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From the bioactive glasses to the star gels

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Abstract The improvement of bioactive glasses is one of the most important subjects in the field of hard tissue replacement. More than 30 years after being discovered by Prof. Hench, bioactive glasses still attract the attention of many researchers all over the World. With this article we want to pay homage to Prof. Hench by means of reviewing the main contribution of our research team to the field initiated by him in 1969. Our efforts, aimed to go further in the understanding of sol-gel glasses bioactivity as well as to improve the mechanical properties of bioactive materials, are explained.

Introduction

In 1969, Larry Hench had an imaginative idea that opened a new research field: the use of glasses as implant materials [1]. The discovering of the first bioactive artificial material gave rise to new strategies in clinical bone repairs and replacement. This research line has provided very interesting results, both academic and applied ones, by means of transforming conventional glasses into glasses with a huge added value [2]. That research field remains opened and it is still providing new and hopeful possibilities in Biomaterials Science.

Bioactive glasses bond to and integrate with living bone in the body without forming fibrous tissue around them [3]. The high reactivity of these glasses is the main advantage for their application in periodontal repair and bone augmentation, because the reaction products obtained from these types of glasses and the physiological fluids lead to the crystallisation of the apatite-like phase, similar to the inorganic component of bones in vertebrate species. Currently, bioactive glasses are also considered as potential scaffolds for tissue engineering [4].

In 1998, our research team started to work in the field of bioactive glasses with the guidance of Larry Hench [5–7]. Since then, we have also tried to go further in the understanding of the kinetic that governs the bioactive process and we have tried to combine the outstanding bioactive properties of glasses with acceptable mechanical properties. This article reflects the more relevant results of our research related with bioactive glasses, which was started thanks to the Prof. Hench's initial works. With this revision we want to pay him homage for his dedication and guidance.

1 Role of P_2O_5 in the surface properties and the *in vitro* bioactivity of sol-gel glasses

From the early 1990s, when the first bioactive sol–gel glasses were prepared in the $CaO–P_2O_5–SiO_2$ system [8], diverse studies were performed to understand the role of the gel glass constituents in the surface properties and the in vitro formation of a carbonate hydroxyapatite (CHA) phase [9, 10]. That way, the role of SiO_2 and CaO was reported, but the effect of P_2O_5 was not fully understood.

To recognize the role of P_2O_5, our research group studied $CaO–SiO_2$ glasses showing that P_2O_5 is not an essential requirement for bioactivity, even for high SiO_2 contents [10]. In addition, two series of $CaO–P_2O_5–SiO_2$ glasses were prepared, first with SiO_2 constant (80%) [11], the second with CaO constant (25%) (in mole-%) [12]. Finally, the nanostructural characterization of glasses by High Resolution Electron Microscopy, HRTEM [13] allowed to determine calcium and phosphorus location in the silica network.

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Regarding the *in vitro* bioactivity, it was concluded that P_2O_5 retards the initial *in vitro* reactivity of glasses, defined as the time required for the formation of a layer of amorphous calcium phosphate. However, once some nuclei are formed, for contents of P_2O_5 up to 5%, the growth of CHA crystals in the layer is quicker and yield to larger crystals. With respect to the textural characterization, it was shown that the surface area increases and the diameter and volume of pores decrease when increasing the P_2O_5 content in glasses with a 25% of CaO. This result allowed us to propose that P_2O_5 bonds to CaO, given that increasing the P_2O_5 content produces similar textural effects as decreasing the CaO content. This assumption was confirmed by HRTEM since distances between the $[SiO_4^{4-}]$ tetrahedra of 0.53 nm were found in a P-free glass of composition SiO_2 80– CaO 20, in mol-%, but only of 0.36 nm were measured in a *P*-containing glass (SiO_2 80–CaO 17–P_2O_5 3), indicating that in the later the calcium was out of the glass network. In addition, in *P*-containing glasses small crystalline clusters (size lower than 10 nm), identified as silicon-doped calcium phosphate nuclei were detected (Fig. 1) [13].

