Melissa Tiskaya, Saroash Shahid, David Gillam, Robert Hill

Queen Mary University of London, Barts & The London School of Medicine and Dentistry, Institute of Dentistry, Centre for Oral Bioengineering, Mile End Road, London E1 4NS, UK.

1. Abstract

Objectives: In recent years, numerous studies have analyzed the role of bioactive glass (BAG) as remineralizing additives in dental restorative composites. This current review provides a critical analysis of the existing literature, particularly focusing on BAGs prepared via the melt-quench route that form an “apatite-like” phase when immersed in physiological-like solutions.

Methods: Online databases (Science Direct, PubMed and Google Scholar) were used to collect data published from 1962 to 2020. The research papers were analyzed and the relevant papers were selected for this review. Sol-gel BAGs were not included in this review since it is not a cost-effective manufacturing technique that can be upscaled and is difficult to incorporate fluoride.

Results: BAGs release Ca^{2+}, PO_4^{3-} and F^- ions, raise the pH and form apatite. There are numerous published papers on the bioactivity of BAGs, but the different glass compositions, volume fractions, particle sizes, immersion media, time points, and the characterization techniques used, make comparison difficult. Several papers only use certain characterization techniques that do not provide a full picture of the behavior of the glass. It was noted that in most studies, mechanical properties were measured on dry samples, which does not replicate the conditions in the oral environment. Therefore, it is recommended that samples should be immersed for longer time periods in physiological solutions to mimic clinical environments.

Clinical Significance:

BAGs present major benefits in dentistry, especially their capacity to form apatite, which could potentially fill any marginal gaps produced due to polymerization shrinkage.

Keywords: bioactive glass, apatite, ion release, melt-quench, restorative composite.

Contents

2. Introduction

In 2013, the intergovernmental negotiating committee agreed on the Minamata Convention on Mercury due to the health concerns regarding mercury exposure to people and the environment [1]. Resin-based composites (RBCs) are the commonly used alternative to amalgam restorations in posterior teeth due to the absence of mercury emissions and their improved aesthetics. They are generally based on a resin matrix and an inert filler. However, the major issue of current RBCs is the formation of a marginal gap upon polymerization (Figure 1) [2].

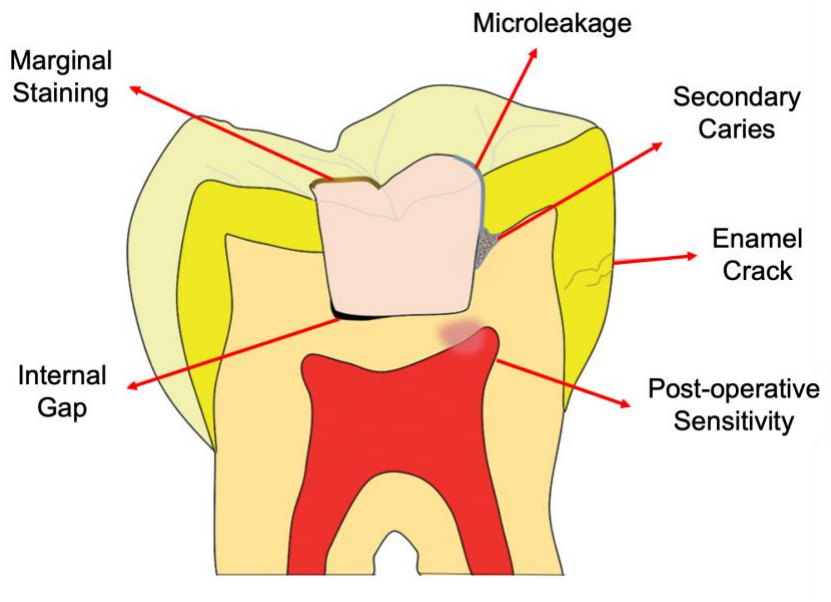

Figure 1: A modified schematic of a tooth, showing the consequences of polymerization shrinkage of RBCs adapted by Soares *et al.* [2].

When a monomer is converted into a polymer, polymerization shrinkage of 1.7 to 6 vol% [3, 4] occurs, depending on the resin composition and the filler volume fraction. This shrinkage creates a marginal gap between the restorative material and the tooth surface, which is sufficient enough for marginal leakage to occur, allowing for the penetration of bacteria, fluids and ions into the gap between the restorative material and cavity walls, resulting in the failure of the dental composite [5].

RBCs do not generally release calcium and phosphate ions or react to form hydroxyapatite (HAp) on the surface of the tooth unless a reactive glass filler is used [6]. The aim of bioactive glasses (BAGs) are to form an apatite-like phase in the marginal gap providing a marginal seal, prevent acid attack by raising the local pH, reducing the likelihood of failure of the composite. Therefore, bioactive dental composites may increase the longevity and clinical outcomes of restorations [7]. These materials also aim to aid in remineralization of hard carious dentin and therefore require less invasive and minimal cavity preparation, as less removal of the carious dentin will be required, and atraumatic restorative treatment type can be performed.

In recent years, numerous studies have analyzed the role of bioactive glass (BAG) as remineralizing additives in dental restorative composites. This current review provides a critical analysis of the existing literature, particularly focusing on BAGs prepared via the melt-quench route that form an “apatite-like” phase when immersed in physiological-like solutions.

3. Bioactivity

There are many definitions for the term ‘bioactive’ discussed in an editorial paper by Vallittu *et al.*, which considers both the medical and dental field [8]. The authors suggest that this term is used too often for advertising purposes and that a consensus should be made by dental materials opinion leaders. It is stated that a material that forms a bond between the tissues and material is bioactive [9], but other definitions suggest that a material is bioactive if it releases ions and induces the formation of HAp when in contact with physiological fluids [6, 10-12]. In 2018, 50 key opinion leaders

discussed the definition of bioactivity in the context of restorative materials and stated that a material can also be bioactive if it contains “component(s) that dissolve and have antimicrobial activity (this includes high-pH materials)” [12]. However, according to this definition, amalgam fillings will be considered bioactive since they release beneficial ions such as silver (Ag^{+}), tin (Sn^{2+}) and copper (Cu^{2+}), even though they do not induce the formation of apatite.

