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Development of glass-related biomaterials for enhanced bone regeneration via stimulation of cell function

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Glasses can be systematically designed according to their composition, and their potential to release ions can also be manipulated by tailoring their structures. Notably, phosphate invert glasses (PIG) can contain various elements that are comparable with silicate glasses due to their acidity. In this review article, novel PIGs containing therapeutic ions for bone regeneration, and anisotropic scaffolds for reconstructing bone quality were reviewed. PIGs have been structurally designed to utilize intermediate oxides, such as TiO₂, Nb₂O₅, ZnO, and MgO. As a result, PIGs with excellent chemical durability are expected to sustain their ion-releasability for bone regeneration and exhibit antibacterial activities. In contrast, PIGs have been designed with improved ion-releasing rates, with some releasing 20 times more ions compared to conventional PIGs. This was accomplished by manipulating the glass structure to contain only orthophosphates and orthosilicates. In other words, these glasses have no long-chain structures. Therefore, such glasses can be carriers of therapeutic ions for composite biomaterials, and are expected to enhance bone regeneration. Fibrous anisotropic scaffolds containing the designed glass have also been developed for the simultaneous reconstruction of bone quantity and quality. These scaffolds were enhanced to encourage bone formation by releasing ions from the glass, which controlled bone quality by direction of the calcified tissue in a single direction. Therefore, PIGs are expected to expand into various biomedical fields, as they can be tailored to have different properties according to their glass network structure.

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1. Introduction

The first bioactive glass, Bioglass® 45S5, was reported by L. L. Hench in 1969.¹ This glass was able to form chemical bonds with human bone, and then release silicate and calcium ions to stimulate bone regeneration.² Because inorganic ions can stimulate cells for bone regeneration,³ this strategy can be used to improve the performance of biomaterials. These materials can be easily controlled due to their systematic compositions, and ion-releasability can manipulate by design their structures. Specifically, phosphate glasses (PG) contain various elements that have been researched and compared to silicate glasses due to their acidity.⁴ Oxide glasses are composed of network formers (NWF), network modifiers (NWM), and intermediates, which can act on the NWFs and NWMs.⁵ NWF in PG is the PO₄³⁻ tetrahedron, which forms a basic unit of the glass network structure, as shown in Fig. 1. The basic unit of PG is represented by Qₙ⁰, where n is the number of bridging oxygen in the PO₄ tetrahedron (n = 0–3).

PG exhibits vitrification in the lower regions of NWF, compared with silicate or borate glasses in general.⁶ Moreover, introducing intermediates into PGs still results in vitrification, despite containing small amounts of NWFs. NWMs in these glasses act as NWF crosslinkers, similar to the intermediates. These glasses also contain more NWMs than NWFs, and are therefore called “invert glasses”.⁴,⁷,⁸ Phosphate invert glasses (PIG) can contain large and various components, and can be manipulated
2. Designing PG containing therapeutic ions

2.1 PIG

PIGs developed by T. Kasuga contain short phosphate groups such as ortho- ($Q_0^0$) and pyro-phosphates ($Q_1^1$) and have the following composition: 60CaO·30P2O5·10TiO2 (mol %, denoted by PIG-Ti).9) Titanium dioxide, which can be classified as an intermediate, can be formed through P–O–Ti bonds in PIG-Ti, resulting in enhanced glassification (GD) and chemical durability.9,12) When heat-treated at 850 °C, PIG-Ti exhibits its beta calcium pyrophosphate (β-Ca3P2O7) and beta-tricalcium phosphate ($\beta$-Ca2P2O7) crystalline phases.9) These crystal phases are reported that exhibit bioactivity in vivo by forming direct bond with bone.13),14) This occurs when it is immersed in simulated body fluid, which is a protein-free solution similar to the inorganic composition of human blood plasma.17) PIG-Ti coated with an Ti–29Nb–13Ta–4.6Zr alloy18) has also been observed to form bonds with bone in vivo.9) Niobium-containing PIG (denoted by PIG-Nb) were prepared by substituting Nb2O5 for TiO2, resulting in a composition of 60CaO·30P2O5·(10–x)Na2O·xTiO2 (mol %, x = 0–10, denoted by PIG-Ti).9) Niobium bonds were easy to dissociate via hydrolysis, which decreased the chemical durability of PIG-Ti. Consequently, the amount of phosphate ions that were released from PIG-Ti/Nb decreased when the Ca/P ratio increased, as shown in Fig. 2(c). This is likely due to the chemical durability of PIG-Ti/Nb, which improved due to the formation of P–O–Ti/Nb bonds.