The nanostructural characterization allows us to explain the differences in the *in vitro* CHA formation mechanism. In P-free glasses bioactivity is controlled by the rapid exchange of calcium in the glass network by protons in solution forming silanol (Si–OH) groups, which attract calcium and phosphorous in SBF to form an amorphous calcium phosphate. Afterwards, a relatively long period is required for the *in vitro* crystallization of CHA. However, for *P*-containing glasses the silanol concentration is lower, retarding the amorphous calcium phosphate formation, but the presence of the mentioned nanocrystals that could act as nucleation centres increasing the CHA crystallization rate.

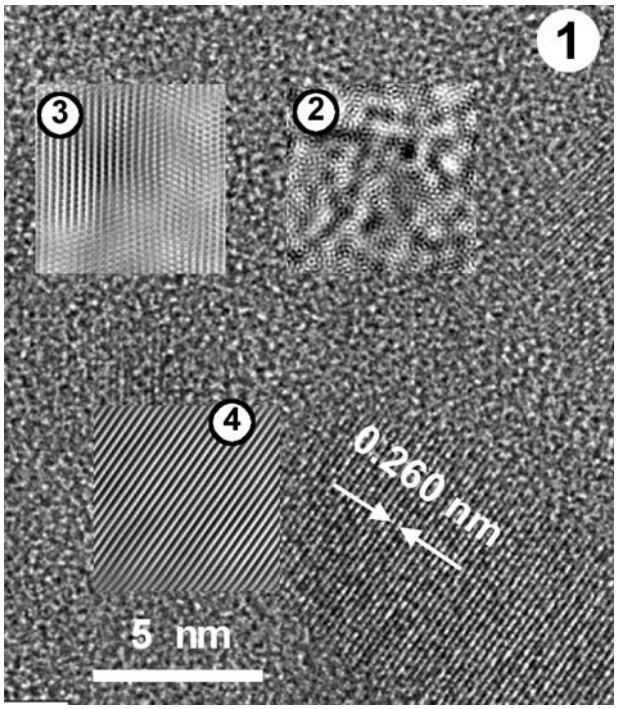

Fig. 1 Electron microscopy study of a gel glass of composition 17%CaO–3%P_2O_5–80%SiO_2. (1) HRTEM image and (2) filtered HRTEM image of the amorphous matrix. (3 and 4) P-rich crystalline areas oriented along different directions with interplanar spacings close to 0.26 nm

2 Models to explain the textural properties of sol-gel bioactive glasses

As mentioned above, the high surface area and porosity provides singular bioactive behaviour to sol-gel glasses. These textural features allow expanding the range of compositions at which silica based glasses show bioactivity, in comparison with melt derived glasses.

However the glass texture is not a static parameter during the bioactive process. Surface area and porosity—micro, meso and macroporosity in the case of glass pieces—change when the glass is in contact with the physiological fluids. This property was very well known in the case of melt-derived glasses. For example, Bioglass® develops a high surface area in contact with physiological fluids, typically greater than 100 $m^2 \cdot g^{-1}$ whereas the surface area before soaking is less than 1 $m^2 \cdot g^{-1}$ [14].

In the case of sol-gel glasses, the values of textural parameters depend on the chemical composition of the glass and stabilisation temperature used [15, 16]. Moreover, the changes of surface area and porosity depend on the kinetic of the bioactive process for each glass composition. Our research group has been concerned with this subject, specially in CaO–P_2O_5–SiO_2 and CaO–SiO_2 systems, and some work have been carried out to throw some light on the textural evolution of sol-gel glasses.

CaO–P_2O_5–SiO_2 system is one of the most widely studied in the field of bioactive so-gel glasses. One of our goals has been to analyze the texture of these glasses as a function of systematic modifications in their compositions [17]. For this purpose, a series of CaO–P_2O_5–SiO_2 glasses were synthesised varying the SiO_2/CaO ratio. This systematic study allowed confirming pre-existing results, such as that the higher the SiO_2 amount the higher surface area, whereas higher CaO content provides more mesopore volume and larger pore diameter. This study demonstrated that the morphology of these pores is modified as function of SiO_2 content. While the glasses with larger SiO_2 content (80% and 75% mol) have inkbottle-type pores with narrow necks, glasses with lower SiO_2 content (58%, 60%, 65% mol) have cylindrical pores open at both ends with occasional necks along the pores. The pore morphology parallels the variations of pore diameter and volume. The transition from narrow-neck inkbottle-type pores to open-ended cylindrical pores apparently takes place

