Phosphate-based glasses are promising materials for a range of applications including biomedical, veterinary and optical. These glasses are distinguished by the presence of at least one terminal oxygen atom, which gives phosphate-based glasses unique properties of which the most interesting is their easily controllable degradation profiles. This article describes the main structural features and applications of phosphate-based glass materials focusing primarily on biomedical applications. The processes utilised for developing varying geometries such as fibres, solid and porous microspheres and coatings are also explored.

Introduction

The research on phosphate-based glasses (PBG) may be traced back a century. Schott and co-workers pioneered early work on phosphates by studying a large number of glass-forming oxides and extended the use of phosphates as optical glasses. Because phosphate glass has a larger index of refraction than silicate glass of the same dispersion, it is better adapted for achromatising borate-flint glasses (1). However, the poor chemical durability of these early optical glasses limited their applications. In the 1950s, amorphous alkali phosphates were explored for use in a variety of applications such as hard water treatments, dispersants for clay processing and pigment manufacturing (2). Further development on PBGs led to the use of neodymium-doped phosphate glasses in high power laser applications (3).

More recently phosphate glasses have been developed for a variety of specific applications. For instance alkali aluminophosphate glasses with the glass transition temperature below 400°C were developed as hermetic seals (4).

The chemical durability and low processing temperature of iron phosphate glasses led to them being investigated for use as nuclear waste hosts (5). Owing to their fast ion conductivity, phosphorus oxynitride glasses have also been explored as solid-state electrolytes (6).

For the use of glasses in biomedical applications, Professor Larry Hench revolutionised the use of glassy materials by the discovery of Bioglass®, known as 45S5, during the late 1960s. There are now three major glass types under investigation for biomedical applications including silicate-, phosphate- and borate-based glasses.

Interest in the use of PBGs has progressively been increasing and these novel materials are being explored in many different fields. One of the unique and highly interesting properties of PBGs is their easily controllable degradation profiles, which can range from hours to days, just by altering their chemical composition (7, 8).
Structure

The main glass network formers include oxides such as silica (SiO$_2$), boron trioxide (B$_2$O$_3$), phosphorus pentoxide (P$_2$O$_5$) and some others (9, 10). These oxides are essential in their formation as they form a random three-dimensional network of glass. For PBGs, the main glass network forming oxide is P$_2$O$_5$ which consists of tetrahedral phosphate anions (see Figure 1). These phosphate tetrahedra bond the bridging oxygen to the phosphorus atom, while the tetrahedron forms P–O–P bonds with the adjacent tetrahedra to produce the glass structure. Neutron diffraction experiments conducted by Hoppe et al. (13) revealed that two different P–O bond lengths existed within PO$_4$ units and these two lengths were related to the phosphorus atom with a terminal oxygen atom and a bridging oxygen atom. The fact that phosphate anions contain at least one terminal oxygen reduces the connectivity of PBGs relative to their silicate-based counterparts (12).

The number of bridging oxygens present in phosphate tetrahedra are used to define the structure of phosphate glasses and these are usually presented using Q$_n$ terminology (where Q$^3$, Q$^2$, Q$^1$ and Q$^0$ represent the number of bridging oxygens per tetrahedron (as highlighted in Figure 1). The types of phosphate glass structures that can be produced range from 3D cross-linked networks of Q$^3$ tetrahedra to metaphosphate chain-like Q$^2$ structures, followed by invert Q$^1$ and orthophosphate Q$^0$ structures, by varying the O:P ratios (11). The 3D Q$^3$ network of pure vitreous P$_2$O$_5$ glass is very unstable owing to its severely hygroscopic nature. The presence of moisture within the composition can form P–OH bonds, which can lead to depolymerisation of the glass structure (14). As such, a wide variety of modifier oxides have been added to PBGs to produce more stable glass formulations (dependant on the end applications), including sodium oxide (Na$_2$O), calcium oxide (CaO), magnesium oxide (MgO), strontium oxide (SrO), ferric oxide (Fe$_2$O$_3$), titania (TiO$_2$) and many others, to achieve the glass properties desired (12, 15, 16, 17).

