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An Overview of The Effects of Thermal Processing on Bioactive Glasses

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Abstract:

Bioglass® 45S5 is widely used in biomedical applications due to its ability to bond to bone and even to soft tissues. The sintering ability of Bioglass® powders is a key factor from a technological point of view, since its govern the production of advanced devices, ranging from highly porous scaffolds to functionalized coatings. Unfortunately this particular glass composition is prone to crystallize at the temperature required for sintering and this may impair the bioactivity of the original glass. For these reasons, a prerequisite to tailor the fabrication of Bioglass®-derived implants is to understand the interaction between sintering, crystallization and bioactivity. In this work the structural transformations which occur during the heat treatment of Bioglass® are reviewed and a special attention is paid to the sintering and crystallization processes. Moreover the bioactivity of the final glass-ceramics is discussed and some alternative glass formulations are reported.

Keywords*: Glass; Thermal Treatment; Sintering; Crystallization; Bioactivity. Sintered steel, Gears, Transmission, Wear*

Extended Abstract

It was 1969 when Hench determined the chemical composition of a special glass that was not surrounded by fibrous tissue when implanted into the body; instead it was able to bond to bone. That lucky composition, successfully employed to realize prostheses by the mid 1980's, was only the first discovered in a family of bioactive glasses called Bioglass®. During the last decade, the effort of many materials scientists has been devoted to the realization of many Bioglass®-based implants such as scaffolds, i.e. porous systems aiming to mimic the complex porous structure of the human bone. To this aim, the sintering ability of Bioglass® powders is a key factor from a technological point of view, since this particular glass composition is prone to crystallize at the temperature required for sintering. Unfortunately, several investigations underline some significant negative effects of crystallization on Bioglass® bioactivity. For these reasons, a prerequisite to tailor the fabrication of Bioglass®-derived implants is to understand the interaction between sintering, crystallization and bioactivity of the resulting glass-ceramics. In this work the structural transformations which occur during the heat treatment of Bioglass® are reviewed. After a brief introduction on the structural transformations of bulk Bioglass® with thermal treatments, the sintering and crystallization of powders is discussed, with a particular emphasis on the biodegradation

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behavior of Bioglass®-derived glass-ceramics. Finally, since the crystallization tendency of the experimental glasses is strongly dependent on their composition, an overview on alternative glass formulations is reported.

1. Introduction

The ability to bond to bone was first detected for glasses belonging to the Na_2O-CaO-SiO_2-P_2O_5 system, with specific proportions of the constituent oxides [1, 2]. The basic properties that distinguish these glasses from conventional sodium-calcium-silicate products, such as window glasses or microscope slides, are (1) a relatively low content of silica, less than 60 mol%, (2) a high Na_2O and CaO content, and (3) a high CaO/P_2O_5 ratio. These peculiarities in the glass formulation confer a high reactivity in aqueous media. In particular, bioactive glasses are able to bond to bone through the formation of a surface layer of hydroxyapatite, which drives and promotes osteogenesis, allowing the rapid formation of new bone. Most of the glasses satisfying the abovementioned compositional parameters have been shown to bond to bone, some even to soft tissues, with the exception of compositions having substantially low molar ratios of CaO to P_2O_5 [1].

The most famous glass of this family is the so-called 45S5, whose name suggests that the SiO_2, whose content is 45 wt%, is the network former, and that the CaO to P_2O_5 ratio is 5:1.

Most of the glasses studied and clinically used today have compositions similar to that of 45S5, but a change in composition may deeply alter the bioactivity [3]. According to the literature, if 5-15 wt% B_2O_3 is introduced instead of SiO_2 or 12.5 wt% CaF_2 is used instead of CaO, the bioactivity of 45S5 is not sensibly changed [2]. However, the addition of as little as 3 wt% Al_2O_3 is sufficient to suppress the ability to bond to bone [4]. Moreover, if a constant amount of P_2O_5 is considered (6 wt%), the bonding ability may significantly change in function of the Na_2O to CaO to SiO_2 ratios, since very specialized glasses are able to bond to both hard and soft tissues, a wider group of glasses is able to bond to bone only, some glasses are quickly degradable in aqueous media and some glasses are not technically feasible [5-7].

Bioactive glasses are mainly used as platelets or particles, or even in powder form, to work as bone defect fillers, dental and middle ear implants, cranial and maxillo-facial reconstruction [8-11]. Nevertheless, more advanced applications require to perform heat treatments on bioactive glasses, in order to obtain special products. For example, glass fibres may be drawn only in specific viscosity ranges, which can be achieved at high temperature. Also coating techniques, such as plasma spraying [12], may cause the glass to crystallize, altering its behaviour in biological environments. However, the most striking example is given by the production of bioactive scaffolds [13], which are porous structures used in last-generation implants to support the spontaneous bone repair mechanisms. Scaffolds are usually produced via well-established techniques, such as the replication method [14] and the polymer burning-out method [15], which unavoidably include a heat treatment to densify the initial glass powder. Unfortunately, the optimal temperature range to sinter the 45S5 is very close to its crystallization temperature, thus causing a wide devetrification of the system. The crystallization may improve the mechanical properties of the scaffold, but it may impair the bioactivity, since it has been reported that the newly formed crystal phases are scarcely bioactive [16-18].

