Biomaterials xxx (2014) 1–8

Contents lists available at ScienceDirect

Biomaterials

journal homepage: www.elsevier.com/locate/biomaterials

Ab initio molecular dynamics simulations of structural changes associated with the incorporation of fluorine in bioactive phosphate glasses

Jamieson K. Christie*, Richard I. Ainsworth, Nora H. de Leeuw

Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ, UK

ARTICLE INFO

Article history:
Received 25 February 2014
Accepted 10 April 2014
Available online xxx

Keywords:
Fluorine
Glass
Bioactive glass
Modelling
Bioactivity

ABSTRACT

Phosphate-based bioactive glasses containing fluoride ions offer the potential of a biomaterial which combines the bioactive properties of the phosphate glass and the protection from dental caries by fluoride. We conduct accurate first-principles molecular dynamics simulations of two compositions of fluorinated phosphate-based glass to assess its suitability as a biomaterial. There is a substantial amount of F–P bonding and as a result the glass network will be structurally homogeneous on medium-range length scales, without the inhomogeneities which reduce the bioactivity of other fluorinated bioactive glasses. We observe a decrease in the network connectivity with increasing F content, caused by the replacement of bridging oxygen atoms by non-bridging fluorine atoms, but this decrease is small and can be opposed by an increase in the phosphate content. We conclude that the structural changes caused by the incorporation of fluoride into phosphate-based glasses will not adversely affect their bioactivity, suggesting that fluorinated phosphate glasses offer a superior alternative to their silicate-based counterparts.

1. Introduction

Phosphate-based glasses [1] are increasingly used as biomaterials for implants in the body, owing to several valuable properties. Certain glass compositions are bioactive, that is, they react chemically when placed in a physiological environment. These glasses dissolve completely in aqueous environments, as found in the body, with a dissolution rate that varies over several orders of magnitude, dependent on composition [1,2]. Since these glasses can be synthesised using the ions normally found in the body, they have been employed in a wide range of biomedical applications [1,3], including fixation of bone fractures [4], tubular forms to aid neural repair [5] and the controlled release of antimicrobials [6] or drugs [7], among many others. Phosphate-based glasses are typically very soluble, and they also decompose to products which can be harmlessly eliminated by the body [1]. The addition of dopants and changes in composition allow for the possibility of tuning the dissolution rate to make the glass suited for a specific application. Although they have been less widely used clinically than other biomaterials [8], the increased solubility of phosphate-based glasses makes them eminently suitable for use as bioactive degradable materials, where the biomaterials or their dissolution products play an active role in tissue engineering.

Fluorine is used in dentistry where it has three beneficial effects: it enhances tooth enamel remineralisation, and inhibits demineralisation and the action of bacterial enzymes [9]. In particular, during enamel remineralisation in the presence of fluoride ions, the phosphate mineral fluorapatite is formed, which is much less susceptible to acid attack than hydroxyapatite, the primary constitutent of enamel. Fluoride-containing silicate-based bioactive glasses (BG) have been synthesised and are used in e.g. toothpaste for sufferers of dentine hypersensitivity. The structure and properties of fluorinated bioactive glasses (F-BG) have also been studied in experiment [10,11] and simulation [12–14]. The incorporation of fluorine into BG has deleterious effects on the bioactivity. During the formation of hydroxyapatite on F-free BG, a thick silica-rich gel layer is formed [15]. In vitro and in vivo studies show that this layer is less homogeneous on F-BG than on F-free BG [16], and under certain conditions is small or even absent [17,18]. The reason for this inhomogeneity has been identified as a structural one. Fluorinated silicate glasses show a very small amount of F–Si bonding [10,13] and hence a separation on medium-range length scales into

* Corresponding author.
E-mail address: jamieson.christie@ucl.ac.uk (J.K. Christie).

http://dx.doi.org/10.1016/j.biomaterials.2014.04.032

phosphosilicate-rich and Na/Ca/F-rich regions [12]. Ionic clustering is known to reduce bioactivity [19–21], and the surface reactivity of the glass will vary across the different regions, which is the likely cause of the disrupted formation of the silica gel layer.

