The role of fluoride in the nano-heterogeneity of bioactive glasses

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Abstract

Fluoride-containing bioactive phospho-silicate glasses have recently attracted interest for dental applications, particularly as remineralising additives in dentifrices, and are potentially attractive for bone regeneration, particularly in patients suffering from osteoporosis. The incorporation of fluoride into phospho-silicate glasses is also attractive from a structural viewpoint: Fluoride complexes modifier ions rather than binding to the silicate network, and it thereby adds a significant ionic contribution to the average character of chemical bonds in the system. Molecular dynamics simulations have suggested that this also results in the formation of nano-heterogeneities. In this paper, we review the current knowledge on the structural role of fluoride in bioactive glasses, with a particular focus on inhomogeneities on a nano-scale.

Keywords

bioactive glass; biomaterials; fluoride; nano-heterogeneity

1 Introduction

The first bioactive glass, Bioglass 45S5, developed by Larry Hench in 1969 [1], has been used clinically to regenerate bone since the mid-1980s [2, 3]. It is currently also being used as the active ingredient in a remineralising dentifrice for treatment of dentine hypersensitivity [4, 5], in air abrasion applications for cutting sound and carious enamel and dentine [6] and for removing orthodontic resin adhesives [7]. Bioactive glasses degrade when in contact with body fluids, and they not only mineralise a surface layer of biomimetic apatite [8] but also release ions [9]. For this reason, they have been increasingly studied as materials for the controlled release of therapeutic ions [9], and a wide range of different modifiers has been incorporated into bioactive glasses [8]. Particularly for dental applications, the controlled release of fluoride is of great interest, as it has long been recognised as an effective means of preventing caries by inhibiting dentine and enamel demineralisation [10]. Fluoride is also known to stimulate bone formation and increasing bone mass *in vivo* [11], and despite documented issues regarding bone strength and fracture resistance [12] its potential as an affordable treatment for osteoporosis has recently been reconsidered [13]. Fluoride-containing and releasing bioactive glasses have therefore been studied by a number of researchers, focussing on various aspects such as the effect of fluoride on glass structure [14-16], ion release and apatite mineralisation [17-19] or crystallisation [20, 21].

Here, we re-examine available data with the aim of understanding the role of fluoride in the nano-heterogeneity of bioactive glasses. Bioactive glasses are typically multicomponent systems, often containing two network formers (SiO_2 and smaller amounts of P_2O_5 [8]) besides large concentrations of various network modifiers (CaO and Na_2O mostly, but also SrO [22], K_2O [23], MgO [24] or Li_2O [25]) as well as other components such as fluorides [26] or chlorides [27], making the occurrence of heterogeneities at a nano-scale more likely. Heterogeneities are understood to be important factors in effects such as phase separation, nucleation and crystallisation [28] or density and rigidity [29] in glasses, but are also likely to affect degradation and ion release [30].

2 Techniques

Owing to their amorphous long-range atomic structure, elucidating the structure of a glass composition by traditional methods such as diffraction is difficult. This difficulty is enhanced in the case of bioactive glasses, which are typically multicomponent with several overlapping correlations in terms of bond lengths. The addition of fluoride ions only makes the structure more challenging to unravel. Two complementary techniques are widely used to help to understand glass structure: solid-state magic angle spinning nuclear magnetic resonance (MAS NMR) and computer modelling, typically through molecular dynamics (MD) simulations.

Solid-state NMR techniques provide local information, typically extending to a few interatomic distances, about the local structure around different atoms. For glass structure, particularly the structure of bioactive glasses, a number of nuclei have been of special interest. ^{29}Si MAS NMR spectroscopy has been used to quantify the proportion of silicon atoms attached to different numbers of bridging oxygen atoms (BO), that is, which have different values for n in the Q_{Si}^n distribution, as different Q species differ in their chemical shift [31]. Owing to broad signals, however, deconvolution of the spectra is generally necessary. ^{31}P MAS NMR is commonly used to study the phosphorus environment (i.e., the proportion of different Q_P^n

species) of phospho-silicate bioactive glasses [32], while ^{19}F MAS NMR has successfully been used to investigate the structure of fluoride-containing bioactive glasses [14]. Other nuclei used in the characterisation of bioactive glass structure include ^{23}Na [14, 33], ^{7}Li [34] and ^{43}Ca [35].