Due to the concomitant development of sintering and crystallization, a very accurate investigation of the effects of heat treatments on bioactive glasses, especially on 45S5, is mandatory. Some basic topics should be fixed:

- The thermal behaviour of bioactive glasses and, most of all, of 45S5 – in bulk and in powder form – should be univocally defined, in order to predict the nature of the new phases and the degree of crystallization associated with a fixed sintering process;
- The effect of crystallization on bioactivity should be accurately assessed. The information reported in the literature on this argument, in fact, is often contradictory [19, 20]. It would be desirable to understand whether the bioactivity mechanisms are completely suppressed or simply slowed down by the formation of the new crystal phases. In this regard, it should be kept in mind that not all the applications require a very quick bio-reaction, so, if the crystallization actually slowed down the bio-reactivity (without eliminating it), it would be possible to tune the bioactivity by means of a controlled crystallization;
- The consequence of a change in the glass composition on both the thermal behaviour and the bioactivity should be considered. In fact, modifying the Na_2O-CaO-SiO_2-P_2O_5 proportions with respect to the canonical formulation of 45S5 or introducing different oxides, it should be possible to change the sintering and crystallization temperatures, as well as the composition of the crystal phases possibly developed during the thermal treatment. However, a different composition is expected to result in a different biological behaviour of both the glass itself and the heat-treated glass.

2. Sintering and crystallization of 45S5

2.1. Heat treatment of bulk 45S5: a brief overview

As already mentioned, according to the available literature, 45S5 is prone to crystallize during heat treatments – which are often required for manufacturing special products or shapes – due to its relatively low percentage of silica and its high content of network modifiers. As regards the phosphorous, the presence of P_2O_5 is expected to play a double role in silicate glasses, including 45S5: on the one hand, it is a network former; on the other hand, the double oxygen bond is thought to promote the formation of phosphate phases and, hence, the crystallization of the glass [18]. Moreover, if the content of P_2O_5 is increased to 9 wt%, an apatite-like crystal phase develops during ordinary thermal treatments and reduces the glass-ceramic bioactivity, since glass-ceramics containing an apatite-like phase are usually much less bioactive than materials containing phosphorous in solid solution [18].

It is still under debate whether 45S5 predominantly shows surface crystallization or bulk crystallization. Arstila et al. [21], in order to investigate the factors governing the crystallization of bioactive glasses, considered several formulations and assumed 45S5 as a reference glass. The DTA and the isotherm crystallization tests on glass plates suggested that 45S5 should show surface crystallization according to Avrami constant values, but bulk crystallization according to the glass stability value T_{gr} (also known as "reduced glass transition temperature"), which is defined as the liquidus temperature-to-glass transition temperature ratio ($T_{gr} = T_l / T_g$). The direct observation by SEM of the plate (cross section) suggested that the heat treatment promoted a liquid-liquid phase separation and that an internal nucleation favoured bulk crystallization. It may be hypothesized that the calculated value for the Avrami constant was affect but the extremely small particle size of the powder used to perform the DTA. In fact, it is known that small particles may undergo surface crystallization also in systems with bulk crystallization. In the same paper [21], the Authors extended their research to six more bioactive glasses. On this basis, they outlined a classification of silicate-based bioactive glasses into two groups: (1) glasses with glass transition temperature around 500°C and onset of crystallization below 750°C, and (2) glasses with glass transition temperature between 550 and 600°C and onset of crystallization around 900°C. The Authors found that the thermal behaviour was closely related to the primary crystalline phase formed in crystallization, since the glasses belonging to the former group mainly developed sodium-calcium-silicate phases, while the glasses belonging to the latter

group mainly formed wollastonite. 45S5 obviously belonged to the sodium-calcium-silicate type. A detailed analysis of the XRD pattern of the heat-treated 45S5 plate clearly showed the presence of sodium-calcium-silicates, but the exact crystal phase could not be identified with certainty, since sodium-calcium-silicates exhibit very similar reference patterns and often give solid-solid solutions [22]. However the best fitting was achieved with the reference pattern of $Na_2Ca_2Si_3O_9$ [21], which was supposed to be the main crystalline phase. On the other hand, Arstila and co-workers, in a later contribution, confirmed that 45S5 plates mainly showed surface crystallization at about 600°C and homogeneous crystallization at higher temperatures, proving the importance of internal nucleation for this glass. In this paper, the prevalent silicate was identified as $Na_2Ca_2Si_3O_9$ [23], while the SEM-analysis of the cross-sections revealed a uniform network texture of crystals surrounded by a thin layer of a glassy phase with a high content of phosphorous.