Additionally, PIG-Ti and its glass-ceramic constituents will form a gel-layer that nucleates hydroxyapatite (HAp) on the surface.15),16) This occurs when it is immersed in simulated body fluid, which is a protein-free solution similar to the inorganic composition of human blood plasma.17) PIG-Ti coated with an Ti–29Nb–13Ta–4.6Zr alloy18) has also been observed to form bonds with bone in vivo.9) Niobium-containing PIG (denoted by PIG-Nb) were prepared by substituting Nb2O5 for TiO2, resulting in a composition of 60CaO·30P2O5·(10–y)Na2O·yNb2O5 (mol %, y = 0–10). PIG-Nb glass-ceramics also exhibited apatite forming abilities,10) and niobium ions released from PIG-Nb with 3 and 5 mol % of Nb2O5 stimulated the differentiation of osteoblasts.20)

PIG-Ti (60CaO·30P2O5·10TiO2 in mol %) and PIG-Nb (63CaO·31.5P2O5·5.5Nb2O5 in mol %) glasses that substituted P2O5 for CaO were prepared by clarifying the structure of the intermediates, and then these compositions were set by systematically increasing the Ca/P ratios.12) The $Q_0^0$ groups in these glasses increased as the Ca/P ratio increased, as shown in Fig. 2(a). This resulted in a decrease in the phosphate chain length in PIG-Ti/Nb with increasing NWMs, such as CaO. The structures of the intermediates (TiO2, Nb2O5) in PIG-Ti/Nb shifted from TiO6, NbO6 octahedra to TiO4, NbO4 tetrahedra, as the Ca/P ratio increased, as shown in Fig. 2(b). The intermediates, such as TiO2 and Nb2O5 in the phosphate glass, consisted of a combination of tetrahedral and octahedral forms, and they acted as NWFs and NWMs, respectively.21),22) Thus, the function of intermediates in PIGs shifted from NWFs to NWMs, due to the shortening of the phosphate chain length.12) Additionally, the intermediates formed bonds with the phosphate groups, such as P–O–Ti/Nb, and these bonds can improve GD and chemical durability.

2.2 PIG with magnesium

In PG, magnesium acts as an intermediate that can affect the material’s properties, depending on the phosphate chain length.23) This compound can, therefore, significantly affect the structure of the glass.24),25) Furthermore, Mg2+ ions stimulate cell adhesion, proliferation, differentiation, and subsequent mineralization.26) Magnesium-containing PIGs (denoted as PIGMg), which substitute MgO for CaO in PIG-Ti, had a greater degree of GD and released more ions.27) Magnesium in phosphate glass also formed P–O–Mg bonds and crosslinks with the phosphate groups. In contrast, P–O–Mg bonds were easy to dissociate via hydrolysis, which decreased the chemical durability of PIGs but improved their ion-releasing abilities.24)

PIGMg-Ti/Nb glasses that substituted P2O5 for MgO have been evaluated for effect of intermediate for their

Fig. 2. Integrated portion of (a) $Q_0^0$ group in PIG-Nbs assessed from the $^{31}$P MAS-NMR spectra. (b) NbOx $(a = 4$ or $6)$ polyhedral groups of PIG-Nbs assessed from Raman spectra, as a function of the Ca/P ratio, and (c) percentage of phosphate ions released into the Tris buffer solution, as a function of the total amount in PIG-Nbs relative to the Ca/P ratio. Error bars represent one standard deviation. Reprinted from Ref. 12. Copyright 2015, with permission from Elsevier.
properties. These include TiO$_2$ and Nb$_2$O$_5$, through MgO substitution, and their compositions were set by increasing their Mg/P ratios, systematically.\textsuperscript{25} The functions of the intermediates in PIG$_{Mg}$-Ti/Nb shifted the functions of NWMs to NWFs, similar to PIG-Ti/Nb, as a result of the shortened phosphate chain length. This is further described in section 2.1. On the other hand, the amount of ions that were released from PIG$_{Mg}$-Ti/Nb increased when the Mg/P ratio increased, unlike in PIG-Nb/Ti.