Addition of alkaline and alkaline earth metal ions disrupts the glass structure through creation of a terminal oxygen (P–O–M) bond by breaking the bridging oxygen (P–O–P) bonds resulting in depolymerisation of the phosphate glass network. Furthermore, the electrical charge of the modifying oxide ions can significantly improve the chemical durability of PBGs (14) as incorporation of metallic ions with small ionic radii and high electrical charges are known to form strong P–O–M bonds, which can be highly resistant to hydration. Addition of metallic oxides such as Fe$_2$O$_3$ and TiO$_2$ have been shown to significantly decrease the dissolution rates of phosphate glasses (18, 19). These trivalent ions have been shown to have a greater influence on the degradation profiles of phosphate glasses than divalent or monovalent ions, which has been suggested to be due to the strengthening of the glass network via their cross-linking effect. For example, addition of 3–4 mol% Fe$_2$O$_3$ was shown to decrease the degradation profiles of PBGs by three or four orders of magnitude (15).

![Fig. 1. (a) phosphate tetrahedral classifications used to define the structure of phosphate glasses, the O:P ratios (Reprinted from (11) Copyright (2018), with permission from Elsevier); (b) Q$^n$ species (Republished with permission of Royal Society of Chemistry from (12), permission conveyed through Copyright Clearance Center, Inc)](https://doi.org/10.1595/205651319X15426460058863)
Applications

Antimicrobial ceramics are important materials and have been extensively investigated for a range of applications, including cosmetics, electrical appliances, fabrics and building materials. A large number of healthcare related products now contain silver, due to its antimicrobial activity and low toxicity. These products include silver-coated catheters, municipal water systems and wound dressings (16).

PBGs containing copper and silver ions have also been investigated as antimicrobial agents. Formulations doped with silver demonstrated potent activity against several pathogens (including Staphylococcus aureus, Escherichia coli, Bacillus cereus, Pseudomonas aeruginosa, methicillin-resistant Staphylococcus aureus (MRSA) and Candida albicans). It was found that incorporating as little as 3 mol% silver was sufficient to mount an effective and long-term antimicrobial effect against these organisms (16). Further structural studies revealed the oxidation state of silver to be in the +1 form, when using a sulfate based (Ag₂SO₄) precursor (20).

Studies have also shown that gallium ions are highly useful for inhibiting Pseudomonas aeruginosa growth and biofilm formation and extremely effective against planktonic and biofilm bacteria in vitro. The mechanism of action suggested was decreasing bacterial iron uptake and by interfering with iron signalling via the transcriptional regulator pvdS (21). As such, quaternary gallium-doped PBGs were produced and tested against both Gram-negative (Escherichia coli and Pseudomonas aeruginosa) and Gram-positive (Staphylococcus aureus, MRSA and Clostridium difficile) bacteria. Results showed that the bactericidal effect was due to Ga³⁺ ions released from the glasses and that a concentration as low as 1 mol% Ga₂O₃ was enough to mount a potent antibacterial effect (22).

PBGs coupled with their controllable degradation, hence ion release profiles, excellent cytocompatibility and mechanical properties are ideal materials for applications where only a temporary and limited time scale of the material is required. As an implant material, this eliminates the need for secondary surgical procedures for removal of the implant, enabling the targeted tissue to fully replace the implant in situ (17). Due to the fully bioresorbable nature of PBGs, glass formulations have been developed with chemical compositions similar to the mineral phase of bone, which makes them particularly promising candidates for developing implantable biomaterials for repair and regeneration of hard tissues (23).

Furthermore, PBGs have been manufactured and explored in various geometries such as in the form of particles (17), discs (7), fibres (8) and more recently as microspheres (18), to enhance their applicability for varying applications.

Phosphate Glass Fibres

PBGs in the form of phosphate glass fibres (PGFs) have been shown to possess excellent cytocompatible and mechanical properties (see Figure 2(a)) (24) and as such have been explored for varying applications such as reinforcing biopolymer matrices and as cell guides for soft tissue repair (15). See Figures 2(b) and 2(c).

The fabrication of continuous fibres has more commonly been achieved via melt drawing but they have also been produced from preformed rods. For example, less fragile glasses can be melt drawn and pulled from a preformed rod to manufacture continuous fibres, whilst highly fragile glasses require rapid quenching of upward drawn fibres processed from a melt (25). Fibres spanning a range of mechanical properties have been produced and have achieved a tensile modulus ~74 GPa and tensile strength ~1.2 GPa (24).