A recently published review on bioactive materials have classed materials containing calcium phosphate particles to be bioactive [13], as they have been reported to release Ca^{2+} and PO_4^{3-}, have a remineralizing capacity and form apatite [14]. However, it is important to note that when they are immersed in physiological fluids, they dissolve and will form pores in the material due to the dissolution of the calcium phosphate particles. This would subsequently result in a reduction of the mechanical properties. This does not occur with BAG fillers, as shown in the SEM images by Al-eesa *et al.* where the glass particles were very clearly reacting upon immersion into physiological fluid, but no pores were formed (Figure 2) [15]. It is also very difficult to manipulate the refractive indices of crystalline calcium phosphates, which hinders achieving translucency and good final aesthetics.

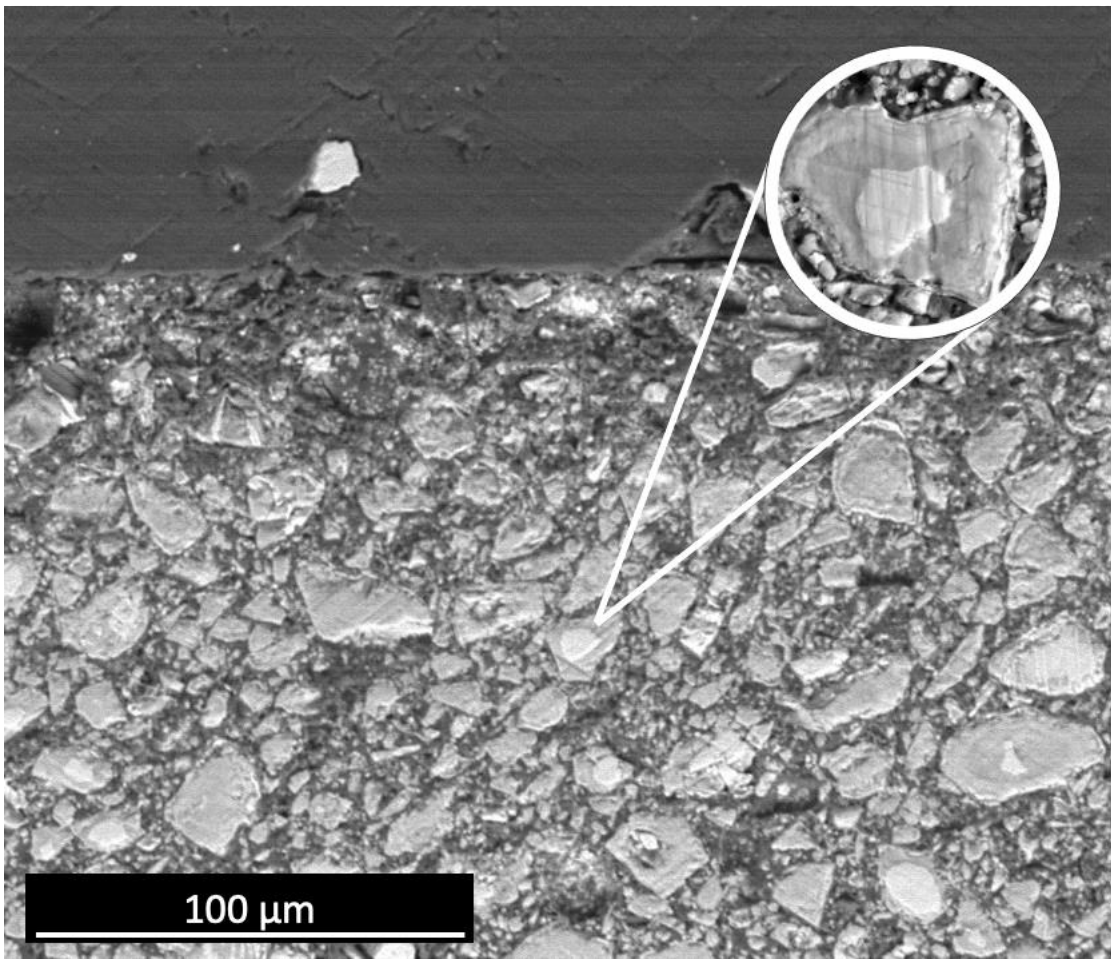

Figure 2: An SEM image of a BAG composite after immersion into artificial saliva at pH4 for two months. A closer magnification in the white circle shows the partial degradation of the glass particles. This figure was requested from and provided by Al-eesa *et al.* [15].

Glass ionomer cements (GICs) are also considered bioactive according to several research papers due to their capacity to release F^-, inhibit demineralization and promote remineralization [13]. The glasses used in GICs have often been incorporated into composites. Here it is important to note that these glasses degrade under acidic conditions (pH 4-5) by hydrolysis of Al-O-Si bonds and they release only small amounts of F^- Ca^{2+}/Sr^{2+} and PO_4^{3-} ions unless the pH is acidic [16]. They do not significantly degrade under neutral conditions, which is where remineralization and

apatite formation are likely to occur. Ionomer glasses do not have the capacity to form apatite upon immersion in physiological fluids, unlike BAGs. Thus, they are not as attractive as BAGs for incorporation into RBCs.

The aim of this paper is to review the published literature on bioactive glass (BAG) containing restorative composites by discussing the BAG composition, effect of network connectivity, refractive indices, silanization, bonding and the particle size of the BAG fillers on the bioactivity of the restorative composite. To maintain the focus of this review paper, only melt-quenched BAGs used for applications such as varnishes, adhesives, bonding agents, air abrasion and filling materials will be discussed. For the purposes of this review, a BAG is defined as a glass capable of forming an apatite layer when immersed in physiological solutions.

4. Methods

Online databases (Science Direct, PubMed and Google Scholar) were used to collect data published from 1962 to 2020. The research papers were analyzed and the relevant papers were selected for this review. Sol-gel BAGs were not included in this review as it is not a cost-effective manufacturing technique that can be upscaled. Furthermore, sol-gel glasses exhibit fluorine volatilization.