These results agree well with the crystallization kinetics described by Clupper and Hench for tape-cast 45S5 [16]. In fact, the Authors found values of the Avrami coefficient very close to 1, by both the Ozawa method and the Augis-Bennett one, concluding that a surface crystallization was predominant for tape-cast 45S5. However they worked with very fine powders (mean particle size: about 3 μm) and they stressed that such result could not be extended to larger particles, due to the unavoidable necessity of taking into account the effect of particle size on crystallization mechanisms (surface/bulk). The predominant crystal phase was identified as $Na_2Ca_2Si_3O_9$ [16], which corresponds to the phase identified by Arstila and co-workers in their papers [21, 23]. $Na_2Ca_2Si_3O_9$ was also observed by Rizkalla et al. [24], who investigated the crystallization kinetics for six glass formulations in the Na_2O-CaO-SiO_2-P_2O_5 system. However, the literature is far from unanimity in identifying this phase. While several authors [14, 25, 26], working with 45S5 powders, identified $Na_2Ca_2Si_3O_9$ as the main crystallized phase, Lin and co-workers stated that 45S5 crystallizes with the formation of $Na_2CaSi_2O_6$ as major phase [27]. Lefebre et al. [28] agreed in identifying $Na_2CaSi_2O_6$ as the main crystallized phase. These Authors proposed a possible scenario of the structural transformations occurring in 45S5 during thermal treatments, as described in the next sections. In particular, as reported by Lefebre and co-workers, it should be noted that $Na_2CaSi_2O_6$ is isostructural to $Na_2Ca_2Si_3O_9$, where 2 Na replace 1 Ca ion, thus confirming the difficulty in distinguishing the various sodium-calcium-silicates.

2.2. Sintering and crystallization of 45S5 powders

The evaluation of the effect of thermal treatments on 45S5 powders is even more difficult, because not only crystallization and phase separation processes are likely to occur, as already observed in bulk samples, but also sintering mechanisms may be active, promoting the densification of the powders in order to reduce the high interfacial energy associated with particle systems [29].

Lefebvre et al. [28] proposed a comprehensive analysis of the thermal behaviour of 45S5 in powder form, combining the results obtained from several techniques (TG-DTA, *in-situ* ESEM, XRD and FTIR).

An outline of the relevant temperatures and corresponding phenomena is sketched in Fig. 1, which also includes additional information about sintering [19]. At 400°C, the departure of OH^- groups can be detected then, at 550°C, a first glass transition occurs. At 570° an accurate observation of the glass particle surface (by *in-situ* high temperature ESEM) reveals a glass-in-glass phase separation. This process is predictable, since two valence ions, namely Si^{4+} and P^{5+}, are present simultaneously in the 45S5 and each ion tends to create a separate phase [30]. At higher temperatures, the glass is no longer homogeneous, since two different immiscible phases are present. This brings two main consequences: first of all, the viscosity increases (with respect to a homogeneous, not-separated glass having the same

composition), since the flow behaviour is dominated by the (prevalent) silica-rich phase, which is very viscous; moreover, the phosphate-rich domains separated from the silica-rich phase are expected to catalyse the following crystallization phenomena, like heterogeneous nucleation sites. In fact, at 610°C an extensive crystallization process takes place. Based on the Avrami exponent of about 1 calculated by Lefebvre et al., the formation of the crystalline phase is the result of a slow nucleation on the surface and infinitely rapid growth of the nuclei. Lefebvre et al. [28] identified $Na_2CaSi_2O_6$ as the main crystalline phase, even if this attribution contrasts with previous theories. In fact, although the $Na_2CaSi_2O_6$ phase corresponds better to the nominal composition of 45S5 [19], it was generally thought that 45S5 crystallizes in the $Na_2Ca_2Si_3O_9$ system [31]. This uncertainty is probably due to the fact that $Na_2CaSi_2O_6$ is isostructural to the high temperature form of $Na_2Ca_2Si_3O_9$. Moreover, as frequently reported in the literature, the crystallization behaviour of 45S5 depends on glass particle size and heating conditions. In fact, the $Na_2Ca_2Si_3O_9$ phase is predominant for high-temperature thermal treatments, namely above 950-1000°C, and it is the major outcome in porous sintered bodies, which require a thermal treatment above the second glass transition temperature of 45S5 (about 850°C) to achieve full densification of struts [14, 32, 33]. Moreover Peitl et al. also confirmed the development of $Na_2Ca_2Si_3O_9$ in bulk samples [18].