Given this problem with fluorinated silicate BG, and the more controllable dissolution of phosphate-based bioactive glasses, it was logical to investigate fluorinated phosphate-based bioactive glasses (F-PBG) that would combine the beneficial effects of fluoride with superior bone bonding properties. Experimentally, it was found to be difficult to synthesise these glasses with consistent fluoride levels due to fluorine volatility [1], but the loss of fluoride could be controlled to a manageable level by minimising the use of P_2O_5.

In this work, we concentrate on the effects of incorporating fluorine on the structure, and hence the bioactivity, of phosphate-based glasses. Computer simulation is an ideal tool to investigate the structure and properties of glasses, as it allows us to understand material properties from the atomistic level, which is particularly useful for F-PBG due to the lack of experimental data. Simulation has been widely used to study the structures and properties of many different types of glasses [22–29], including those implanted into the body for biomedical reasons [19,20,30–32], as well as providing insight into the interactions of the glass with the physiological environment [33–35]. We use first-principles Born-Oppenheimer molecular dynamics (MD) simulations to create realistic, unbiased models of two phosphate glass compositions with different fluorine contents, where the interatomic forces are computed from a quantum-mechanical representation of the electronic structure. Although the high computational cost of this approach limits us to relatively small models, this disadvantage is offset by the high accuracy inherent in this parameter-free approach, which does not rely on the generation of an empirical force field. Models of diverse glass compositions prepared using first-principles MD have previously been used to complement experimental studies and provide vital information on the atomic structure and properties and their effect on the suitability of the different glasses for biomedical applications [13,36–38].

2. Materials and methods

Born-Oppenheimer molecular dynamics simulations were performed by the mixed plane-wave/Gaussian-basis-set CP2K code [39], using the generalised gradient approximation (GGA) to density-functional theory (DFT) with PBE exchange-correlation functionals [40]. All atomic species were represented using a double-zeta valence polarised (DZVP) basis set [41]. The plane-wave energy cutoff was 700 Ry, and the MD timestep was 1.0 fs. Periodic boundary conditions were used throughout.

Two compositions were modelled, based on the metaphosphate glass composition, one with 2 mol % CaF_2 (hereafter called F2) and one with 6 mol % CaF_2 (F6). The glass compositions were also chosen to have the same ratio of numbers of P atoms to O atoms as each other and as the reference metaphosphate composition. The precise compositions are given in Table 1. The densities of the fluorinated compositions were not obtainable experimentally, nor available via glass property modelling databases, and we have therefore estimated the effect on the density of incorporating fluorine to the metaphosphate composition, based on the fractional increase of density observed when fluorine was added to ternary silicate-based glasses by Brauer et al. [42] For the starting configurations, atoms were placed randomly and independently in a cubic periodic box subject only to the constraint that no two atoms were closer than about 80–90% of their expected interatomic separation. The size of the box was chosen to give the appropriate density (Table 1) and kept constant throughout the simulation. To ensure that there were sufficient fluorine atoms in each model to obtain reliable statistics of their structures, the F6 model contains 197 atoms, of which six are fluorine, but due to its lower F content, the F2 model contains 363 atoms, of which four are fluorine.

For each composition, an MD run was started from the initial quasi-random configuration in the NVT ensemble at 2500 K until the model was well equilibrated, which was confirmed by computing the actual and mean-square atomic displacements. This typically took 20 ps of MD simulation time. Then, each model was run for 10 ps in NVT ensembles at each of the following temperatures: 2200 K, 1900 K, 1600 K, 1300 K, 1000 K, 750 K and 500 K, before being run for 20–25 ps in the NVT ensemble at 300 K. The production run, overwhich all data given in this paper are averaged, constitutes the last two-thirds of this room-temperature run. This protocol corresponds to a total simulation time of 110 ps, and an effective cooling rate of just over 30 K ps^{-1}. Although this cooling rate is substantially faster than that used to prepare glasses experimentally, simulated cooling rates of this order of magnitude have been used to prepare accurate structural models of glasses in agreement with experimental results using first-principles [13,37,38] molecular dynamics, whereas even the cooling rates achieved in classical molecular dynamics simulations [22,29] are less than an order of magnitude slower.