5. Bioactive glasses

Hench *et al.* first developed BAGs in 1969 and suggested that a BAG dissolves or degrades in physiological-like fluids, forming hydroxycarbonated apatite (HCA) [17]. They were originally developed as bone substitutes, but in the last fifteen years have been increasingly used as an additive in remineralizing desensitizing hypersensitivity

toothpastes [18-22]. These glass compositions are based on a SiO_2-P_2O_5-CaO-Na_2O system. Some typical BAG compositions are provided in Table 1.

Table 1: Selected common BAG compositions [17, 24-28], where NC is the network connectivity and RI is the refractive indices of the different glass compositions.

Glass	mol %					NC	RI
	SiO_2	P_2O_5	CaO	Na_2O	CaF_2		
45S5 [17]	46.10	2.60	26.90	24.40	0.00	2.11	1.56
45S5F [23]	46.10	2.60	16.90	24.40	10.00	2.55	1.53
S53P4 [24]	53.80	1.70	21.80	22.70	0.00	2.54	1.54
BAG-F [25]	42.70	4.00	26.20	26.10	1.00	2.11	1.55
BioMinF [26]	36.00-40.00	4.00-6.00	28.00-30.00	22.00-24.00	1.50-3.00	2.16	1.52
QMNA1 [27]	35.00	6.06	43.00	6.00	10.00	2.24	1.57
Example 7 (Cention N) [28]	48.00	0.00	31.00	8.00	10.00	2.38	1.50

Hench *et al.* explained the mechanism of dissolution and apatite formation (Figure 3) in many stages [17]. However, stage 1 and 2 does not specify the type of glass present, therefore one can assume that window glass, which is a Q^3/Q^4 type glass since there are three to four bridging oxygens bonded to the silicon, can be bioactive according to this mechanism. Yet, it was later observed that glasses are bioactive when the network connectivity (NC) is around 2 (Q^2 type glass, where there are two bridging oxygens bonded to the silicon). Therefore, bioactivity is highly dependent on NC (discussed further in section 6). Moreover, this mechanism only considers Na^+ cations, when in reality other cations will be present, most commonly Ca^{2+}. The addition of small amounts of CaF_2 to the glass composition and its capacity to form fluorapatite (FAp) [29] is not considered in this mechanism, and therefore this mechanism is restricted

to the formation of HCA, although many different apatite phases can be present such as FAp, chlorapatite, HAp, strontium-substituted apatite, and mixed apatites.

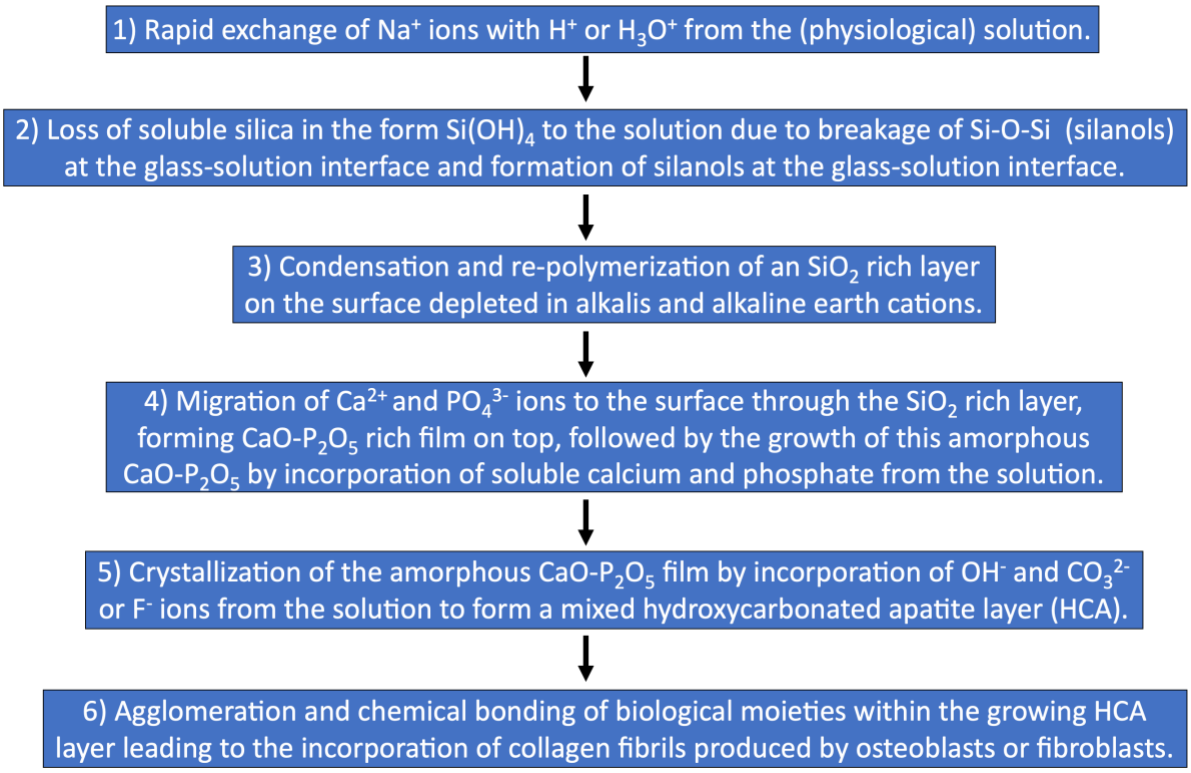

Figure 3: Mechanism of degradation/dissolution and apatite formation of BAGs by Hench *et al.* [17].

FAp, $Ca_5(PO_4)_3F$, is more acid resistant and less degradable than both HCA and HAp as the OH^- ion in apatite distorts the lattice slightly due to its large ionic radius, whereas the F^- ion has a smaller ionic radius, and fits perfectly in the hexagonal apatite lattice perfectly, thus FAp is more chemically and thermodynamically stable [30]. This makes fluoride attractive to dentistry, as the oral environment is often exposed to acidic conditions [31]. The critical pH respectively for HAp and FAp is approximately 5.5 and 4.5 respectively, depending on the individual [32].