Remarkably, the magnesium in PIGs significantly affects the material’s structure and properties, as described above. To better explain the effects of substituting CaO with MgO in CaO-P$_2$O$_5$-Nb$_2$O$_5$ glasses, glasses mainly composed of phosphate groups with $Q_p$\textsuperscript{0}, $Q_p$\textsuperscript{1}, and $Q_p$\textsuperscript{2} were prepared (denoted by MPG, PPG, and OPG, respectively), and their structures and ion-releasing behaviors were evaluated.\textsuperscript{28} The degree of GD of a material is an indicator of its glass-forming ability, which can be calculated as follows:\textsuperscript{29,30}

$$GD = \frac{T_c - T_g}{T_g} \left[ \frac{K^*}{K} \right]$$

(1)

where $T_g$ is the glass transition temperature, and $T_c$ is the crystallization temperature at the onset of crystallization. The GD of MPG improved when the MgO substitution ratio increased. Conversely, PPG, and OPG, i.e., invert glasses, exhibited maximum values at 50% MgO substitution, as shown in Fig. 3(a). This property was due to the structure of the phosphate groups in the glasses. The main component of MPG was $Q_p$\textsuperscript{2}, which is a chain structure, and the substituted MgO in MPG was used to modify the phosphate chain in the form of an NWM. The improvement of GD in MPG, due to the increased MgO substitution ratio, can be discussed in terms of field strength ($F$), as defined by Dietzel according to:\textsuperscript{31}

$$F = \frac{Z_i}{d^2} \text{[valence}/\lambda^2\text{]}$$

(2)

where $Z_i$ is the ionic charge, and $d$ is the interatomic distance between the cation and the oxygen. The $F$ of Ca is 0.33, and Mg is 0.45 or 0.53, depending on whether it follows a 6 or 4 coordination number structure, respectively. In the case of MPG, GD improved when the MgO substitution ratio increased. This was due to the presence of more Mg, and it had a larger $F$ than Ca, which was coordinated with the phosphate chains.

PPG and OPG, i.e., invert glasses, were composed of short phosphate groups, such as $Q_p$\textsuperscript{0}, and $Q_p$\textsuperscript{1}, and groups were coordinated with cations.\textsuperscript{31,32} Thus, the structures and properties of these invert glasses were significantly influenced by the cations in these glasses. Glasses that contained two or more cations exhibited a “mixed cation effect (or mixed alkali effect)”, and had non-linear trends as a result of their various properties.\textsuperscript{31,32} These effects are due to an increase in the amount of energy required for alkali ion movement, as the ions in mixed alkali glass are situated at energetically preferential sites.\textsuperscript{31} Hence, invert glasses, i.e., PPG and OPG, had a mixed cation effect when the MgO substitution ratio was 50%, due to their glass network structure.

The ion-release ratio for MPG decreased when the MgO substitution ratio increased, as shown in Fig. 3(b), due to a greater $F$ for Mg than Ca. The ion-release ratio was smaller for PPG than for MPG or OPG, and PPG exhibited a mixed cation effect when the MgO substitution ratio was 50%. The Mg in PIGs preferentially bonds with phosphate groups to form P-O-Mg bonds,\textsuperscript{24,25,28} Thus, the P-O-Nb bonds in OPG, which create coordinated phosphate groups, formed more P-O-Mg bonds as MgO substitution increased. The bonding strength of P-O-Mg was weaker than that of P-O-Nb, since the $F$ of Mg and Nb was 0.53 and 1.50, respectively. Moreover, the P-O-Mg bonds were easy to hydrolyze, and this resulted in decreased chemical durability as previously mentioned. Consequently, the amount of ions that were released from OPG increased, as MgO substitution increased.