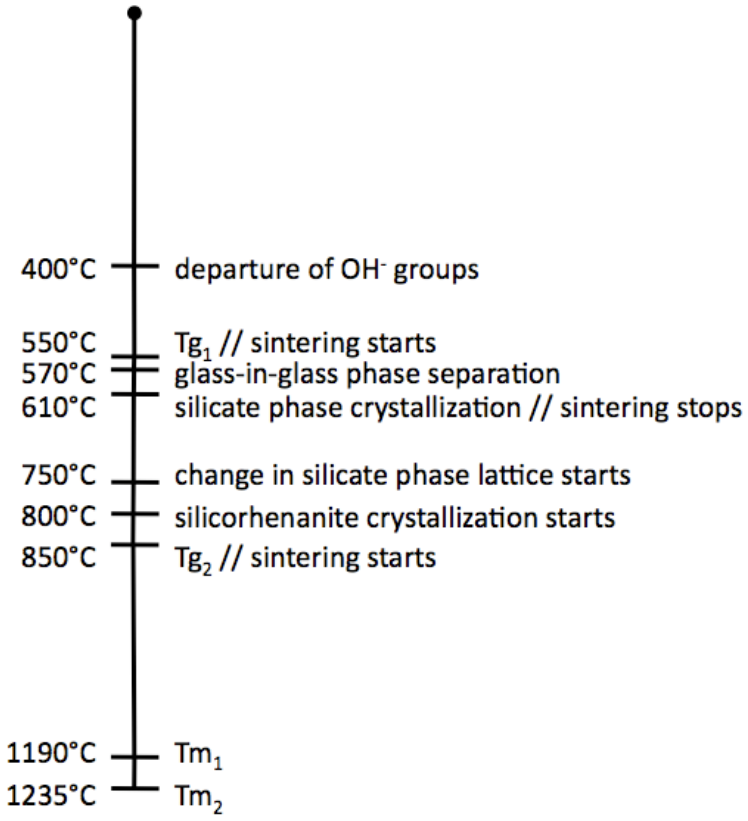

Fig. 1 Temperature line for 45S5

A differential grain growth leads to a quick development of the larger silicate crystallites at the expense of the smaller ones. At the same time, the remaining phosphate glassy phase migrates and surrounds the silicate crystallites, whose surface acts as a nucleation agent for a new crystal phase. In fact, the crystallization of an apatite-like phosphate phase, $Na_2Ca_4(PO_4)_2SiO_4$ (silicorhenanite), is observed in the 800-950°C range. More exactly, Lefebvre et al. [28] suggested that the orthophosphate ions in the glass concur to the crystallization of the silicorhenanite, while the diphosphate ions remain in the surviving

amorphous phase. In the 750-950°C range, moreover, the lattice parameters of the $Na_2CaSi_2O_6$ crystal phase change; in particular, *a* decreases smoothly, while *c* increases suddenly at about 800°C, in coincidence with the appearance of the silicorhenanite. Now, the residual amorphous phase undergoes a glass transition at around 850°C and, if the temperature further increases, in the 1070-1278°C range the two crystalline phases melt.

The sintering behaviour of 45S5 is deeply influenced by the ongoing transformations in the glass structure. Basically, according to Boccaccini et al. [19] three main stages can be identified: a first step of rapid densification from T_{g1} (about 550°C) up to about 600-610°C, when glass-in-glass phase separation and crystallization occur; a plateau from about 610°C to T_{g2} (about 850°C); again, an important densification above T_{g2} (about 850°C). From a physical point of view, if the temperature exceeds T_{g1}, the glass softens and densification may occur via viscous flow sintering. However, if the temperature increases to 600-610°C, both glass-in-glass phase separation and crystallization take place. As a result, the viscosity dramatically increases and the sintering process stops. The transition from the first densification step and the plateau is usually abrupt, because the densification stops when the new crystalline phase creates a continuous, percolating network. Nevertheless, the limit temperature is not univocal, because, as previously stated, the crystallization behaviour depends on the heating rate and particle size [28, 34]. Then, the densification process starts again above T_{g2}. The leading mechanism for the second densification step is not clear so far. It has been proposed that, above T_{g2}, the residual amorphous phase gets soft enough for viscous flow sintering to occur, but also liquid phase sintering through diffusion by dissolution/precipitation may take place.

Recently, these results have been confirmed by Bretcanu et al., who have thoroughly investigated the sintering process of 45S5 under various heating conditions [35]. The heating microscopy tests, performed at 20°C/min up to 1150°C, showed that the shrinkage associated to the first sintering step, between around 500°C and 600°C, is about 12%, while the shrinkage associated to the second step, between around 950°C and 1100°C (when the system starts to melt), is about 36%. Similar tests carried out at different heating rates (10°C/min; 3°C/min) revealed that a low heating rate causes a prolonged exposure of particles to high temperature, thus promoting crystallization at the expense of viscous flow sintering. On the contrary, high heating rates increase the duration of the first sintering step and, hence, the corresponding shrinkage of the glass powder compacts. For cylindrical samples, the comparison between the radial shrinkage and the axial shrinkage for various heating rates proved a slightly anisotropic behaviour, also affected by the on-going crystallization. Instead, if isothermal conditions are applied, 45S5 compacts should be treated at 1050°C for 140 min. to achieve optimal densification. As frequently observed in the literature, also the characteristic temperatures identified by the DTA are deeply influenced by the heating rate. In particular, if the heating rate increases, the first glass transition temperature and the main crystallization temperature increase, while the melting onset temperature decreases. The Hruby coefficient, calculated for different heating rates on the basis of these characteristic temperatures, varies between 0.25 and 0.30 and confirms the high ability of 45S5 to crystallize. Additional data obtained by the DTA at different heating rates can be used to calculate the Avrami exponent, whose average value is 0.95, suggesting that a surface crystallization is predominant. However, as previously reported, this result is conditioned by the very small particle size (< 5 μm) of the powder used by Bretcanu et al. in their research, since Arstila et al., working on the behaviour of glass bulks, underlined that also internal nucleation should be considered for 45S5 [21, 23]. Indicative characteristic temperatures for sintering are reported in Fig. 1 as well.