6. Network connectivity model

Hill *et al.* questioned the BAG degradation mechanism in Figure 3 and developed a network connectivity (NC) model (NC_{old}) for predicting the dissolution and apatite forming capability of BAG fillers (equation 1) [33]. This is important in BAG design, as the NC will determine the overall dissolution and bioactive properties of the final restorative composite material. This model treats BAGs as linear silicon-based polymers and calculates the NC of the silicate network. In a pure SiO_2 glass, each silicon is linked via a bridging oxygen (a Si-O-Si) to four other silicons, providing a NC of 4.0 (Q^4). When network modifying oxides (NMOs) are introduced (such as Na^+ Ca^{2+}, Sr^{2+} or Mg^{2+}), the glass network is disrupted, giving rise to non-bridging oxygens (NBOs). In a calcium metasilicate glass containing equimolar ratios of CaO and SiO_2, each CaO introduces two NBOs (O^--Si-O-), breaking up the three-dimensional network. Each silicon becomes linked to two other oxygens and the NC=2.0 (Q^2 glass). The glass corresponds to a linear silicate chain and may be considered as a silicate polymer of $[SiO_3^{2-}]_n$. Reducing the CaO content results in the NC increasing beyond 2.0 and the polymeric chains become increasingly cross-linked.

$$NC_{old} = \frac{4[SiO_2] - 2[\sum NMO]}{[SiO_2]}$$

Equation 1: The original NC model before discovering phosphate is present as orthophosphate. NMO is the network modifying oxide concentration (in mol%) [33].

Based on this concept, dissolution and bioactivity would theoretically be expected to be highly dependent on the NC and an average sharp cut off for bioactivity would be expected at a NC of 2.0 assuming that only the linear crosslinked chains are present. Experimentally, dissolution and bioactivity often extend above a NC of 2.0, towards a

cut off value of 2.4 although Edén *et al.* stated that bioactivity is present up to a NC of 2.6 [34, 35].

The NC_{old} model predicted the bioactivity and apatite forming capacity reasonably well for simple silicate glasses that are phosphate-free but does not adequately work for glasses with higher phosphate contents than the 45S5 glass or compositions containing MgO or ZnO. Another problem when calculating NC is that structural assumptions must be made about the role of the various oxides. In the NC_{old} it was assumed that the phosphate formed Si-O-P bonds, however O'Donnell *et al.* [36-38] later showed the phosphorus formed, orthophosphate (PO_4^{3-}), was locally charge balanced by Ca^{2+} and Na^{+} ions and was therefore not part of the silicate network. This lead to the modification of the NC model (NC_{new}) in equation 2, considering that phosphate is present as orthophosphate (by equation 1) [39]. Note that when NC is discussed from this point on, it refers to NC_{new}. Increasing the NMOs at the expense of SiO_2 decreases the NC, thus making the glass more degradable.

$$NC_{new} = \frac{(4[SiO_2] - 2[\sum NMO] + 6[P_2O_5])}{[SiO_2]}$$

Equation 2: The modified NC model after discovering phosphate is present as orthophosphate. NMO is the network modifying oxide concentration (in mol%) [39].

O'Donnell *et al.* investigated the structural role of phosphate in BAGs and the influence of phosphate on the physical properties, dissolution behavior and capacity of the glasses to form apatite in simulated body fluid (SBF) [36-38]. Phosphorus was shown to exist as orthophosphate and when the phosphate content was increased, whilst maintaining a fixed NC by adding additional CaO and Na_2O, the time to form an

apatite-like phase decreased and the amount of apatite present increased. Edén *et al.* developed a split network model and calculated values that correspond exactly to those for the modified NC and also demonstrated the importance of the phosphate content by stating that if phosphorus remains as orthophosphate and the NC remains constant, the bioactivity is enhanced with increasing phosphate content of the BAG. [34].

Attempts were also made to produce high phosphate content BAGs with fluoride, but problems were encountered with crystallization of the compositions. Mneimne *et al.* reported that the amount of phosphate plays a crucial role in apatite formation since increasing the phosphate content of the glass whilst keeping the sodium content low and NC constant increases the amount and speed of apatite formation [31]. These investigators also reported that a low phosphate-containing glass takes approximately three days to start forming apatite, whereas high phosphate-containing glasses take less than a day.

7. Refractive index of bioactive glass fillers

Having a refractive index (RI) match (within 0.02) between the resin and BAG fillers is important to eliminate the light scattering at the glass-resin interface both for the efficient light curing and the final aesthetics of the composite to give translucency**.** Most commonly used dental resins have a RI range from 1.47 to 1.56, depending on the composition of the resin [40]. In the case of fluoride-free glasses, the RI of the glass can be calculated (equation 3) using Appen factors (Table 2), which are empirically derived factors calculated based on previous measurements of RI.

$$\mathrm{RI} = \frac{\sum_{i=1}^{n} n_{d,i} c_i}{100}$$

Equation 3: The equation used to calculate the RI, where $n_{d,i}$ is the Appen factor (Table 2) for the respective oxide component and C_i is the mol% of the oxide component.

However, Appen factors for the metal fluorides are not available in Appen's paper so the RI of fluoride-containing glasses could not be readily predicted [41]. Therefore, an Appen factor for CaF_2 containing glasses was developed (Table 2) [42]. This enables the design of fluoride-containing BAGs with a specific RI. The RIs of common BAG fillers were calculated using equation 3 and Table 2 (shown in table 1).

Table 2: Appen Factors for the different components commonly used in BAG [41, 42].

Compound	Appen Factor
SiO_2	1.46
Al_2O_3	1.52
Na_2O	1.58
ZnO	1.71
MgO	1.61
K_2O	1.58
CaO	1.73
SrO	1.78
P_2O_5	1.31
SrF_2	1.47
CaF_2	1.42

One of the problems with eliminating alkali metals (such as sodium) or reducing them to low levels is that a higher melting temperature is required. Once the processing temperature exceeds 1500°C, the costs of production increases dramatically. Incorporating fluoride reduces the melting temperature significantly, offsetting the increase required through loss of alkali metals. Fluoride additions are also known to reduce the RI of ionomer glasses used in GICs. Adding fluoride in the form of CaF_2

has also shown to reduce glass transition temperature due to the reduction of electrostatic forces between NBOs [29].