2.3 Orthophosphate invert glasses

OPG is composed of 70% $Q_p$\textsuperscript{0}, as orthophosphate is the main constituent in this type of glass. OPGs with 50% MgO substitution had a greater GD and a smaller ion-release ratio due to the mixed cation effect, as shown in Fig. 3. To improve the ion-releasing ability of OPGs, 15MgO-15CaO-8P$_2$O$_5$-2Nb$_2$O$_5$ (mol ratio, denoted by OPG-8P) glass was designed with a greater (Mg + Ca)/P ratio.\textsuperscript{33} OPG-8P Raman bands that correspond to $Q_p$\textsuperscript{0} (965, 590, 430 cm$^{-1}$) and NbO$_4$ (840 cm$^{-1}$) are shown in Fig. 4(a). The $^{31}$P magic angle spinning nuclear magnetic resonance (MAS-NMR) spectra results also showed a single peak, which was associated with the $Q_p$\textsuperscript{0} group, as shown in Fig. 4(b). Therefore, the NWF of OPG-8P was composed of $Q_p$\textsuperscript{0} and NbO$_4$ tetrahedra, i.e., ortho-structures. The glass network structure of OPG-8P was due to the formation of P-O-Nb and P-O-Mg bonds, which crosslinked with the $Q_p$\textsuperscript{0} groups. Thus, OPG-8P exhibited a larger GD value than PIGs, despite containing fewer
phosphates. By contrast, the ion-releasing ratio of OPG-8P was doubled for OPG, as the P–O–Mg bonds are easily hydrolyzed. Consequently, MgO was introduced as an intermediate and could be used to manipulate the mixed cation effect. This was found to be especially useful when designing glass structures, and these methods can be used further to improve the glass-forming and ion-releasing abilities of these materials.

2.4 Orthophosphosilicate glasses
Silicate ions can stimulate the proliferation of osteoblasts by increasing the presence of insulin-like growth factor II, and also stimulate alkaline phosphatase and osteocalcin, i.e., osteoblast differentiation. However, phosphates and silicates in glass network structures cannot readily make P–O–Si bonds, and as a result, they are easily phase-separated. Thus, phosphosilicate glass systems have been reported with metaphosphate or metasilicate networks that contain NWMs in the form of orthosilicates and orthophosphates, respectively. OPG-8P glasses have been reported with a niobia network in OPG-8P glasses. OPG-8P-Si has several glass network structures, such as Q_{p0}^i, Q_{p0}^0, NbO_4, and magnesia, as mentioned in section 2.3. Novel phosphosilicate glasses (denoted by OPG-8P-Si) have been designed by incorporating SiO_2 into OPG-8P, as silicate groups can enter the niobate network (RF-sputtering) can be used to coat implants with PIG-Nb.

Silver and zinc ions have well known antibacterial properties; however, excessive amounts of such ions will result in cytotoxicity. Introducing antibacterial ions, such as Ag⁺ and Zn²⁺, into PIG-Nb can be a useful strategy as the properties of the glass will result in the controlled release of such ions. Radio-frequency magnetron sputtering (RF-sputtering) can be used to coat implants with PIG-Nb that contains antibacterial ions, and the coated layer will thus retain its antibacterial properties long term.

3. PIG with antibacterial properties
Glasses with small amounts of Ag_2O in PIG-Nb have been created (denoted by PIG-Ag), as Ag⁺ ions have

Fig. 4. (a) Laser Raman spectra and (b) $^{31}$P MAS-NMR spectra for OPG-8P and OPG with 50% MgO substitution, respectively. Reprinted from Ref. 33. Copyright 2016, with permission from Elsevier.