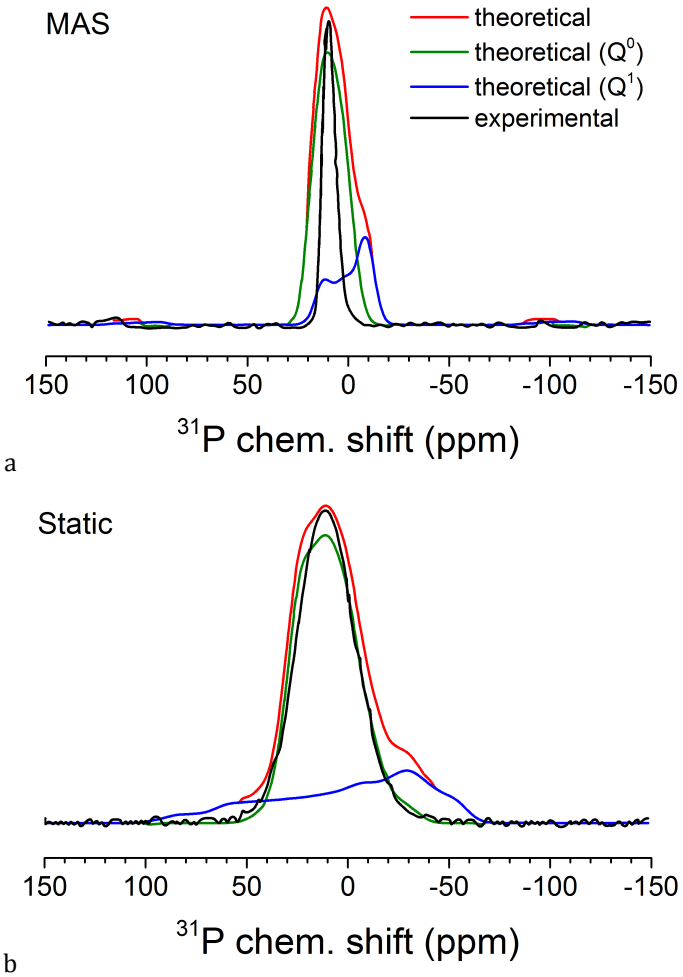

Figure 1: Comparison of experimental and theoretical MAS and static ^{31}P NMR spectra of melt-derived bioactive glass 45S5 (46.1 SiO_2-2.6 P_2O_5-26.9 CaO-24.4 Na_2O, in mol%): (a) The experimental ^{31}P MAS NMR spectrum (black, top) shows one single broad peak only, assigned to isolated orthophosphate groups, charge-balanced by modifier ions. Spectra obtained from classical MD (CMD) simulations show additional interconnection between PO_4^{3-} and SiO_4^{4-} groups, which are absent in the experimental spectrum. (b) Experimental static ^{31}P NMR spectra and static spectra obtained from CMD simulations show a similar disagreement: no signal for Q^1_P groups, indicating Si-O-P bonds can be distinguished in experimental spectra in contrast to theoretical spectra. Experimental and theoretical results taken together suggest absence of Si-O-P bonds in Bioglass 45S5, indicating that all phosphorus is present as isolated orthophosphate groups (data taken from [37] with permission, © American Chemical Society).