Several studies have reported that RI of the resins that were tested increased upon polymerization [43, 44]. However, it is sometimes difficult to match the RI of the resin and fillers, therefore one proposed solution for the RI mismatch is reducing the BAG particle size to reduce light scattering and improve depth of cure (DoC) [45]. Contrasting results were observed by Li *et al*., who reported that using a particle size of 15 μm had a higher DoC in comparison to using 2 μm [46]. It must be noted that maximum light scattering will occur when the particle size is comparable to the wavelength of light (≈500 nm or 0.5 μm), whereas above and below this value light scattering will reduce. Thus, reducing the particle size from 15 μm to 2 μm would be expected to increase light scattering and reduce the DoC.

8. Effect of ion substitutions in BAG fillers

Altering the composition of the glass can change the RI and NC of the material. For example, incorporating network modifying oxides such as SrO or ZnO increases the RI [41, 42], whereas adding CaF_2 reduces the RI, facilitating RI matching to the resin in a composite or to the glass and polysalt matrix in GICs [47, 48]. Sodium in the BAG takes up water readily due to its hygroscopic nature, which in turn weakens the composite material, reducing the mechanical properties and, as a consequence most BAG fillers aim to have a low sodium content [49]. Ion substitutions such as F^-, Mg^{2+}, Zn^{2+} and Sr^{2+} are common in BAGs, and all contribute to the final properties, such as the NC, RI and opacity, of the dental composite.

8.1 Fluoride

Hill *et al.* studied the structure of a wide range of fluorine containing glasses including fluorosilicate and fluoro-alumino-silicate glasses using ^{19}F solid state magic angle spinning-nuclear magnetic resonance (ssMAS-NMR) and observed that in all of these systems, fluorine was often present as F-M(n) species [16, 50-57]. These studies were the basis for developing fluoride-containing BAGs, leading to the substitution of CaF_2 for CaO in the original Hench *et al.* studies and patent [23].

Substituting CaO for CaF_2 reduces the NBO content of the glass, increasing the NC, which produces a more cross-linked glass with a higher NC. This in turn causes the BAG filler to dissolve and form apatite much more slowly or not at all. Alternatively, adding CaF_2 to the composition without substituting for CaO or Na_2O does not affect the NC. Hill *et al.* did not substitute CaF_2 for CaO, but instead added CaF_2 to the composition of the glass, keeping the ratios of all other components fixed in a low P_2O_5 content glass [29]. The silicon speciation, analyzed using ^{29}Si ssMAS-NMR, remained constant, verifying no change in the NC and the fluorine was complexed largely by calcium/sodium and formed F-M(n) species where M is Ca or Na and n is 3 or 4 [29]. The glasses used in this study formed FAp, rather than HAp and presented F^- release. Lusvardi *et al.* substituted CaF_2 for Na_2O in the 45S5 BAG and observed enhanced chemical durability, but observed a reduction in chemical durability when CaF_2 was substituted for CaO [58]. This may be due to water sorption by NaF, swelling and cracking the glass structure.

Brauer *et al.* subsequently investigated the dissolution behavior and *in vitro* bioactivity of low phosphate content glasses on adding CaF_2 [59]. The glasses formed FAp when the CaF_2 content was ≤ 5 mol% and released fluoride in addition to Ca^{2+} and PO_4^{3-} ions. However above 5 mol%, the glasses formed fluorite (CaF_2) at the expense of FAp and formation of an apatite layer in SBF decreased with increasing fluoride content in the glass. A solution to this may be to deliver Ca^{2+}, PO_4^{3-} and F^- ions together in appropriate ratios to form FAp and avoid the formation of CaF_2 [31]. These glasses with their low phosphate content were not commercially attractive because of the relatively small amounts of FAp formed and the relatively long time to form apatite [59]. Pedone *et al.* confirmed the fluorine speciation and the absence of Si-F bonds from Brauer *et al.* by using more advanced ssMAS-NMR techniques including rotational-echo double-resonance (REDOR) [29, 60]. Christie *et al.* performed molecular dynamics simulations of fluoride-containing BAGs and further confirmed the fluorine speciation found by Brauer *et al.* [61].

Prasad *et al.* investigated the effect of substituting CaF_2 for CaO in S53P4 and observed a delay in apatite formation due to the increase in NC with increasing substitutions of CaF_2, emphasizing the effect of NC on bioactivity [62]. S53P4 has a low P_2O_5 content (1.7 mol%), which could be another reason for the overall slow apatite formation. The milling procedure and immersion method is unclear, so it is difficult to understand the amount of glass powder and SBF used for the samples. Another drawback of this paper was that it did not go a step further by deconvoluting the ^{29}Si ssMAS-NMR spectrum and recalculating the NC, to determine if the experimental NC is the same. The NC equation assumes that F-Ca(n) species are

present, with no Si-F bonds, so calculating the experimental NC would have confirmed if the equation is still applicable.

Mneimne *et al.* investigated the role of fluoride in amorphous high phosphate content BAGs of a fixed NC. [31] The fluoride-containing glasses with < 9 mol% CaF_2 formed FAp in under six hours. Lynch *et al.* [63] showed a similar behavior in multicomponent glasses containing strontium. The optimum CaF_2 concentration was reported to be in the range 5-7 mol% and fluorite formation was suppressed slightly by a higher phosphate content in the glass [64].

Mneimne *et al.* also prepared one sodium-free BAG (QMMM7), which partially crystallized to FAp during quenching and is the basis of the low or zero sodium-containing glasses for incorporating into resin matrices and for low sodium glasses that can be used for air abrasion cutting of enamel [31, 65]. The lower sodium content results in a glass with a higher glass transition temperature (T_g) and an increased hardness that is more efficient for cutting enamel. The glasses developed for this purpose had a reduced CaF_2 content (3 mol%) compared to the 9 mol% CaF_2 content in the QMMM9 composition to suppress the crystallization to FAp upon quenching to facilitate obtaining an amorphous glass. This BAG composition was used in the studies by Caluwe *et al.* [66], where the BAG filler was incorporated into GICs. The investigators demonstrated that this was more bioactive than the 45S5 composition, despite it crystallizing partially to FAp.