Fig. 5. $^{31}$P (left) and $^{29}$Si (right) MAS-NMR PSG spectra. Reprinted from Ref. 42. Copyright 2017, with permission from Elsevier.
antibacterial properties even at low concentrations. Silver was introduced into PIG-Nb in the form of Ag⁺ ions or Ag nanoparticles. Ag⁺ ions were combined with phosphate as NWMs. The Ag nanoparticles were dispersed into the glass matrix, as shown in Fig. 6. Primary osteoblasts that were cultured on PIG-Ag showed no significant differences compared to PIG-Nb (without Ag₂O). Therefore, the introduced silver in PIG-Nb could be manipulated, and its ion-releasing behavior did not result in cytotoxicity. PIG-Ag that contained more than 1 mol % of Ag₂O exhibited antibacterial activity for gram-negative bacteria (Escherichia coli, E. coli), as shown in Fig. 7(a). These glasses also showed antibacterial effects on gram-positive bacteria (Staphylococcus aureus, S. aureus). Therefore, PIG-Ag had excellent controlled, ion-releasing behavior and antibacterial activity without cytotoxicity.

3.2 Antibacterial PIG with zinc ions
Zinc also exhibits antibacterial activity and can be used to improve the chemical durability of PG. Moreover, trace amounts of Zn²⁺ ions enhance bone formation and are useful inhibitors of human dental plaque. For example, \( \text{zZnO} \cdot (65 - z)\text{CaO} \cdot 30\text{P}_2\text{O}_5 \cdot 5\text{Nb}_2\text{O}_5 \) (mol %, \( z = 0-65 \), denoted by PIG-Zn) glasses were prepared by RF-sputtering, and were used as a coating for implants. The GD values of PIG-Zn are similar to metaphosphate glasses, and PIG-Zn exhibits excellent glass-forming abilities. When introduced, Zn²⁺ ions act as NWFs and form P-O-Zn bonds, and these bonds improve the material’s chemical durability. As a result, the amount of Zn²⁺ ions that were released was controlled, so that it was less than 0.1 mM. Antibacterial activity for PIG-Zn on E. coli was observed when it was combined with larger compounds, such as 23% ZnO, as shown in Fig. 7(b). This activity was also observed for S. aureus. Consequently, PIG-Zn was modified so that it released trace amounts of Zn²⁺ ions, which resulted in antibacterial activity.

4. Bioactive glass/poly(lactic acid) anisotropic scaffolds for bone reconstruction
Bone is an anisotropic structure, due to the orientation of the collagen fibrils and the bone apatite (BAp) crystals in the c-axis. The degree of BAp crystals c-axis orientation is one of the indices of bone quality, and is strongly correlated with the mechanical properties of bone. Moreover, the anisotropic collagen/BAp matrix can be induced by aligning osteoblasts. Thus, manipulating the orientation of these cells is a valuable tool for recovering anisotropic bone.

Fibrous scaffolds can be prepared via electrospinning methods and then used as biomimetic templates for damaged tissue. PLLA is one of the most widely used biodegradable polymers in the biomedical field. Using this material, fibrous scaffolds can be fabricated via electrospinning to investigate the alignment of the fibers. Scaffold morphology may be modified by controlling the collector speed. The fiber orientation degree has been shown to increase as the collector speed increases. Additionally, the degree of cellular orientation on the scaffolds was shown to increase when the collector speed increased, and fiber and cell orientation degrees exhibited a linear correlation. The degree of BAp crystal c-axis orientation, which produced by primary osteoblasts on the scaffolds cultured for 4 weeks, also increased as the collector speed increased, as shown in Fig. 8, and it corresponded with the fiber and cell orientations. Therefore, PLLA scaffolds with controlled fiber orientations can be effectively used to reconstruct bone quality.

4.1 Bioglass/PLLA anisotropic fibrous scaffolds
The introduction of bioactive glasses into fibrous anisotropic scaffolds may be possible for simultaneously improving bone quality and quantity. PLLA anisotropic fibrous scaffolds that were discussed in the previous section were found to be effective for reconstructing bone quality. However, to improve the reconstruction of bone quantity, therapeutic ions released from bioactive glasses can be used to enhance bone formation.