Molecular dynamics (MD) simulations are based on Newton's second law of motion, $F = ma$. In each MD timestep, the interatomic forces are approximated, and the atoms moved under the resultant accelerations over a timescale of typically femtoseconds. In the next timestep, the interatomic forces are then recomputed from the new atomic positions. A full MD trajectory typically consists of hundreds of thousands or millions of timesteps. The preparation of a glass in MD mimics the experimental preparation of a melt-quench glass: the model is equilibrated above the melting point, and then quickly cooled down to room temperature, where a production run is performed. Although the cooling rate in simulation is many orders of magnitude faster than in experiment, this method produces reliable glass structures in

agreement with experiment [36]. MD gives access to the atomic positions at all timesteps during the simulation, but only classical MD – in which the forces are approximated by an empirical expression – can produce large enough models to observe nano-heterogeneity directly. One useful technique is the direct computation of NMR spectra of simulated glass models in the GIPAW method, which has been applied to bioactive glass compositions [37].

3 The structure of bioactive glasses: silicate, phosphate and the role of modifiers

Typical bioactive glasses, including the commercial compositions Bioglass 45S5 (46.1 SiO_2-2.6 P_2O_5-26.9 CaO-24.4 Na_2O; in mol%) and BonAlive S53P4 (53.9 SiO_2-1.7 P_2O_5-21.8 CaO-22.7 Na_2O), are highly disrupted phospho-silicate glasses with large network modifier concentrations (up to 50 mol%). As a result, they contain large concentrations of non-bridging oxygens (NBO), and their silicate network consists of Q_{Si}^2 groups mostly (usually about 90%, with the remaining percentages being made up by Q_{Si}^3 and possibly Q_{Si}^1 [14, 37]).

Si and P are both found at the centre of tetrahedra with four oxygen atoms as nearest neighbours. Phosphate is present as orthophosphate, Q_P^0 (PO_4^{3-}), mostly [37, 38]. Some Si-O-P bonds have been reported, mostly based on MD simulation data [37, 39] but also recently from solid-state NMR spectroscopy experiments [38], while other studies claimed that no such bonds exist (Figure 1; [37, 40]). Either way, one cannot really speak of a mixed silicate-phosphate network, as the majority of the phosphate is certainly present as isolated orthophosphate groups, charge-balanced by modifier ions. Solid-state NMR results did show, however, that the proportion of Q_P^1 increases with increasing P_2O_5 and SiO_2 content [41, 42], where Q_P^1 may refer to P-O-P or Si-O-P units. Glasses in this compositional range, however, tend to have low bioactivity [39, 43].

Phosphorus present as orthophosphate is chemically bonded to a much greater proportion of non-bridging oxygen atoms than silicon is. Modifier oxides, such as sodium oxide or calcium oxide, tend to be basic oxides and therefore react preferentially with P_2O_5, which is more acidic than SiO_2, which is shown in P_2O_5 scavenging modifier ions from the silicate part of the glass network to form orthophosphate, Q_P^0 [44]. Increasing the phosphate content therefore leads to increased polymerisation of the silicate glass network [45] if no additional modifiers are added for charge-balancing purposes [44].

The structure of these phospho-silicate glasses has been described as containing phosphate-rich nano-domains [37], which leads to the question how the orthophosphate groups are distributed within the silicate matrix. MD simulations suggested that in low-phosphate-content bioactive glass compositions, phosphate groups are distributed randomly, while phosphate clustering was observed for high phosphate contents (12 mol% P_2O_5) with the glass separating into distinct silicate-rich and phosphate-rich regions (Figure 2 [39]). Data on P-P separation from combined MD simulation/solid-state NMR experiments later confirmed the finding that larger agglomerations of phosphate, containing three or more phosphate groups, only occurred in glasses with phosphate contents above 4 mol% [46]. By contrast, recent ^{31}P spin-counting solid-state NMR experiments showed nanometre-sized phosphate clusters consisting of five to six orthophosphate groups in a sodium-free version of Bioglass 45S5 (Figure 3 [38]). These results suggest that the occurrence of clustering is dependent on the phosphate content of the glass, with phosphate clusters being more likely to be present in high phosphate content compositions. The phosphate content of commercial bioactive glass compositions, however, is typically rather low (< 3 mol% P_2O_5).