8.2 Magnesium

Watts *et al.* investigated the substitution of CaO by MgO on the BAG structure and observed that the T_g decreased when the MgO content increased, as the bond strength of Si-O-Mg is lower than Si-O-Si, weakening the overall glass network [67]. In this paper, it was considered that 14% of the MgO contributed to the silica network, and 86% acted as a network modifier.

Souza *et al.* substituted MgO for CaO in 45S5 at different levels whilst maintaining a constant NC and observed using DSC that there was a decrease in T_g and an increase in T_c with increasing MgO content [68]. This observation has been supported by other investigators [69, 70], and the decrease in T_g and increase in T_c indicates an increase in the processing window for crystallization, suggesting that the addition of MgO suppresses crystallization of the apatite crystals. This could be useful information when using the melt-quench technique to make glasses, as many glasses tend to crystallize upon quenching, so the addition of MgO could be a solution.

Araujo *et al.* studied the bioactivity of MgO-containing BAGs with low Ca/P ratio and reported that BAGs with a higher MgO content formed apatite slower than BAGs with a lower MgO content [71]. This suggests that high contents of MgO can inhibit apatite layer formation, thus bioactivity. Jallot *et al.* investigated the role of Mg^{2+} during spontaneous formation of a calcium phosphate layer and observed that *in vivo*, Mg^{2+} suppressed apatite formation and presented greater solubility [72]. The investigators concluded that this cation may be incorporated into the apatite nuclei and inhibit small crystals. In addition, several studies reported that Mg^{2+} stabilizes the intermediate

amorphous calcium phosphate, delaying apatite formation especially at high concentrations [72-76].

LeGeros *et al.* stated that Mg^{2+} cations presented limited substitution into the apatite lattice and formed tricalcium phosphate [77]. Hill *et al.* confirmed this limited ability of Mg^{2+} ions to be incorporated into the lattice and suppress apatite crystal growth by blocking the surface sites on FAp crystals [67].

8.3 Zinc

Incorporating ≤ 0.4 mol% ZnO has shown to speed up apatite formation [78], but this is a very small amount and will not be very beneficial in terms of any antibacterial effects. Balamurugan *et al.* reported that incorporating 5 mol% ZnO into BAGs did not inhibit bioactivity [79], and this was confirmed by other researchers [80, 81], who also observed that replacing CaO and P_2O_5 with ZnO increases rate and amount of apatite formation. On the other hand, Shahrabi *et al.* reported that this amount will decrease the bioactivity [82]. When a high amount of ZnO was added (20 wt%), it been reduced degradation and capacity to form apatite [83]. Similarly, studies have reported that substituting CaO for ZnO has reduced the glass transition temperature, since Si-O-Zn bonds are weaker than Si-O bonds, weakening the glass network [84].

Addition of ZnO has shown to retard apatite formation by reducing the number of nucleation sites of apatite [85-88]. This explains some of the results reported by numerous researchers, where both glass dissolution and apatite formation were delayed by increasing the ZnO content [89-91]. In particular, Sánchez-Salcedo *et al.* who added 4 and 6 mol% ZnO observed no evidence for apatite formation on FTIR,

until seven days later, compared to a group with 0 mol% ZnO, which formed apatite within 2-4 days [90]. Similar results were observed by Huang *et al.*, who observed that adding 3 mol% ZnO whilst keeping the NC constant suppressed apatite formation [88]. This paper does not however give any details on how the NC was calculated, as they have not used the NC model by Hill *et al*. [39]. They have not assumed ZnO to behave as a NMO, so it is difficult to understand how NC was calculated and kept constant [88].

In contrast, Singh *et al.* has claimed apatite formation of samples containing 21 mol% ZnO-Fe_2O_3 within one day when samples were immersed in SBF. There is evidence for the loss of NBOs, however the FTIR data does not show the crucial split bands for 560 cm^{-1} and 600 cm^{-1}, so bioactivity cannot be concluded [92]. Further evidence from Bini *et al.*, has shown that the continuous addition of ZnO increases the glass' resistance to crystallization, which will aid in producing an amorphous glass [80]. Several researchers also claim that ZnO reduces nucleation sites for HAp, but when the glass is immersed into SBF, few but large crystals of apatite forms. There is evidence for this by XRD, where after immersion into SBF for 10 days, the diffraction lines sharpen, suggesting larger crystal formation [92].

Numerous studies have suggested that ion substitutions such as ZnO could have antibacterial effects as well as aid in mineralization of dental pulp stem cells [81, 93]. One study has used the halo zone test to measure the antibacterial activity of two magnesium-containing glasses, with 0 or 5 mol% ZnO incorporation, against *P.aeruginosa* bacteria [94]. It was observed that adding ZnO into the composition

showed antibacterial activity and bioactivity. However, results were not provided for the composition containing MgO only, which should have similar results since both MgO and ZnO are known to behave similarly. One of the compositions contain approximately 5 mol% of both MgO and ZnO, which could explain the lack of apatite formation, as both MgO and ZnO are known to inhibit apatite crystal formation, and the fact that both are present in this composition at a total of 10 mol% reduces the apatite forming capacity.

Blocherberger et al. studied the effect of substituting ZnO or MgO for CaO in the 45S5 glass composition and observed that when the glass was immersed into tris buffer (TB) with a physiological pH of 7.4, the original 45S5 and MgO-incorporated 45S5 showed comparable ion release and apatite forming capacity, but the ZnO-incorporated 45S5 showed no significant ion release [95]. However, when immersed into an acidic solution, acetic acid, the ZnO-incorporated 45S5 showed higher ion release and showed signs of apatite formation in the FTIR and XRD data. This suggests that the ZnO containing bioactive glass presented lower solubility in neutral conditions and higher solubility in acidic conditions, making it attractive to dentistry, where the antibacterial Zn2+ will be released in an acidic environment that is favored by bacterial.