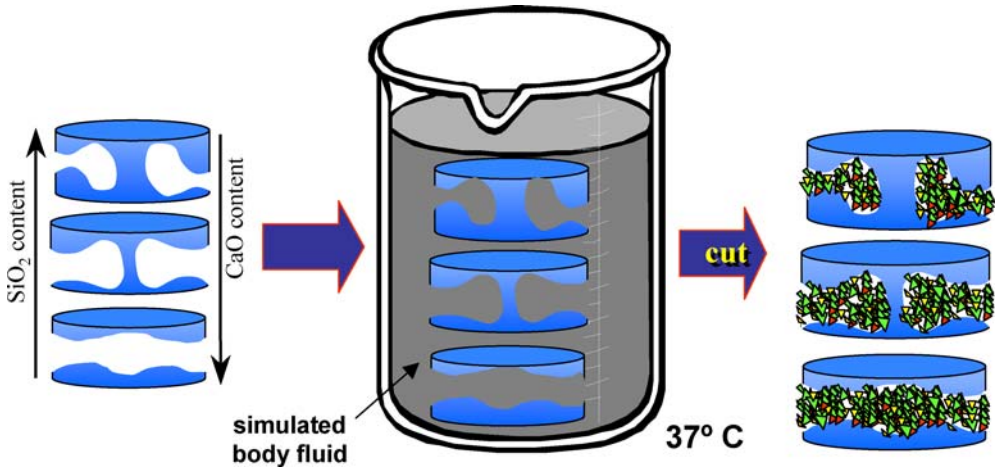

Fig. 2 Schematic model of the mesopore morphology as a function of SiO_2:CaO ratio. The figure also shows an scheme of apatite formation within the mesopores after soaking in SBF. For the sake of clarity, the apatite layer grown all over the particle free surface is not shown

when the pore diameter increases. The higher Ca content leads into the increase of the pore size and volume and causes a change of morphology from inkbottle pores to cylindrical pores. Since the higher ionic concentration occurs into the mesopores, the apatite growth (nucleation and crystallization) will depend on this porosity. This model is schematically plotted in Fig. 2.

The first stages of the bioactive process are critical for the subsequent behaviour. Actually, a faster initial ionic release leads to faster textural changes and apatite formation. However, there is not much information about the textural changes that these glasses undergo from the very first bioactivity stages until the apatite formation on the surface. In this sense, we have also dealt with the textural evolution of sol-gel glasses when soaked in simulated body fluid [18]. Figure 3 shows the surface area (S_{BET}) evolution of a sol-gel glass as a function of soaking time. The nominal composition of the glass is SiO_2 58 – CaO 36 – P_2O_5 6 (% mol). The glass powder was disk shaped and soaked in SBF at 37°C for several times under static conditions. As can be seen, the curve profile indicates several stages that involve two decreases and two increases of S_{BET}. The S_{BET} changes are closely related with the surface chemical changes observed by FTIR and SEM for the same soaking periods. In this way, Fig. 3 shows that during the very first burst release or calcium, the glass losses around 40% of surface area. During the Si-OH formation the S_{BET} value is partially recovered; the formation of amorphous calcium phosphate is associated with a new S_{BET} decrease and finally the S_{BET} increases due to the crystallization of a new apatite-like phase. The chemical and microstructural changes let us to understand and explain the textural evolution observed in Fig. 3 in terms of the Hench's bioactivity theory [19].

