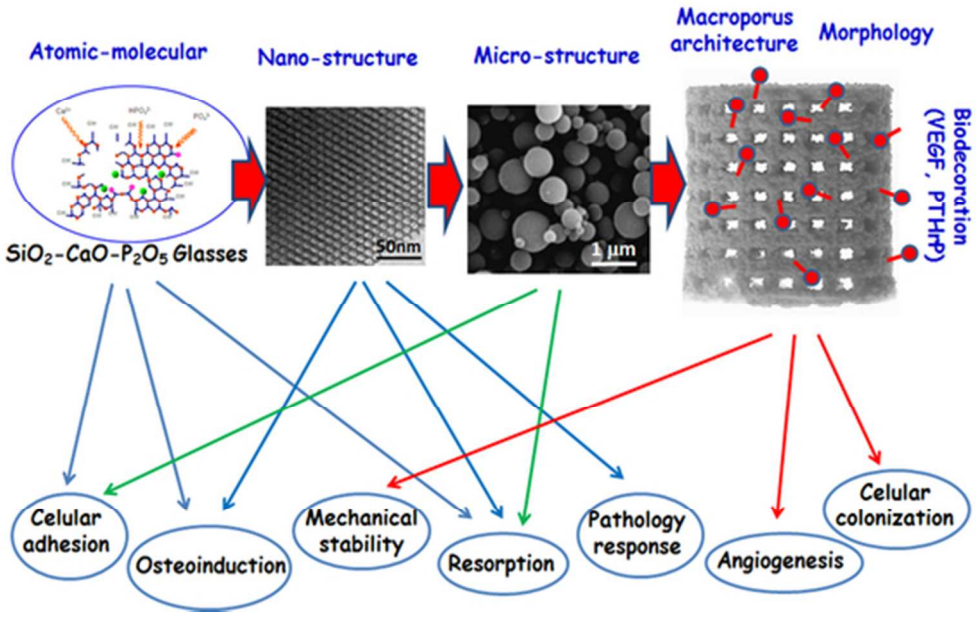

Figure 1. The four levels of matter organization at which the bioactive glasses must be designed and the essential biological features exerted for each level.
48x29mm (300 x 300 DPI)

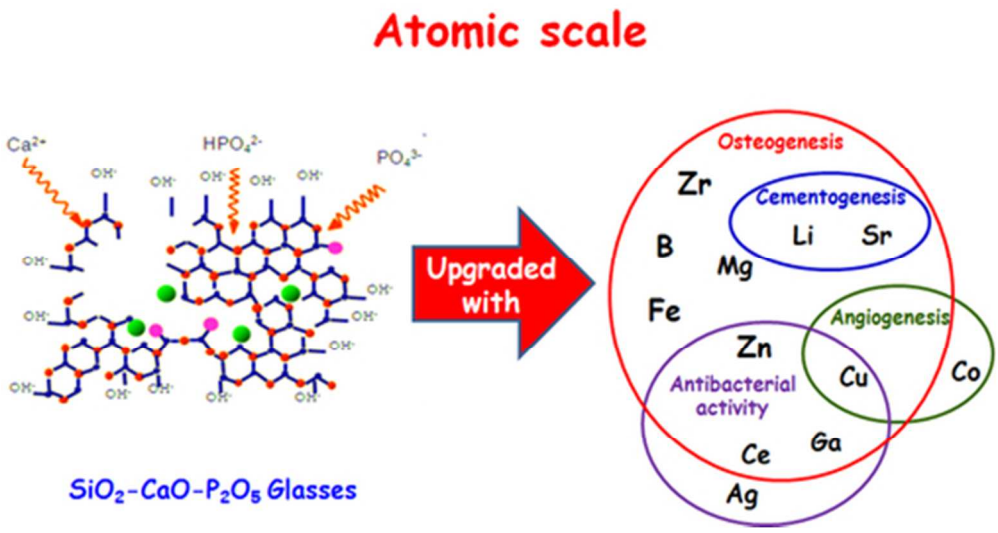

Figure 2. Inorganic ions with its biological activity investigated to upgrade SiO2-CaO-P2O5 bioactive glasses designed as scaffolds for bone BTE applications.
43x23mm (300 x 300 DPI)

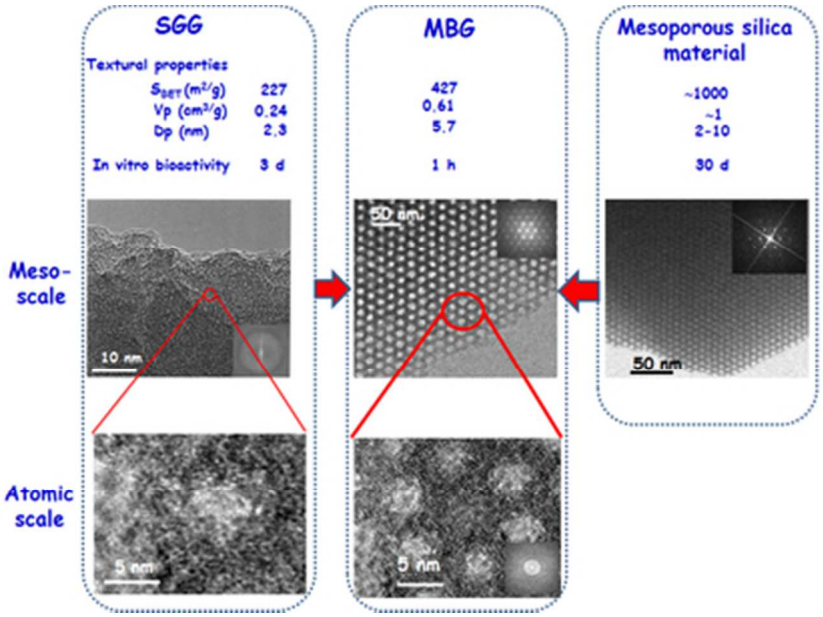

Figure 3. HRTEM images and ED patterns of typical examples of a SGG, a MBG and a mesoporous material. Average values of textural properties and time required to be coated by an apatite layer after be soaked in SBF are also included.
35x25mm (300 x 300 DPI)

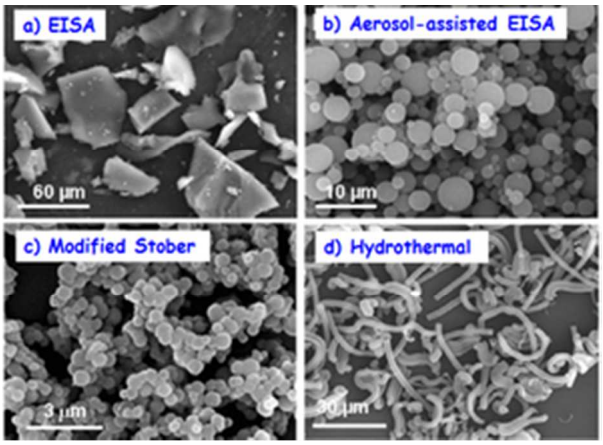

Figure 4. Different microstructures of MBGs particles prepared by different strategies. (a) Evaporation induced self-assembly (EISA) method. (b) Aerosol assisted EISA method. (c) Modified Stöber method. (d) Hydrothermal SBA-15 synthesis
25x18mm (300 x 300 DPI)