8.4 Strontium

Strontium-containing BAGs were developed by replacing CaO with SrO due to its capacity to upregulate osteoblasts and downregulate osteoclasts [96-99]. It also has a high atomic number, which confers radiopacity [100], improving radiography diagnosis. Strontium has a mild anti-caries and antibacterial role and is thought to

have a synergistic action with fluoride in preventing caries [93, 101-103]. The initial glasses developed had a low phosphate content and it was reported that strontium expanded the glass network resulting in faster degradation and dissolution of the glass as well as faster apatite formation [96]. The faster dissolution and pH rise were also confirmed by Massera *et al.*, but in this study it was observed that the apatite formation was delayed [104]. Structural neutron scattering studies and molecular dynamics simulations later confirmed this observation too [105, 106]. Strontium lies below calcium in in Group II of the periodic table and exhibits complete solid substitution for calcium in all apatites [96].

Sriranganathan et al. showed that high strontium contents in fluoride-free high phosphate content BAGs inhibited apatite formation [107], potentially because the HAp forms below pH 9 via an octacalcium phosphate (OCP) precursor phase and only small amounts of strontium can replace calcium and be incorporated in OCP [108]. However, in the presence of fluoride, apatite forms directly without going via OCP and where fluoride is present in the media or in the BAG, strontium does not suppress apatite formation [109]. OCP is however unstable compared to HAp, especially at pH above 5 [110]. In addition, when carbonated apatite was precipitated in the presence of both Sr^{2+} and F^{-}, almost all of the available Sr^{2+} and F^{-} was used up by the crystals, suggesting improvement of the crystallinity of apatite and acid resistance [111]. Similar results were reported by Thuy *et al.*, where the combination of $Sr^{2+}$and F^{-} enhanced remineralization [103].

Adding SrO into the glass network by completely replacing CaO with SrO reduces the amount of the NMO content in the glass, since Sr^{2+} is heavier than Ca. This results in an increase in silica content and NC, so the glass becomes less degradable, hence is less bioactive [112]. Hesaraki *et al.* substituted 10 mol% of SrO for CaO in a SiO-P_2O_5-CaO-SrO system and observed a delay in apatite formation when immersed into SBF [113]. However, if SrO is substituted for CaO in a weight basis, apatite formation is more rapid [114, 115].

Fredholm *et al.* investigated strontium-containing BAG structures and physical properties and reported that substituting SrO for CaO decreases the T_g due to expanding the glass network, as the strontium cation is larger in size than the calcium cation, hence weakening of the glass, lowering of T_g and an increase in the thermal expansion coefficient [97]. This paper helps to understand the role of SrO in the glass structure. ^{29}Si ssMAS-NMR and FTIR spectra have shown very little change in the glass network, and no change in the ^{31}P ssMAS-NMR spectrum, regardless of strontium substitution. FTIR showed that with a higher content of SrO, there were more intense carbonate signals, suggesting incorporating Sr^{2+} increases surface reactivity, which could form HCA or other forms of carbonated apatite in physiological fluids.

Although strontium has great benefits for the tooth, it has a higher Appen factor than Ca^{2+}, which increases the RI of the glass [41, 42]. Therefore, this should be considered when designing BAGs, as a RI mismatch between the resin and BAG fillers will reduce the aesthetics and DoC.

9. Effect of silanizing the glass fillers

Incorporating fillers into the resin matrix improves the material properties of the two components if they are bonded (i.e., via a silanization procedure). If the filler is not bonded to the resin matrix, it could potentially weaken the resin [116]. Silanization of the glass particles are undertaken to couple the fillers with the resin matrix, in order to improve its mechanical properties. Silanization also makes the glass more hydrophobic and improves its dispersion in the resin. Silanizing agents are covalently attached to the fillers as coupling agents to increase their binding abilities [45]. The methacrylate groups of the silanizing agent is covalently bonded to the Si-OH groups of the BAG (Figure 4) [117]. The most commonly used silanizing agent is γ-methacryloxypropyl trimethoxysilane (γ-MPS).

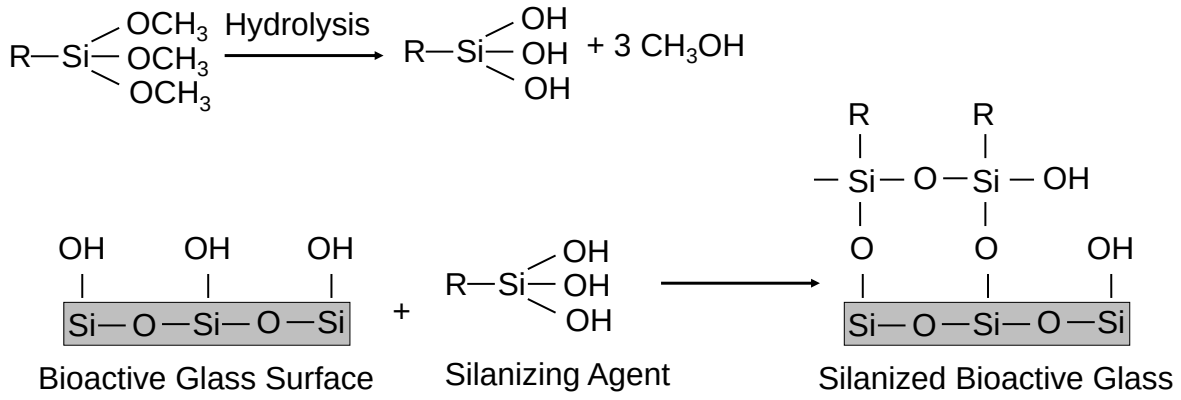

Figure 4: The silanization mechanism involved in coupling the resin matrix with the BAG fillers adapted from a paper by El Zohairy *et al.* [117].

Oral *et al.* investigated the effect of silanization and filler loading on physical properties [118] and reported that silanizing the BAG fillers with γ-MPS decreased the solubility of the composite, allowing a slow dissolution, but also showed the lowest water absorption properties. This suggests that silanizing the BAG fillers could prevent early

dissolution of the glass, which may also slow down ion release and apatite formation abilities of material, however no ion release data was presented. Silanization did not affect the flexural strength (FS) but decreased the flexural modulus (FM). Dry composite specimens showed lower FS and FM with increasing glass filler loading, whereas for water-stored (for 60 days) specimens, FS did not differ apart from the samples with the highest BAG loading (12 wt%), which decreased from 80 to 75 MPa. Mechanical testing values after storage in solution are more applicable to the oral environment than dry specimens, as the dental composite will continuously exposed to saliva. This also means that the immersion media used in studies should mimic the oral environment, so using artificial saliva (AS) instead of water would have been a more appropriate approach. In addition, the BAG filler loading used was 3-12 wt%, which is a very low filler loading and as such it may be difficult to see the effect of the BAG fillers.