Fibre reinforced composites (FRC) can be developed to provide a wide range of mechanical properties. Due to the anisotropic nature of bone, the longitudinal mechanical properties are greater than those in the transverse direction, which can be matched by designing unidirectional FRCs (26). As such, one area heavily explored for use of PGFs has been to develop fully bioresorbable composites as fracture fixation devices with the aim to match the properties of natural bone (23, 25, 26).

Composite plates based on polyactic acid (PLA) reinforced with PGFs have been explored with varying fibre content and lay-up geometries. Unidirectional composites with fibre volume fractions of ~30% and ~55% were produced and achieved flexural properties of 115 MPa and 170 MPa for strength and 16 GPa and 15 GPa for modulus respectively (25). Other studies showed PLA reinforced with random PGF mats with volume fraction of ~14% achieved flexural properties of 90 MPa and 5 GPa, respectively (25). However, one issue encountered with development of these biocomposites was rapid reduction of mechanical properties when immersed in aqueous media, due to loss of interfacial properties between the fibre and matrix.
More recently, biocomposites have been developed via an in situ polymerisation (ISP) process. The target fibre volume fraction and catalyst (Sn(Oct)₂), was mixed with ε-caprolactone and injected into a PTFE mould at room temperature and compared to their laminate stacked (LS) counterparts. In all tests conducted, the ISP composites outperformed the LS composites, revealing significantly less media uptake and mass loss throughout the degradation period and the initial flexural properties of the ISP composites were also substantially higher (27).

Applying the ISP process to ε-caprolactone was fairly straightforward as this monomer was in liquid form, enabling it to be injected into the moulds. However, developing an ISP process for PLA proved to be much more difficult, as the monomer was a solid. As such, a new heated ISP technique was developed to manufacture PLA-PCL copolymers and PLA based fully bioresorbable PGF reinforced composites (28).

These studies showed that biocomposites manufactured via the ISP method with 35% fibre volume fraction achieved ~450 MPa and ~24 GPa...
for initial (non-degraded) flexural strength and modulus respectively. Moreover, when immersed in PBS at 37°C this composite maintained its flexural strength and modulus at ~300 MPa and ~17 GPa respectively, for 15 days, and the flexural properties maintained matched the mechanical properties of human cortical bone. This mechanical enhancement and retention was attributed to the significantly enhanced fibre/matrix interfacial adhesion achieved from the ISP process (28). Figure 3 shows the fracture surfaces of biocomposites manufactured via different routes (29).

Another study has also explored developing novel core-clad PBG fibres which could provide further potential control over their degradation properties and hence staged release profiles of specific biotherapeutic ions, which have not previously been achieved (19).

**Novel Porous Microspheres**

Microspheres exhibit greater advantages over irregular-shaped particles such as improved flow properties, which are particularly beneficial for biomedical applications, enabling delivery via minimally invasive surgical injection procedures into defects, for example. Furthermore, filling a defect site with microspheres could be more advantageous than scaffolds, which tend to have predetermined shapes. Phosphate glass microspheres doped with TiO$_2$ were produced and cell culture studies using MG63 cells over a seven day period showed that the microspheres provided a stable surface for cell attachment, growth and proliferation (18).

However, microspheres with porous morphology could enable consistent distribution of cells, growth factors, drugs and other biological components throughout the entire porous microsphere network site alongside providing diffusion of nutrients and waste products (30). Also, controlling the size, shape and distribution of the pores within the microspheres would govern properties such as surface area, density and degradation profiles which could be tailored to the desired application.