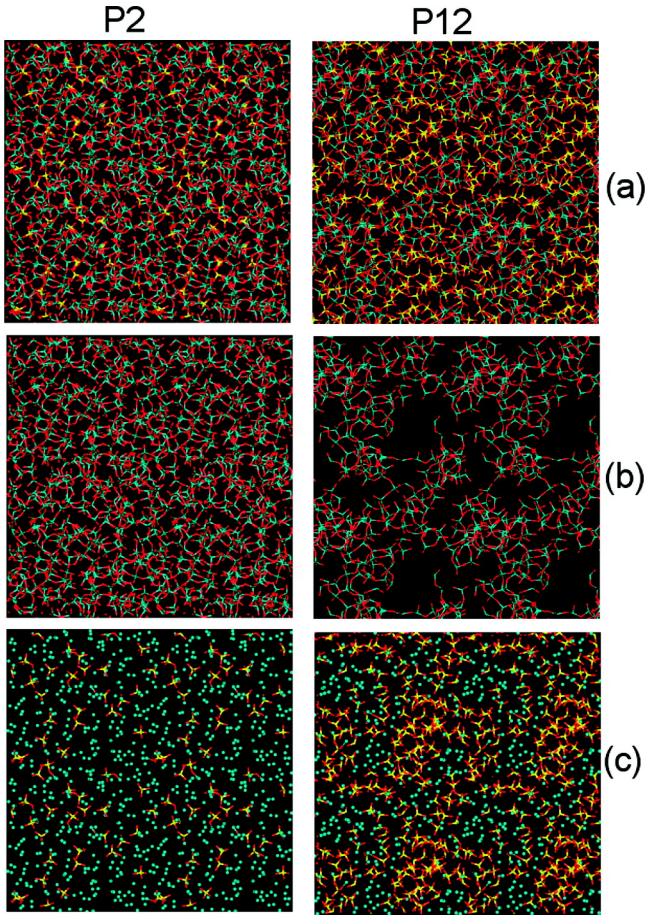

Figure 2: Structure of glasses with 2 mol% P_2O_5 (P2) and 12 mol% P_2O_5 (P12) with (a) only silicon (turquoise), phosphorus (yellow) and oxygen (red) atoms displayed, (b) only the silicate network displayed, (c) only the phosphate groups displayed with the Si atoms represented as spheres. (Image taken from [39] with permission; © American Chemical Society.)

The extent of clustering also depends on the silicate content. MD simulations [45] have shown that for compositions based on Bioglass 45S5 with constant phosphate content the amount of phosphate clusters, typically containing four or five phosphate groups, a number consistent with NMR data from a comparable, sodium-free composition [38], increases with increasing silicate content. By contrast, such clusters were negligible for compositions with silicate network connectivity lower than 2.9 [41, 46]. Clustering is likely to be relevant only for glass compositions which do not have a bioactive effect, i.e. with higher silica contents and a high network connectivity [8, 43]. Typical bioactive glass compositions, therefore, seem unlikely to show phosphate clusters or separation into phosphate-rich and silicate-rich phases.

The spatial distribution of modifiers in these glasses can also be accessed through MD simulation, typically by comparing modifier-modifier coordination numbers to the numbers expected if the modifier atoms were homogenously distributed [47]. Results from X-ray absorption spectroscopy have suggested the presence of "network regions" consisting of network formers, such as silica, and "inter-network regions" consisting of modifiers, which resulted in the formulation of the modified random network model by Greaves [48].