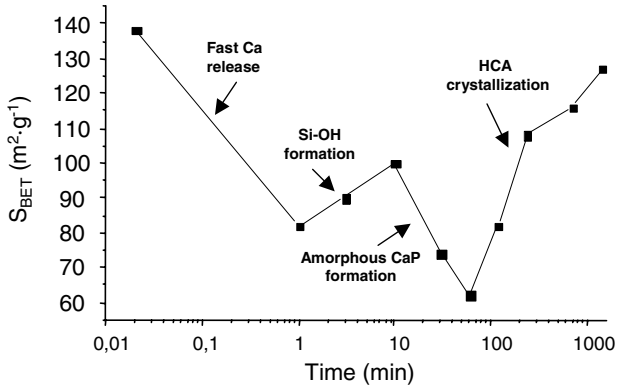

Fig. 3 S_{BET} variation of a glass with the immersion time

Our research group has also studied the macro-porosity created when glass powder is shaped into pieces [20, 21]. This macro-porosity presents a macro-pore volume of around 0.33 $cm^3 \cdot g^{-1}$ with an average pore size of 2 μm. These pores correspond to inter-granular spaces and should be considered when using glass pieces obtained by powder compression (not monolithic). We observed that the initial and massive Ca^{2+} release led to an addition of porosity, even at macro-pore level (0.35 $cm^3 \cdot g^{-1}$). The CHA layer grew on the glass surfaces as could be observed by SEM. This new phase covers the inner part of the macro-pores, progressively decreasing the pore size (0.9 μm) and volume (0.09 $cm^3 \cdot g^{-1}$) as could be demonstrated by Hg intrusion porosimetry.

3 Calculation of the activation energy (Ea) for SiO_2 release to quantify the glasses bioactivity

Most of the methods to evaluate the *in vitro* bioactivity use the rate of formation of the apatite layer as a qualitative measure of the bioactivity. The apatite formation is strongly influenced by the chemical composition and the textural properties. The presence of network modifiers (Na_2O and CaO) is a very

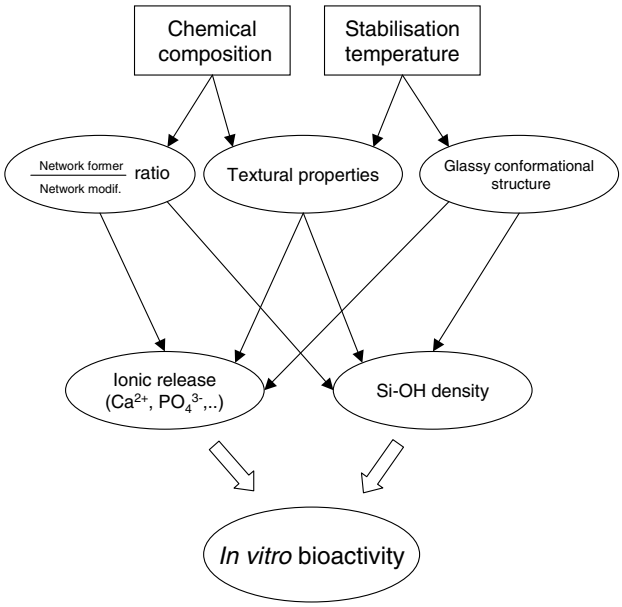

Fig. 4 Scheme representing the synthesis conditions and parameters that influence the bioactive process in sol-gel glasses

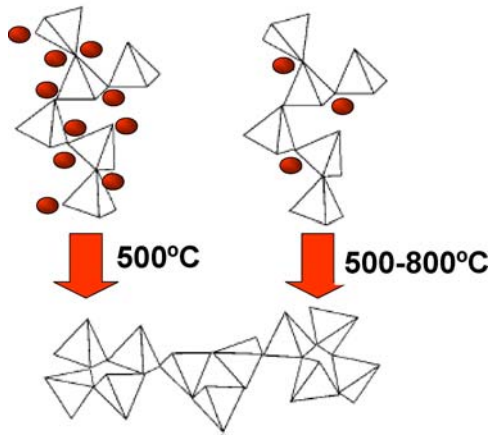

Fig. 5 Configurational changes in sol-gel glasses with the stabilization temperature. The glass with higher Ca content (left) requires lower temperature to carry out the transition from chain to rings configuration. Tetrahedra represent SiO_4 units and spheres represent Ca^{2+} cations

important factor. However, several authors had demonstrated that CHA is also formed on pure silica with high surface area [22, 23]. On the other hand, the textural properties also play an important role in the bioactive process, as can be seen when studying the bioactivity in sol-gel glasses. However, high surface area or porosity is not mandatory for the bioactivity either, because several melt-derived glasses, ceramics and glass ceramics with low textural parameters show good bioactive behaviour, but not if they not develop high surface area.