3. Bioactivity after thermal treatment

Crystallization does not necessarily mean loss of bioactivity. For example, it has been proven that a range of low-alkali silica glass-ceramics (commercially known as "Ceravital") are able to bond to bone, even if this property is suppressed by the addition of Al_2O_3, Ta_2O_5, TiO_2, Sb_2O_3, or ZrO_2, even in small amount. The bone-bonding ability has been demonstrated also for a glass-ceramic composed of apatite and wollastonite crystals in a residual glass matrix, usually known as apatite/wollastonite (the short form A/W being more commonly used). [5]. Nevertheless, the effect of a crystallization process on the bioactivity of 45S5 and similar glasses is still under debate.

In a pioneering contribution, Li et al. [20] found that crystallization could substantially suppress the bioactivity of a bioactive glass (containing, in wt%, SiO_2 48, P_2O_5 9.5, Na_2O 20 and CaO 22.5), since the ability to form a hydroxycarbonate apatite (HCA) layer in a Simulated Body Fluid (SBF) survived only if the glass-ceramic retained more than 90% of residual amorphous phase. In fact, if the glassy phase was sufficiently abundant, the immersion in a simulated physiological solution promoted the formation of a surface apatite layer on top of a silica-rich one. However, if the material was almost completely crystallized, only the silica-rich layer could be observed, suggesting that the precipitation of the apatite depended on the presence of a residual glassy phase in the glass-ceramic. On the contrary, Peitl and co-workers [36] performed heat treatments in the 550-680°C temperature range, causing a controlled crystallization from 8 to 100 vol%. During immersion in SBF, also the fully crystallized samples could develop a crystalline HCA layer, but the onset time of the process changed from 10 hours for the original glass to 22 hours for the completely crystallized sample. In particular, the reaction rate significantly reduced when the degree of crystallization was higher than 60 vol%.

The extensive research carried out by Clupper and Hench on tape-cast and sintered bioactive glass-ceramics confirmed that 45S5 might be bioactive even after crystallization, since the presence of the crystal phase $Na_2Ca_2Si_3O_9$ simply slows down the development of apatite *in vitro*, without suppressing it [37, 38]. A further contribution to understand the effect of crystallization on bioactivity was given by Chen et al. [14], who focused on the bioactivity of 45S5-derived glass-ceramic scaffolds. They proposed that the bioactivity could survive after crystallization since the $Na_2Ca_2Si_3O_9$ crystal phase, which they observed in their scaffolds, is bioactive by itself [18]. Moreover they suggested that the $Na_2Ca_2Si_3O_9$ phase, when immersed in a simulated physiological solution, could transform into an amorphous phase, a process that could justify not only the survival of bioactivity, but also the abovementioned decrease in kinetics of apatite formation on 45S5-derived glass-ceramics. In fact, according to Chen et al., the same bone-bonding mechanisms of bioactive glasses, described by Hench et al, should be applicable to $Na_2Ca_2Si_3O_9$ crystallites. It is well known that, when immersed in body fluids, bioactive glasses (including 45S5) dissolve and a hydrated silica-gel layer develops on their surface; then, an amorphous calcium phosphate forms from the silica gel; to conclude, apatite crystallites nucleate and grow from this amorphous substrate [39-43]. Hence Chen et al. hypothesised that these reaction stages could occur also in presence of $Na_2Ca_2Si_3O_9$ crystallites, which however possess a slower dissolution rate with respect to the parent glass [14]. On the other hand, the transformation of a crystalline phase into a reactive amorphous phase has been observed also in other systems. For example, hydroxyapatite and similar calcium phosphates experience an analogous transformation in an *in vivo* environment [44]. However, the "amorphization" of hydroxyapatite is much slower than that of 45S5. For example, it has been reported that hydroxyapatite particles develop a 0.5 μm thick amorphous layer after 3 months of implantation and that the particles do not bio-degrade sensibly even after 6 months [44]. From this point of view, however, it is worth noting that Chen et al. worked with highly porous glass-ceramic scaffolds, characterised by an extremely wide surface area, further increased by

the hollow centre of the struts. Therefore the Authors recognised that the kinetics of the transformation, though not fully understood, was certainly enhanced by the high surface energy of the system [14].