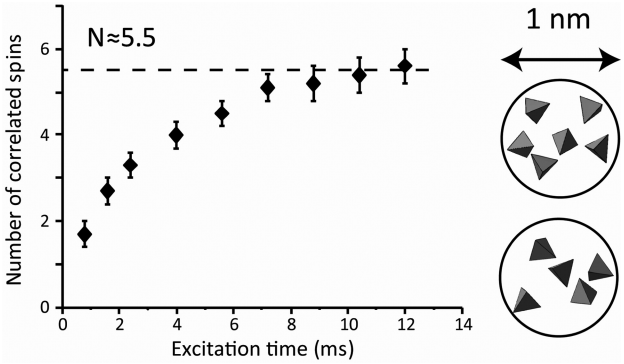

Figure 3: Results from ^{31}P spin-counting solid-state NMR experiments show the number of correlated spins (N) increasing with the excitation time, reaching a plateau at N = 5.5. This suggests the presence of well-separated clusters consisting of five and six PO_4 units, indicating that the glass structure is heterogeneous on a nanometric length scale. (Image taken from [38] with permission, © American Chemical Society).

For the Bioglass 45S5 composition, both sodium and calcium are randomly distributed around the silicon and phosphorus atoms, but at higher silicate contents, sodium shows a preference to aggregate around silicon, and calcium around phosphorus [45]. These results were confirmed later by combined MD/solid-state NMR studies [33], which showed near-random mixing for (bioactive) glasses with low silica content (such as Bioglass 45S5) but a slight preference of calcium for phosphate at higher silica contents. MD simulations also suggested sodium and calcium forming clusters, containing 2-8 modifier cations in high-silicate-content glasses also show [45], which to our knowledge has not been confirmed by solid-state NMR experiments as yet.

4 The role of fluoride in glass structure and nano-heterogeneity

Based on the similarities in ionic radius of O^{2-} and F^-, Dietzel suggested substitution of oxygen with fluorine in silicate glasses upon incorporation of fluorides [49]. Based on similarities in polarisability for the fluoride and oxygen ion, Rabinovich agreed with this view, [50]; however, he already distinguished between silica-rich glasses (acidic glasses), where Si-F bonds are likely to occur, and glasses rich in modifiers and NBO (basic glasses), where fluoride is likely to bond to modifier cations [50]. Owing to their large concentrations of modifier ions and NBO, bioactive glasses clearly fall into the latter group.

So far, the structure of fluoride-containing bioactive phospho-silicate glasses has been investigated using solid-state NMR spectroscopy and MD simulations mostly. Results from both methods [14-16] agree that direct bonds of fluorine atoms to silicon atoms (Si—F) exist, if at all, in small numbers only. Instead, fluorine is present as fluoride, charge-balanced by modifier ions [14, 15]. This means that, similar to the phosphate environment in these glasses (Figure 4a), the fluoride environment (Figure 4b) does not form part of the silicate network (Figure 4c). As a result, if fluorides are incorporated into the bioactive glass composition replacing modifier oxides, this will result in increased silicate network polymerisation [16]. By contrast, if fluorides such as calcium fluoride or sodium fluoride are added to the glass composition while maintaining the O/Si ratio, silicate network polymerisation and network connectivity have been shown to remain constant [14].