Table 1
The simulated compositions (in CaF_2 mol %) and their densities and sizes. The fluoride-free F0 composition is included for reference.

Composition	P_2O_5	Na_2O	CaO	CaF_2	Density (g cm^{-3})	Number of atoms	Cell size (Å)
F0	50.0	20.0	30.0	0.0	2.585 [43]	Not simulated	
F2	49.0	19.6	29.4	2.0	2.593	363	17.0718
F6	47.0	18.8	28.2	6.0	2.610	197	13.9227

3. Results

The aim of this work is to characterise the atomic structure of fluorinated phosphate-based glasses, and the likely effect of the inclusion of fluorine on their bioactivity. The structures of various fluorine-free phosphate-based glasses with related compositions have already been characterised through simulation [29] and experiment [6,44–49], and in this section we will therefore concentrate on the structure around the fluoride ions.

Fig. 1 shows views of the simulated F2 and F6 compositions. The basic building block of the (F-free) phosphate glass network is the PO_4 tetrahedron. In a fully connected phosphate glass, three of the oxygen of each PO_4 group are bridging oxygen (BO) atoms which are also bonded to another PO_4 tetrahedron, whilst the fourth is a terminal oxygen (TO) atom, double-bonded to the phosphorus atom. The presence of modifier atoms like sodium and calcium causes P–O–P bonds to break, thereby forming non-bridging oxygen (NBO) atoms and fragmenting the network which increases the solubility.

3.1. Local environments of phosphorus

For both compositions, the first peak in the phosphorus–oxygen partial pair-correlation function, $g_{PO}(r)$ (Fig. 2(a)), occurs at similar distances and resolves the two types of P–O bonding: the shorter distance (bond length 1.50 Å) is the P-TO peak, and the larger (1.63 Å) is the P-BO peak, in agreement with previous simulations of F-free phosphate glasses [29]. Hoppe et al. [49] showed the experimental P–O bond lengths to be sensitive to the molar ratio $y = n(M_{2/\nu}O)/n(P_2O_5)$, where $n(x)$ is the molar content of moiety x, and ν is the charge of the modifier M. According to this observation [49], compositions with $y = 1.0$, like ours, have P-TO distances of 1.51 Å and P-BO distances of 1.62 Å, very close to those found in these simulations. In $g_{PF}(r)$ (Fig. 2(b)), only one peak at 1.58 Å is seen for both compositions, at distances intermediate to the two P–O bond lengths. In an F-free glass, the P–O coordination number would be exactly four, reflecting the tetrahedral structure around the P; however, in these glasses, we find a P–O coordination number slightly below four: 3.96 for F2 and 3.93 for F6. On examining $g_{PF}(r)$ and the P–F coordination numbers, which are 0.04 for F2 and 0.07 for F6, we see that a small amount of the oxygen atoms in the PO_4 tetrahedron have been replaced by fluorine atoms. The phosphorus atoms are essentially always (99.8% for F2, 100.0% for F6) four-coordinated when both oxygen and fluorine are taken into account. When P–F bonding occurs, one of the fluorine atoms takes the place of one of the oxygen atoms in a PO_4 unit,

Please cite this article in press as: Christie JK, et al., *Ab initio* molecular dynamics simulations of structural changes associated with the incorporation of fluorine in bioactive phosphate glasses, Biomaterials (2014), http://dx.doi.org/10.1016/j.biomaterials.2014.04.032