The transformation of $Na_2Ca_2Si_3O_9$ crystallites into an amorphous phase was confirmed for 45S5-derived scaffolds also by Boccaccini et al. [19]. The Authors modelled the degradation mechanisms in three basic steps. (i) First of all, a preferential dissolution takes place at the interface between $Na_2Ca_2Si_3O_9$ crystallites and residual glassy phase. The so-produced gaps between crystalline particles and amorphous matrix allow the physiological solution to penetrate deep inside into the material and to promote a diffused ion leaching from the crystalline phase. (ii) As a consequence of the ion exchange, which occurs at preferential locations such as dislocations and sub-grain boundaries, the crystallites progressively break down into very fine grains. Meanwhile, the amorphous matrix is dissolved. (iii) Since the ion exchange causes a large amount of point defects, the periodic lattice of the crystalline phase increasingly distorts and, in the end, changes into an amorphous phase [19].

Even if the kinetics of crystallite degradation and consequent apatite formation is slow, the preserved bioactivity of 45S5-derived glass-ceramics offers new, interesting opportunities, since sintered and crystallized systems are mechanically more reliable than the original parent glass. Moreover, the reaction rate of the biomedical device can be adjusted to match the natural healing rate of bone tissue by governing the crystallisation degree via a proper thermal treatment [14].

4. Alternative glass formulations

In order to control and/or modify the glass behaviour during a thermal treatment (increased/decreased crystallization tendency; modified sintering temperature; etc.), several new formulations have been proposed. Moreover, specific glass compositions have been designed to respond specific needs (tailored coefficient of thermal expansion; improved high-temperature workability; etc.). However, as previously mentioned, the bioactivity of a glass is deeply conditioned by its chemical composition, since slight modifications might dramatically reduce or even suppress the ability to develop a surface apatite layer in physiological solution [3, 6, 7, 45]. In fact, it should be kept in mind that compositions in the Na_2O-CaO-SiO_2 system (6 wt% P_2O_5) with SiO_2 between 52 and 60 wt% are able to bond to bone very slowly and compositions with more than 60 wt% SiO_2 are bioinert; moreover, the addition of multivalent cations such as Al^{3+} or Ti^{4+}, even in small amounts, further limits the bone bonding ability [1], unless properly balanced – at least to a certain extent – by the addition of other additives, such as B_2O_3 [46, 47]. Hence, when the glass formulation is changed to pilot its behaviour during a thermal treatment or to suit its properties, it is essential to test the bioactivity of both the glass itself and the resultant sintered and/or crystallized product.

After the pioneering work by Lockyer et al. [48], who investigated the structure of a range of glasses covering the "inert", "resorbable" and "bioactive" region of the Na_2O-SiO_2-CaO-P_2O_5 system (with a constant 6 wt% of P_2O_5), the contribution by Peitl et al. mentioned in the previous sections is one of few papers that systematically investigate the effect of the glass composition and degree of crystallization on the in-vitro behaviour [18]. The Authors considered various compositions, with and without P_2O_5, and performed several heat treatments in order to achieve controlled degrees of crystallization. Independently of the glass composition, the only crystal phase in all the glass-ceramics was $Na_2Ca_2Si_3O_9$, while no apatite-like phase was detected. The Authors demonstrated that all the parent glasses and the derived glass-ceramics were able to develop a HCA surface layer in physiological solution. However the on-set time of HCA precipitation was much higher for the phosphorous-free glasses, which incorporated the required phosphorous from the solution as previously observed for other bioactive glasses not containing phosphorous [7, 49]. The crystallization of

these glasses had a minor effect on the on-set time of HCA formation, which increased from about 26 hours for parent glasses to about 32 hours for completely crystallized materials. Instead the crystallization of the phosphorous-containing glasses dramatically slowed the HCA development, whose on-set time rose from about 8 hours to about 24 hours. A detailed evaluation of the reaction kinetics in physiological solution proved that specific phosphorous-containing glass-ceramics could behave almost as well as 45S5, but with much better mechanical properties. This finding suggests that, due to an accurate formulation, unique crystalline materials could be produced that might combine comparable bioactivity and superior mechanical properties with respect to the well-established 45S5 [18, 50].

As previously mentioned, due to their brittleness and poor mechanical properties, bioactive glasses can not be used in bulk form in load-bearing applications. In order to overcome this limit, bioactive glasses are frequently applied as coatings on tough substrates. Ideal candidates for the production of substrates for biomedical devices are high-strength ceramics, such as alumina and zirconia. However special glass and glass-ceramic coatings must be realized to match the coefficient of thermal expansion of ceramic substrates and to achieve a sufficient adhesion [51, 52]. Also metallic substrates, especially titanium and titanium alloy ones, are frequently used in biomedical prostheses. Unfortunately, the problems to solve are even more severe. In fact, the coefficient of thermal expansion of conventional bioactive glasses is often sensibly higher than that of metals. Moreover reactions may occur at the interface between the coating and the substrate, and the metal may degrade during the coating deposition process [53]. Lopez-Esteban et al. [54] proposed a new family of glasses in the SiO_2-Na_2O-K_2O-CaO-MgO-P_2O_5 system, especially designed in order to facilitate the deposition of a glass coating on a titanium substrate by enamelling. In fact, with respect to the standard 45S5 formulation, the partial substitution of Na_2O by K_2O and CaO by MgO was intended to modify the coefficient of thermal expansion of the glass, to match that of titanium and titanium alloys. The formulation of the new glasses was completed by the optimization of the thermal processing to deposit the coating. Interestingly, a controlled reaction was promoted at the interface, in order to induce the formation of a thin (100-200 nm) interfacial layer, which promoted the adhesion. The bioactivity of the new glass coatings was tested and confirmed by *in-vitro* immersion in SBF.