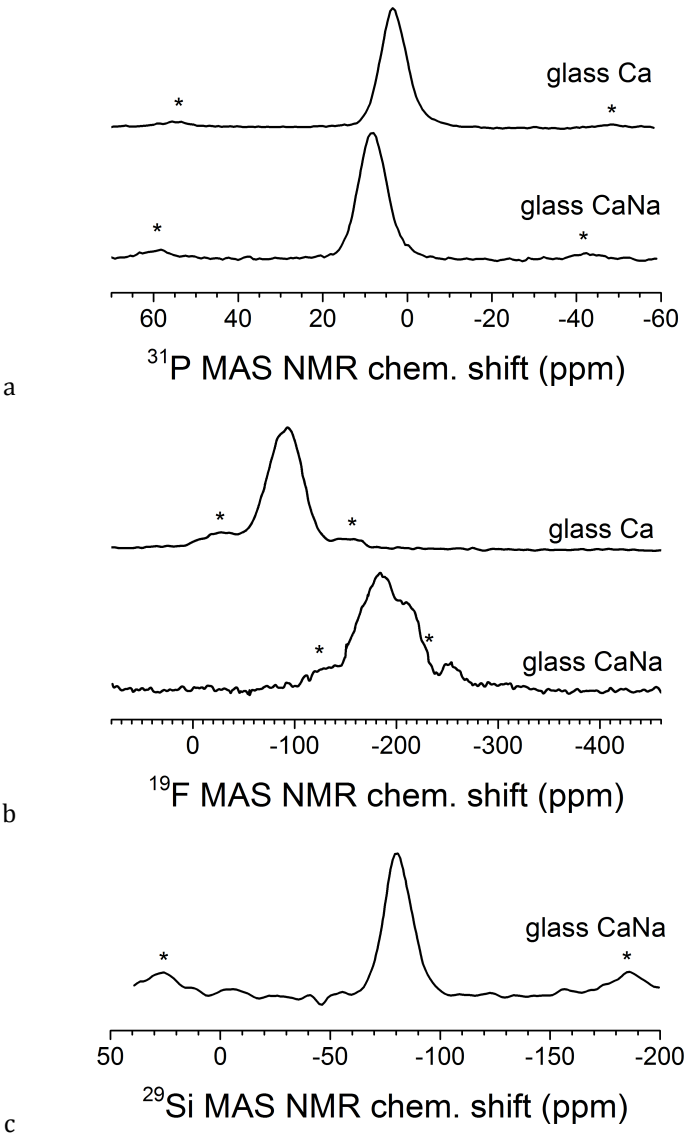

Figure 4: (a) ^{31}P, (b) ^{19}F and (c) ^{29}Si, MAS NMR spectroscopy results of two bioactive glasses 44.9 SiO_2-1.0 P_2O_5-20.9 CaO-23.9 Na_2O-9.3 CaF_2 (CaNa) and 44.9 SiO_2-1.0 P_2O_5-44.8 CaO-9.3 CaF_2 (Ca) showing silicon atoms present in Q_{Si}^2 groups and phosphorus in orthophosphate, Q_P^0, mostly, as well as fluoride ions being charge-balanced by sodium and calcium ions (data taken from [14]).

As experimental glasses were optically clear and thus did not show any obvious signs of phase separation [14], this raises the question of how the fluoride environment interacts with the silicate and the phosphate environments. Results from MAS NMR spectroscopy [14] and *ab initio* MD simulations [15] indicate a significant ionic contribution to the chemical bonds, which means that the fluoride environment in the glass is similar to that present in crystalline fluorides. Large-scale classical MD simulations of fluorinated bioactive glass [16] showed that the preferential interaction of fluoride with network modifiers leads to segregation into fluoride-rich and fluoride-poor regions of the glass (Figure 5). *Ab initio* MD simulations, while not being large enough to examine the clustering directly, allowed for detailed assessment of the local bonding. They confirmed the very low amount of Si-F bonds and showed that almost all fluorine atoms are in a mixed environment with both sodium and calcium atoms in their first coordination shell. No preference for bonding to either sodium or calcium was found [15], in contradiction to an earlier work which had proposed fluorine preferred to bond to sodium [16].

Taken together, these results strongly suggest that fluoride-containing glasses are structurally heterogeneous on a nano-scale.