![Fig. 3. (a) and (b) SEM images of fractured surfaces unidirectional composites manufactured via laminate stacking process; (c) and (d) SEM images of fractured surfaces of biocomposites manufactured via ISP process. (29). (Reproduced with permission)](https://doi.org/10.1595/205651319X15426460058863)
As can be seen in Figure 4, a range of PBG formulations have recently been developed into microspheres with uniquely engineered and interconnected porous structures. Figure 4(a) shows that bulk glass microspheres can be manufactured with uniform geometry, via the flame spheroidisation process, whilst Figure 4(b) highlights the distribution and pore morphologies achieved from developing highly porous PBG microspheres. More interestingly, this study also revealed that surface pore sizes could be tailored by altering the process parameters used with the flame spheroidisation process (such as air:fuel ratio, flame length and the retention time of particles within the flame), including the ratio of glass particles to porogens used during the process. Figure 4(c) shows a scanning electron microscopy (SEM) image of a porous PBG microsphere exhibiting a range of small surface pores. Figures 4(d) and 4(e) highlight a mixture of larger and smaller surface pores in comparison. This study also showed that larger surface pores as well as larger interconnected channels could also be developed (as shown in Figure 4(e)), which could potentially enable faster ingress of fluids or media, through the entire porous microsphere construct. Smaller surface pores could also be beneficial for controlling release of encapsulated components such as drugs and/or other biological components. Whereas the larger pores could be utilised to accommodate cells (such as, stem cells) in order to promote tissue regeneration activities (30).

The manufacturing process developed herein is also being applied to borate and silicate glasses and glass ceramic materials are also currently being explored in the laboratory of the Ahmed group at the University of Nottingham.

Fig. 4. (a) the production of bulk microspheres; (b) the yield of porous glass microspheres which can be achieved by the process developed; (c) surface morphology containing smaller surface pores; (d) porous glass microsphere with a mixture of small and large surface pores; (e) porous glass microsphere with comparatively larger surface pores. The varying pore morphologies are achieved by controlling process parameters (Reprinted from (30). Copyright (2018), with permission from Elsevier)
Recently, PBGs have also been explored as biotherapeutic ion releasing films on metallic implants to stimulate bone regeneration (such as on hip stems), where integration between the implant and the host tissue is highly desirable. The process utilised involved physical vapour deposition via radio frequency magnetron sputtering (31), which is an extremely flexible coating technique that can be used to coat almost any material. The sputtering process basically involves removal of atomised material from a solid (target) by energetic bombardment of its surface by ions or neutral particles.

The ability to incorporate an array of different ions opens up possibilities for varying applications such as adding Ag\(^+\) or Cu\(^{2+}\) as potential antimicrobial layers. To try and understand the complex atomic momentum exchange interactions associated with sputtering, the structural properties of melt quenched PBG coatings have been investigated, along with the trends associated with non-stoichiometric transfer from target materials to deposited coatings. Figure 5 below highlights the types of coating morphologies achieved (before and after degradation) (32).

The main challenges of magnetron sputtering of PBGs is the variance between sputtered coatings and their melt quenched counterparts. Magnetron sputtered PBGs have shown reduced phosphate content and hence lower sputtering rates of phosphate ions, whilst the network modifying ions (such as calcium, sodium, magnesium or iron) were deposited at higher rates. It was shown that the rates of ejection occurred in order of increasing dissociation energy (Na > Ca > Mg > Fe). The bonding chemistry of the sputtered glasses was also very different, due to the almost instantaneous quenching of the sputtered material. Furthermore, lower sputtering powers (<100 W) are required to prevent target cracking during deposition (33).

The mechanical properties of PBG coatings were also previously studied (34, 35). Stuart et al. concluded that as deposited and heat-treated coatings showed interfacial tensile adhesion in excess of 73.6 MPa, which surpassed the International Organization for Standardization (ISO) and US Food and Drug Administration (FDA) requirements for hydroxyapatite (HA) coatings. It was also reported (34) that scratch testing of the coatings on polished substrates revealed brittle failure mechanisms, however coatings that were deposited onto sandblasted substrates to mimic commercial implant surfaces, did not suffer from tensile cracking or trackside delamination showing substantial interfacial improvements (between 8.6 N and 11.3 N).

Conclusions

In summary, phosphate-based glasses are unique materials due to their fully controllable resorbable nature and can easily be doped with a wide variety of ions. They have been explored mainly for biomedical applications (i.e. bone tissue repair and fixation) and also for applications as wide ranging as optical and nuclear waste storage. These materials have also been developed in various unique geometries, such as fibres and more recently as highly porous microspheres, which has
enabled a wide variety of alternate applications to be explored. Promising mechanical properties of PBG-based glass coatings have also been reported which were deemed suitable for use on orthopaedic implants.

References

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