An alternative glass formulation, derived by that of 45S5 substituting all the Na_2O with K_2O, was proposed by Cannillo et al. [55] to limit the tendency to crystallize during processing and, hence, to preserve the amorphous nature of the material in the final coatings deposited via both enamelling and plasma spraying. Also in this case, in spite of the change in composition, the ability to develop a surface layer of HCA when immersed in SBF was confirmed by *in vitro* tests [56].

These outcomes on the *in vitro* behaviour of K_2O- and MgO- modified glasses and glass coatings are coherent with the results obtained by Brink and co-authors for numerous glasses in the system Na_2O-K_2O-MgO-CaO-B_2O_3-P_2O_5-SiO_2. In fact, in a pioneering work, published in 1997, the Authors investigated the bioactivity (expressly defined as the bone-bonding ability) of 26 glasses belonging to this family. With this aim, *in vivo* tests were performed by inserting glass implants into rabbit tibia for 8 weeks. For most of the glasses containing < 59 mol % SiO_2, two distinct layers were observed at the glass surface after implantation, one containing silica and another containing calcium phosphate. The development of these two layers was considered as a sign of bioactivity. A detailed evaluation of the glass-bone tissue interaction proved that bioactivity occurred for glasses containing 14-30 mol% alkali oxides, 14-30 mol % alkaline earth oxides and <59 mol % SiO_2. Instead the Authors observed that phosphate-free glasses were not bioactive, even if some of them could develop a mixed structure of silica and calcium phosphate [57].

However, it is worth noting that the role of phosphorous is still under debate [58], since a wide bioactivity region has been identified in the Na_2O-CaO-SiO_2 ternary system and

little differences in HCA formation have been reported between the standard 45S5 and the corresponding phosphorous-free Na_2O-CaO-SiO_2 glass [59, 60].

Moreover, in order to evaluate the effect of phosphorous on the bioactivity of glasses and glass-ceramics, specific contributions have been dedicated not only to the 45S5 family, but also to other systems. For example, Marghussian et al. [61] focused on the MgO-CaO-SiO_2-P_2O_5 system and investigated the effect of progressive replacement of P_2O_5 by SiO_2 on the crystallization behaviour, mechanical properties and in vitro bioactivity. By decreasing P_2O_5, the final glass-ceramics progressively showed lower amounts of apatite and higher amounts of wollastonite, which resulted in improved values of diametral compression strength and indentation fracture toughness. *In vitro* tests proved that a surface layer of HCA could develop even on the samples containing the minimum amount of apatite, suggesting that the decrease in P_2O_5 content in the glass samples and the subsequent decrease in apatite phase in the glass-ceramics did not impair the bioactivity of these materials. The *in-vitro* bioactivity of CaO-MgO-SiO_2 based glasses, with and without P_2O_5 and other additives (such as B_2O_3, Na_2O, CaF_2), was also corroborated by the activity of Agathopoulos et al. [62] and Pereira et al. [63].

Working with formulations similar to those proposed by Brink et al. [57], Vitale-Brovarone and co-workers stressed the importance of the alkaline content on the *in vivo* behaviour [64]. In fact, it is known that osteoblasts usually prefer a slightly alkaline medium, but glasses and glass-ceramics with a high alkaline content can cause excessive changes in the medium pH and, hence, they can inhibit osteoblast activity and cause cell necrosis [65]. In order to limit the pH changes, Vitale-Brovarone formulated a new glass (CEL2) with a lower monovalent oxide content (< 20 mol%) and a higher P_2O_5 percentage (3 mol%) with respect to conventional bioactive glasses (proposed composition for CEL2: 45% SiO_2, 3% P_2O_5, 26% CaO, 7% MgO, 15% Na_2O, 4% K_2O, with a 4:1 Na_2O/K_2O ratio). The same glass was also used to produce bioactive glass-ceramics and scaffolds [64].

However, it should be stressed that the behaviour of a glass depends not only on its amount of alkali oxides, but also on the co-presence and interaction of different alkali oxides, such as Na_2O and K_2O, due to the so-called "mixed alkali effect" [67].