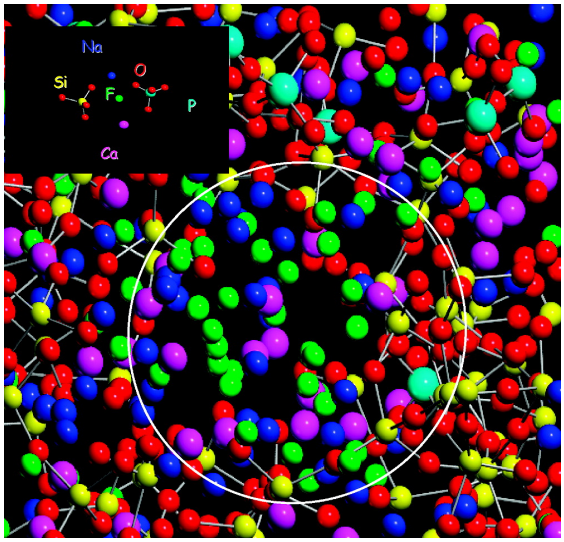

Figure 5: Snapshot from MD simulations of a fluoride-containing bioactive glass (46.1 SiO_2-2.6 P_2O_5-11.9 CaO-24.3 Na_2O-15 CaF_2, in mol%) showing region enriched in fluoride ions and modifier cations, Ca^{2+} and Na^+ (area within white circle; image taken from [16] with permission, © American Chemical Society).

5 Effects on properties

Fluoride strongly affects various glass properties, and this pronounced effect can be explained by its structural behaviour, including structural heterogeneities. Fluoride is well known to reduce viscosity, glass transition temperature and melting temperature. Attempts have been made to explain this by the formation of CaF^+ ion pairs [51]. Considering our knowledge of fluoride complexing modifiers, such as calcium ions, and formation of modifier and fluoride-rich regions within the glass structure, other explanations are more likely. For example fluoride complexing, and thereby (fully or partially) charge-balancing modifier ions, such as calcium, could effectively reduce the modifier ion's field strength, resulting in weaker ionic links between NBO. In addition, results have shown that the molar volume increases significantly upon incorporation of calcium fluoride [52], suggesting an expansion of the overall glass structure. Such an expansion may well result in silicate chains (and thus NBO) being further apart from each other, thereby weakening ionic bridges between them.

Effects of heterogeneities are particularly noticeable in the crystallisation behaviour. For low phosphate content (1.7 mol%) bioactive glasses, silicates constituted the main crystal phases upon heat treatment of fluoride-free or low-fluoride compositions [20]. With increasing calcium fluoride content, fluorite (CaF_2) emerged as the main crystal phase in these glasses [20]. By contrast, in glasses with higher phosphate contents (2.6 to 6 mol%), orthophosphate phases formed during heat treatment, including fluorapatite for low sodim-content fluoride-containing compositions [16, 53]. Particularly crystallisation of fluorapatite suggests that the fluoride-rich regions interact or possibly mix with the phosphate groups. Whilst there is currently no direct evidence for this interaction from e.g. MD simulation, it is compatible with results showing the increased intermixing of both phosphates [45] and fluoride [15] ions with the network modifiers present in the glass. These results further indicate that crystallisation of either fluoride phases

or phosphate phases only occurs once a certain, critical concentration of these components is exceeded in the glass composition. This suggests that fluoride- or phosphate-rich regions of a certain size are necessary to reach the critical size for nucleation and, subsequently, crystallisation of phosphates or fluorides.

Incorporation of calcium fluoride resulted in an increase of both glass density and molar volume of sodium calcium phospho-silicate glasses [52]. Despite fluoride complexing both sodium and calcium ions, it was possible to predict the glass density based on the densities of the fluoride-free glass and that of fluorite [52, 53]. This further confirms that, owing to ionic forces dominating the chemical bonding in fluoride-rich regions, these sites bear some structural resemblance to crystalline calcium fluoride.

Despite this similarity, calcium fluoride-containing bioactive glasses readily release fluoride ions when immersed in aqueous solutions [17, 18, 54, 55], which is in pronounced contrast to fluorite with its very low solubility in water. A most likely explanation is that, despite the above-mentioned structural similarities, the difference in solubility is caused by the difference in structural order. In bioactive glasses, fluoride is present in an amorphous state. Amorphous structures are thermodynamically less stable than the corresponding crystalline one, and therefore can be more susceptible to water attack and dissolution. The resulting release of fluoride ions makes these glasses of particular interest for dental applications to prevent dental caries [3, 5, 56].