The cation release and the textural properties are important factors to consider, but they do not explain the bioactive behaviour by themselves. One of our objectives has been to find a quantitative parameter, which allowed predicting the bioactivity behaviour of a silica based glass. Figure 4 is a scheme of the conditions and parameters that determines the *in vitro* bioactivity. By changing the chemical composition and stabilization temperature of $CaO–P_2O_5–SiO_2$ sol-gel glasses, we could observe that the three most important properties—from the point of view of the *in vitro* bioactivity—could be controlled, i.e. network former (NF): network modifier (NM) ratio (network connectivity), textural properties (S_{BET} and porosity) and structural density. The network connectivity directly depends on the chemical composition. The lower the ratio the more bioactive the glass is. The textural properties depend on both the chemical composition and stabilization temperature, and it determines the bioactive behaviour through the ionic release and Si-OH surface density. Finally, the structural density, determined by the glassy conformational structure, mainly depends on the stabilization temperature for each composition. Figure 5 is a schematic representation of these processes in our glasses. The conformational flexibility of the silicate tetrahedra allows the structural evolution from very reactive chains to more stable condensed ring. When calculating the activation energy (Ea) for the silicon degradation, we observed that the variation of this value was closely related with the variation of network connectivity, textural parameters and structural density. In order to calculate the Ea of Si release we carried out the bioactivity test at 24°C, 37°C and 55°C, measuring the silicon concentration after 6 hours. Using Eq. (1) we observed the curves fit to Arrhenius plots for all the samples.

$$\mathrm{Ln[Si]} = \mathrm{Ln[Si_0]} - \mathrm{Ea/KT} \quad (1)$$

The Ea values for Si release were obtained from the slope of the curves.

Lower Ea values were obtained for those glasses that: (a) presented lower network connectivity, (b) showed higher surface area and porosity for the same chemical composition and (c) showed lower structural density. The three characteristics mentioned above determine the better bioactive behaviour of sol-gel glasses, and the value of the Ea for SiO_2 degradation results from the influence of the three of them. Therefore, by measuring the Ea for SiO_2 degradation we can predict whether a glass is bioactive or not. Preliminary studies suggested that Ea for silica degradation lower than 0.35 eV results in bioactive glasses, whereas those with Ea higher than 0.5 eV are not [24, 25]. The Ea gap between 0.35 and 0.5 eV might be considered as the boundary between bioactive and non-bioactive glasses.

4 New protocols to evaluate the *in vitro* bioactivity of bioactive glasses

It is widely accepted that *in vitro* studies, monitoring the formation of a CHA layer on the surface of a material, predict its bioactive behaviour when implanted. However, in the *in vitro* study of materials with high reactivity in aqueous solutions, such as bioactive glasses, remarkable variations in the ionic concentration and pH of solution take place, reaching values far from physiological ones, which made questionable the value of these assays. Thus, some authors proposed the exchange of the reaction solution at time intervals [26–28]. In our *in vitro* bioactivity studies of gel glassesin SBF, noticeable increases of pH, around 0.6 units from the initial 7.4, as well as other variations in the ionic concentration of Ca(II), P(V) and Si(IV) were detected just after a few minutes of assay [29]. Such pH increases could favour the CHA formation even in weakly bioactive materials. In addition, the periodical solution exchange to eliminate said effects in glasses would require so short time intervals that the formation process of the CHA layer could be affected by the sample manipulation.

To solve all these problems, our research group proposed a new *in vitro* protocol where the solution is continuously renewed (*dynamic*) (Fig. 6). The *in vitro* bioactivity of several glasses was studied in *dynamic* and compared with that without the renewal of the in vitro solution (*static*) [30]. The solution renewal at 1 mL/min allowed maintaining the ionic concentration and pH of solution almost constant. Some differences in the CHA layer formation process were observed as a function of the protocol. In *static*, a faster initial formation of the amorphous phosphate layer was detected, but for higher soaking times the situation was equivalent in both cases. In *dynamic*, the size of the apatite crystals formed is bigger. Regarding the layer composition in *dynamic*, the Ca/P molar ratio was considerably lower than in *static* (1.2 *vs*. 1.6). This variation was explained from the differences in pH. The lower pH in *dynamic* (7.4) increases the HPO_4^{2-} concentration in solution compared with *static* where pH is close to 8. Thus, *dynamic* would favour the formation of calcium deficient apatite, which might coexist with other calcium phosphates of lower Ca/P molar ratio. In addition, the bigger size of the aggregates of CHA crystals formed in *dynamic* was explained from the continuous supply of calcium and phosphate ions.