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45S5, which is representative of bioactive glasses, and glasses that substitute CaO with MgO or SrO in 45S5, can be used as bioactive glass/PLLA anisotropic fibrous scaffolds.\(^64\) The cellular orientation on the scaffolds can be successfully controlled to consider the morphology. Moreover, the proliferation of osteoblasts can be significantly upregulated by incorporating bioactive glasses, as these glasses release therapeutic ions, including silicates, Ca\(^{2+}\), Mg\(^{2+}\), and Sr\(^{2+}\) ions. On the other hand, the fiber diameter of the scaffolds is typically smaller than 6\(\mu\)m, and the osteoblasts may adhere to several fibers due to spreading. As a result, the degree of cellular alignment was 0.6 (maximum: 1.0), which may be further improved to reconstruct bone quality.

### 4.2 PSG/PLLA anisotropic fibrous scaffolds

Novel anisotropic scaffolds have been prepared by introducing PSG as a carrier for therapeutic ions, as mentioned in section 2.4, via the electrospinning method with a PLLA matrix.\(^8\) The fiber diameter of the anisotropic PSG/PLLA fibrous scaffolds was recorded as approximately 10\(\mu\)m, and the degree of fiber alignment was greater than 0.87 (maximum: 1.0). The primary osteoblasts on the scaffolds also adhered to a single fiber surface and were aligned in the fiber-oriented direction, as shown in Fig. 9(a). As a result, the degree of cellular alignment on the scaffolds was greater than 0.87. Moreover, the degree of orientation in the BAp c-axis of the calcified tissues due to the primary osteoblasts was significantly greater than the standard reference (ICCD card: 74-0566), as shown in Fig. 9(b). Osteoblast proliferation on the PSG/PLLA scaffolds resulted in a significantly greater number than PLLA alone. Furthermore, the calcified area in the PSG/PLLA scaffolds was significantly greater than that of the PLLA alone. This novel development stems from the fact that the PSG/PLLA scaffolds exhibited a particular arrangement of osteoblasts. Furthermore, there was a calcification direction as a result of the morphology (i.e., bone quality), and the ions that were released from PSG improved bone formation (i.e., bone quantity).

### 5. Summary

In this article, novel bioactive glasses that contain therapeutic ions for bone regeneration, and anisotropic scaffolds for bone reconstruction, were reviewed. It was found that the glass network structures, and ion-releasing properties of PIGs can be manipulated according to phosphate species, and intermediates, such as TiO\(_2\), Nb\(_2\)O\(_5\), ZnO, and MgO. For example, PIG-Nb, PIG-Ag, and PIG-Zn have excellent chemical durability, and can sustain releasing ions for bone regeneration and antibacterial activity. In contrast, PGSs have been designed to improve their ion-releasing and glass-forming abilities, and these glasses had ion-releasing capabilities that were 20 times greater.

Furthermore, novel anisotropic PSG/PLLA scaffolds have been designed to focus on the ion-release properties of PIGs. These scaffolds were manipulated according to cellular orientation and the direction of calcification, as determined by their morphology. The ions that were released from the PIGs also stimulated cellular proliferation and calcification. It should be noted that PIGs can be tailored for various biomedical applications by manipulating their glass network structures. As a result, PIGs may be used for not only hard tissues, such as bone but for soft tissue regeneration as well.

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**Fig. 8.** Correlation between the integrated intensity ratio of BAp 002/310 from the X-ray profile, i.e., degree of BAp c-axis orientation along the collector rotation direction, and the fiber collection speed. Inset represents a schematic of the apatite orientation analysis, using a transmission micro X-ray diffraction system. Reproduced from Ref. 63 with permission from the Royal Society of Chemistry.

**Fig. 9.** (a) Fluorescence images of primary osteoblasts cultured on PSG/PLLA scaffolds. Arrows indicate the collector rotation direction. Green: F-actin, blue: nuclei, red: vinculin. (b) Integrated intensity ratio of BAp 002/310 for the scaffolds after cultivation for 6 weeks, i.e., degree of BAp c-axis orientation along the collector rotation direction. Reprinted from Ref. 8 with permission from The Ceramic Society of Japan.
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