During *in vitro* immersion experiments in simulated physiological solutions, fluoride-containing bioactive glasses also formed mineralised surface layers, as a result of the release of ions, such as phosphate or fluoride, from the glass [17, 18, 54, 55]. Minerals precipitated included calcium carbonate [17], fluorite and apatite, which was shown to be carbonate and fluoride-substituted [18, 54, 55]. The typical pH rise observed during immersion of bioactive glasses in aqueous solutions, caused by an ion exchange between modifier cations from the glass and protons from the solution, was shown to be significantly less pronounced if the glasses contained fluoride [17, 18]. This was originally explained as a direct result of fluoride release from the glass [17, 18]. However, later, more detailed studies revealed it was linked to the amount of silicate phase present during immersion experiments, and that contributions from the fluoride part were negligible [27, 54]. Changes in glass degradation with fluoride content were shown to be linked to changes in silicate polymerisation, if fluorides were substituted for modifier oxides [14, 18].

Owing to the known positive effects of fluoride ions on bone formation *in vivo* [11], fluoride-containing bioactive glasses have been studied as potential fluoride-releasing implant materials for the treatment of osteoporosis. *In vitro* cell culture results on fluoride-containing bioactive glasses showed contradictory results with regard to cell proliferation, toxicity and bone mineralisation [26, 57]. These differences may be related to the use of different cell lines or experimental design (particulate *vs.* monolith bioactive glass), but they may also be related to differences in glass design and resulting structure: As in some of the studies the silicate network polymerisation changed upon incorporation of fluoride [57], and as changes in silicate polymerisation are known to be linked to bioactivity [8, 43], results from *in vitro* cell tests may have been affected by changes in bioactive glass degradation and bioactivity [17].

One of the crucial steps in the bioactive mechanism of Hench-type bioactive glasses is the formation of a silica-rich gel layer on the surface of the glass, prior to the deposition of biomimetic apatite on the glass surface [58]. The presence of fluoride does not prevent the formation of this layer, nor does it stop the

eventual development of the apatite or fluorapatite. Some investigators reported that the formation of this layer is deleteriously affected [17, 59] by fluoride inclusion. Typically, however, fluoride is incorporated in the glass by directly replacing Na_2O or CaO with CaF_2, which also alters the network connectivity, and it is difficult to disentangle the effect of fluorine inclusion from the effect of changing the network connectivity.

6 Conclusions

We have reviewed the structure of multicomponent bioactive glasses containing fluoride. Different techniques, particularly solid-state NMR and computer simulations, have been applied to study this, and they have revealed that the structure of the glass network is not homogeneous at large length scales. For fluoride-free compositions, the phosphate groups connect preferentially to network-modifying cations, causing regions of the glass to be richer or poorer in phosphate than the average, albeit this effect is not strong for typical bioactive compositions. Fluorine is usually present as isolated fluoride ions, which form strong ionic bonds to the network modifiers rather than bonding to the silicate network, as all techniques show a very low or zero proportion of Si-F bonds. This causes structural nano-heterogeneities in fluoridated glass by forming regions of the glass, which are rich in fluoride and network modifiers. These effects are noticeable in the crystallisation behaviour, where crystallisation of fluoride or phosphate phases occurs only when a critical concentration of these moieties has been reached. Despite strong ionic bonds in the fluoride-rich regions, fluoride ions are released readily from the glass when in contact with aqueous solution, resulting in precipitation of fluoride-containing crystalline surface layers of fluorite or fluorapatite. While results from cell culture experiments with bone cells are contradictory, and thus no clear statement can be made regarding the suitability of fluoride-containing bioactive glasses for orthopaedic applications, the release of fluoride ions from these glasses suggests potential applications in dentistry.

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