From our studies we conclude that *dynamic* protocol allow to deep inside aspects related with the CHA formation mechanism. However, the simplicity and speed of conventional *static* assay made it the most appropriate protocol to check the glasses bioactivity in most of the cases.

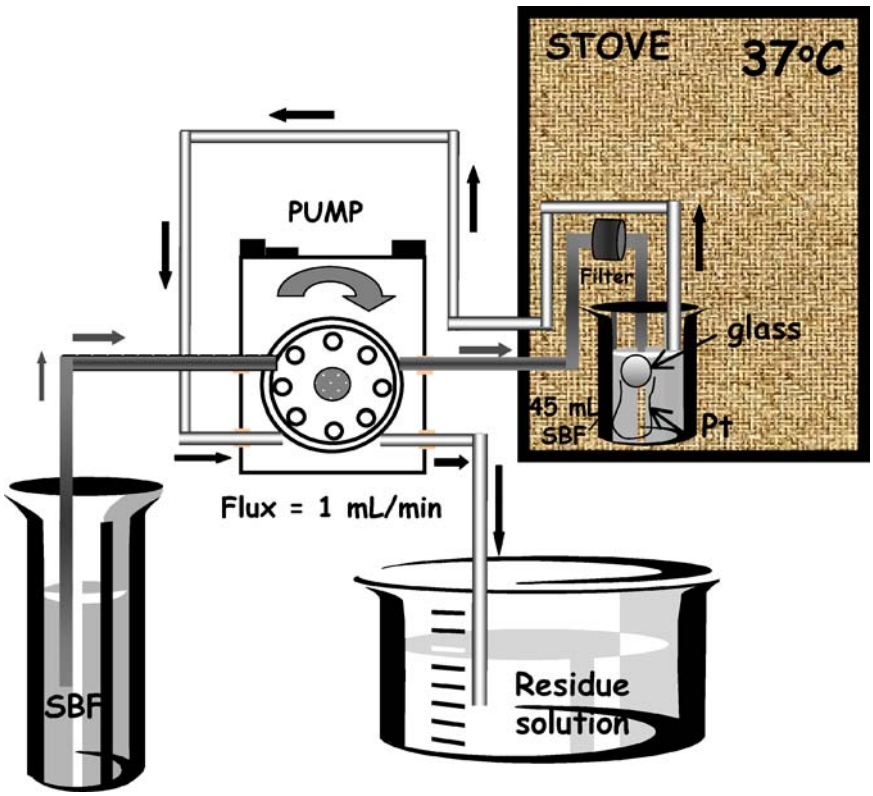

Fig. 6 Schematic description of the *dynamic in vitro* bioactivity assays. The continuous flow of the body fluids is modeled by the continuous renewal of the SBF solution

5 Organic-inorganic hybrids to expand the clinical application of bioactive glasses

In recent years, organic-inorganic hybrids has become an important subject for materials and medical researchers. For clinical applications, the preparation of bioactive hybrids able to bond to living tissues is an important task. Our research group has developed bioactive coatings of $CaO–SiO_2$–poly(dimethylsiloxane) (PDMS) organic-inorganic hybrids on Ti6Al4V substrates [31]. The addition of PDMS confers new mechanical properties to the material, including some elastic behaviour, and simultaneously decreases the degradation rate of the coating. The coatings were carried out by the dip-coating method. This technique is based on the sol-gel process and allows the deposition of organic-inorganic hybrids at soft temperatures onto metallic substrates. These substrates are immersed into the aqueous multicomponent sols and then thermally treated. The coating method allows (i) corrosion of the metallic substrate to be avoided because of the formation of a barrier to ion release from the implant to the body, (ii) the formation of the apatite layer on the surface to be improved (fixing the implant), and (iii) a material intermediate between bone and the implant to be produced, damping their different mechanical properties. The viscosity of the sol together with the withdrawal speed of the substrate plays a key role in the final properties of the films. In the case of $CaO–SiO_2$–PDMS organic-inorganic hybrids, the viscosity was observed independent of the shear rate, i.e. showed Newtonian flow behaviour, for aging times lower than 16 hours. Longer aging times led to extensive network formation resulting in a thixotropic flow behaviour, where the viscosity shows an irregular behaviour. In general, a nanocrystalline apatite-like layer was formed over the film surface when soaked in SBF for 7 days.