Unfortunately, the bone-bonding ability is a necessary, but not sufficient pre-requisite to use a material in a biomedical device. In addition, the bio-degradation rate should fit the natural bone remodelling time. Since some glasses react too quickly for some purposes, their resorption rate should be reduced using them as glass-ceramics (after a proper thermal treatment) and/or changing their composition. In fact, the incorporation of some metallic oxides, such as MgO and TiO_2, in the glass network can sensibly slow down the bio-resorption kinetics. For example, Roy found that the *in vitro* reactivity of Na_2O-MgO-SiO_2 glasses gradually decreased reducing the Na_2O/MgO ratio [68]. In order to tune the degradation rate of calcium phosphate glasses and glass-ceramics, Dias et al. evaluated the addition of MgO and TiO_2 to glasses in the pyro- and orthophosphate regions. Then, the glasses were sintered and crystallized following different heat treatments, designed according to DTA results. Depending upon the glass composition and the heat treatment conditions, various contents of α- and β-$Ca_2P_2O_7$, $CaTi_4(PO_4)_6$ and TiP_2O_7 were detected in the final glass-ceramics. All these phases are biocompatible, but their degradation rates *in vivo* are different. So, the Authors concluded that it is possible to control the glass-ceramic bioresorption rate by properly selecting its composition and its treatment [69]. On the other hand, the retarding action of MgO on the solubility of calcium phosphate glasses was also proved by Franks et al., who analysed the effect of a progressive replacement of CaO with MgO in Na_2-CaO-P_2O_5 glasses [70].

To conclude, special glass compositions may be designed for specific applications. For example, special formulations can be proposed in order to induce the crystallization of single-phase glass-ceramics, in order to avoid the likely mismatch of the coefficients of thermal expansion of the different crystal phases and residual amorphous matrix observed in

standard 45S5-derived materials. With this aim, Agathopoulos et al. proposed a new formulation in the SiO_2-Al_2O_3-B_2O_3-MgO-CaO-Na_2O-F system in order to obtain only one crystal phase, namely akermanite ($Ca_2MgSi_2O_7$), as a result of heat treatment [71].

5. Conclusions and future perspectives

Because of their high bioactivity degree, bioactive glasses are excellent candidates for implant materials and coatings. On the other hand, processing techniques may cause the glass to crystallize, altering its behaviour in biological environments. This fact is particularly true for highly porous implants, such as Bioglass® derived-scaffolds, which would be too brittle without an extensive sintering; unfortunately, a full crystallization of the glass usually happens prior to significant densification by sintering, with possible negative effects on the bioactivity of the resulting glass-ceramic material. For these reasons, a very accurate investigation of the factors affecting crystallization and its consequences on bioactivity are key issues. Some basic concepts can be summarized as follows:

- 45S5 is prone to crystallize during heat treatments due to its relatively low percentage of silica and its high content of network modifiers;
- The crystallization tendency of the experimental glasses is strongly dependent on their composition, in particular on their alkali oxide content: the higher the alkali oxide content, the lower the crystallization temperature. Moreover, the chemical composition mainly determines the glass bioactivity, the crystallization path and the resulting crystalline phases at the end of the thermal treatments;
- As regards the widely used 45S5, the formation of sodium calcium silicate crystals (i.e. $Na_2CaSi_2O_6$ or $Na_2Ca_2Si_3O_9$) is dominant and occurs slightly above the glass transition temperature. However, the literature is far from unanimity in identifying the primary crystalline phase, since $Na_2CaSi_2O_6$ is isostructural to $Na_2Ca_2Si_3O_9$;
- Although some authors underline the inhibitory effect on bioactivity due to the crystal phase, however the findings of many studies agree that crystallization slightly decreases the kinetics of HA layer formation on the implant surface, but there is no loss in bioactivity.

These considerations, in particular the last one, allow one to look with optimism at the possibility to perform heat treatments on bioactive glass powders, in order to obtain special products such as scaffolds. Additionally, not all the applications require a very quick bio-reaction. Therefore, if the crystallization actually slowed down the bio-reactivity, it would be possible to control and tune the bioactivity by means of a controlled crystallization, i.e. by tailoring the glass composition and the thermal processing conditions according to the requirements of the application. To this aim, the investigation is open and continuously ongoing. Indeed it should be noted that, although the model proposed by Hench to describe the bioactivity of the 45S5 glass family is three decades old, only recently some models to explain the *in vitro* dissolution of sodium calcium silicate crystals and the development of a HA layer have been proposed.

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***Садржај**: Биостакло ® 45S5 се широко користи у биомедицинским апликацијама због способности везивања за кости и чак мека ткива. Способност синтеровања биостакла ® 45S5 је кључни фактор са технолошког аспекта јер управља производњом савремених уређаја од високо порозних скела до функционалних превлака. Нажалост овај састав стакла има склоност кристализацији на температури синтеровања и то може имати утицаја на биоактивност оригиналног стакла. Из ових разлога да би се могло управљати производњом импланта од овог типа стакла потребно је разумети интеракцију између синтеровања, кристализације и биоактивности. У овом раду направљен је преглед структурних трансформација које се дешавају током термичког третмана биостакла и специјална пажња је посвећена процесима синтеровања и кристализације. Разматрана је биоактивност финалне стакло-керамике и дате су неке алтернативне формулације стакла.*

***Кључне речи**: Стакло, термички третман, синтеровање, кристализација, биоактивност.*