Another interesting approach is synthesizing organic-inorganic hybrids based in bioactive gel glasses and a biocompatible hydrophilic organic polymer, such as poly(vinyl alcohol) (PVAL) that would tailor the hybrid degradation. Actually, PVAL has been widely proposed for controlled release systems due to its biodegradability. We have also reported on this system obtained as monoliths and characterized before and after being soaked in SBF [32]. The biodegradability and bioactivity of the hybrids were studied as a function of the PVAL content. We could observe that the addition of PVAL helped the synthesis of crack-free monoliths able to be coated with bone-like apatite when soaked in SBF, i.e. to present in vitro bioactivity. On the contrary, higher amounts of P_2O_5 made the hybrids synthesis difficult and decreased their *in vitro* bioactivity, although also contributes to the material degradability. Thus, hybrids with very high amounts of both PVAL and P_2O_5 showed such a fast degradation that apatite formation is impeded.

6 Star gels bioactive materials

The evolution of organic-inorganic hybrid materials chemistry allows to improve the mechanical properties of silica based compounds. In 1995 DuPont Corp. developed the 'star gel' materials [33]. '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. These groups would form a silica-like network through the sol-gel process. This characteristic structure allows having precursors with flexibility at a molecular level, which is an important feature when used as implant materials. At a macroscopic level, 'star gels' exhibit behaviour between conventional glasses and rubbers in terms of mechanical properties.

Our research group has developed new 'star gels' with bioactive behaviour. This goal has been reached by incorporating calcium to the star gel network. Since their suitable mechanical properties have been widely tested [34, 35], these materials are excellent candidates for bone regeneration in the case of medium and large defects.

Bioactive star gels (BSG) were obtained by hydrolysis and condensation into network structures of the precursors plotted in Fig. 7, together with different amounts of a calcium alkoxide [36]. ^{29}Si CP-MAS NMR spectroscopy was used to determine the Ca^{2+} incorporation into the inorganic SiO_2 network. In both BSG materials, the T^1 and T^0 contributions were observed to increase as the amount of Ca^{2+} introduced into the hybrid network was enlarged. The percentage of T^3 species was decreased when Ca^{2+} was added, probably due to the role of Ca^{2+} in the network, i.e. reducing the cross-linking density and, therefore, reducing the amount of fully condensed Si-O-Si structures. Summarizing, it can be stated that Ca^{2+} is incorporated to the star gel network, without forming crystalline segregated phases and acting as a network modifier into the inorganic silica component. The bioactivity evaluation was carried out by soaking the 'star gel' monoliths into simulated body fluid (SBF), developing a new apatite layer on the surface after 7 days. In conclusion, we have developed bioactive 'star gels' by means of incorporating Ca^{2+} cations into the 'star gels', which can be obtained as monoliths of any shape and size

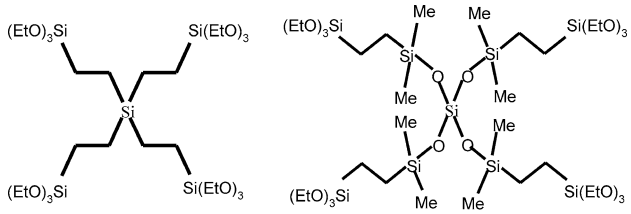

Fig. 7 Example of typical star gel precursors

and are able to develop an apatite phase on their surface when soaked in SBF. Taking into account the tested mechanical properties these bioactive 'star-gels' are excellent candidates for osseous regeneration in medium and large bone defects.

7 Conclusions

The discovery of bioactive glasses by Prof. Hench opened an amazing research field that, more than 30 years later, is still under development. This article collects the contribution of our research group to the knowledge of bioactive glasses, and it is also an appreciation to Prof. Hench for his guidance in this field. The role of P_2O_5 in sol-gel glasses, the study of the kinetic of SiO_2 degradation, the evolution of sol gel glasses textural properties and the development of new protocols constitute our main contribution to the understanding of the bioactive process in sol-gel glasses. Finally, this article also shows a new insight to overcome the main lack of the glasses: the mechanical properties. By synthesising organic-inorganic hybrid materials (PDMS-SiO_2-CaO or star gels) we can obtain bioactive implants with better mechanical properties.

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