Nicolae *et al.* studied the effect of UDMA and triethylene glycol dimethacrylate (TEGDMA) mixtures and non-silanized 45S5 BAG incorporation on the mechanical and physical properties of resin and resin-based composite materials. These investigators observed that composites containing up to 20 wt% BAG showed no significant deterioration in FS and FM [119]. However, the investigators reported that the lack of filler silanization may result in significant strength deterioration for composites containing greater than 20 wt% BAG. Silanization is however very important, as it couples the glass filers and matrix, improving mechanical properties such as FS. Mechanical testing was only performed on non-immersed samples, which does not mimic the oral environment, as the material will constantly be in contact with

the oral fluid. Therefore, storage of the samples would have allowed a direct comparison between immersed and non-immersed samples.

Studies by Par *et al.* have reported that adding 45S5 as a BAG filler to a composite material still presented significant curing, and that non-silanized BAG fillers can diminish the depth of cure [120-122]. Water present on the non-silanized glass surface may inhibit the polymerization process as well as cause the BAG fillers to react with the atmosphere, resulting in degradation of the BAG. This water can be reduced by silanizing, as the material will become more hydrophobic and difficult to wet.

10. Bonding the composite material to the tooth

4-methacryloyloxyethyl trimellitate anhydride (4-META) is used to improve the adhesion of the material to the dentin, reducing the need for a bonding agent [123]. It is added to the composition of the resin, so that an additional bonding agent is not required. 4-META contains both hydrophobic and hydrophilic groups and aids in the infiltration of the monomers from the resin into the hard tissue. When the 4-META molecule hydrolyzes in the presence of water during the silanization procedure, the hydrolyzed molecule is known as 4-MET. The carboxylic acid groups on the 4-MET chelate the Ca^{2+} in dentin or enamel to provide a chemical bond (Figure 5) [124, 125].

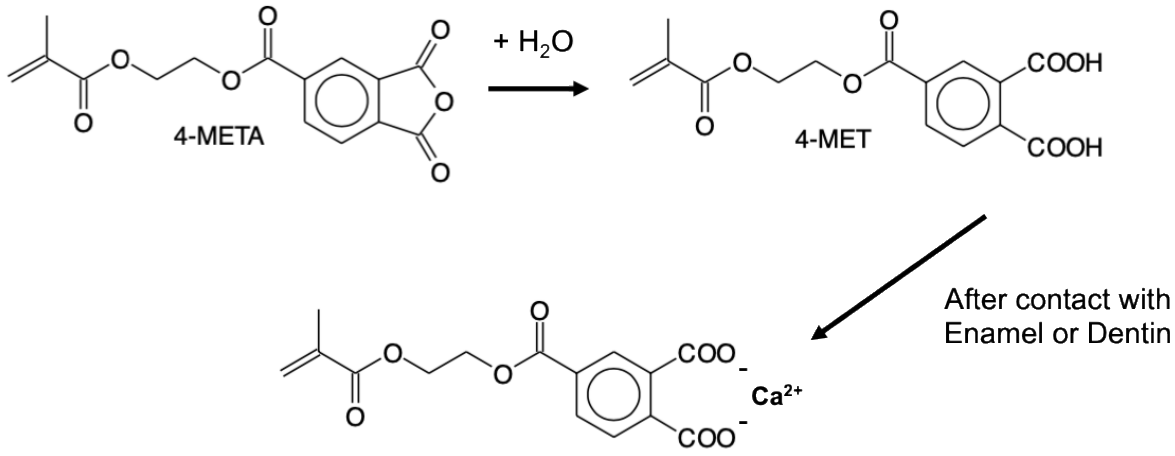

Figure 5: The hydrolysis of 4-META molecule to 4-MET, and the chelation reaction between 4-MET and enamel or dentin adapted from a paper by Fujisawa *et al.* [125].

It is currently used in situations where microleakage due to polymerization shrinkage occurs such as in partial dentures and adhesives. It has been shown to increase bond strength between two dental alloys [126] and observed to decrease staining, microleakage and failure of denture bases [127]. Al-eesa *et al.* added 4-META into their resin composition as they reported that it will enhance the bonding between the teeth and orthodontic brackets [128].

Using a bonding agent will also increase the bonding between the tooth and composite filling material, acting as an interface between the two layers. It has also been reported to reduce the marginal gap, reducing or eliminating microleakage [129]. However, bonding agents are very technique sensitive [130], where the conditions should be free of contamination and moisture, and a rubber dam must be used. Dentists cannot always achieve these conditions, leading to failure of the bonding agent. Most

importantly, the majority of bonding agents contain 2-hydroxyethyl methacrylate (HEMA), which is known to present cytotoxic effects on the pulp and gingival tissue when uncured [131].

11. Effect of particle size of BAG fillers

Reducing the particle size of the BAG fillers provides a good surface finish of the composite material [132], which could prevent bacterial attachment as they usually bind to rough surfaces. However, a small particle size (i.e., 5 nm to 1 μm) gives rise to problems such as the large surface area increasing the degradation rate of the BAG [133] as well as CO_2 and H_2O pick up from the atmosphere [134]. On the other hand, using a larger particle size (i.e., above 100 μm) minimizes the dissolution of the BAG filler, thereby delaying apatite formation. This is important since BAGs are designed to degrade slowly, releasing beneficial ions over a long period of time. The degradation mechanism's first step involves water to initiate the formation of apatite [17]. The smaller the particle size, the larger the surface area and the faster the BAG particles will react and pick up moisture.

Overall, it is difficult to suggest an ideal particle size for BAG fillers in dental composites as papers in the published literature have varying glass compositions and, as such comparing the different data to establish a relationship is impossible. However, using BAG particle sizes in the range 5 to 45 μm can ensure that there is degradation of the BAG fillers and apatite is formed within 28 days.

12. Incorporating BAG fillers into Resin Matrices

Orthovita Inc. (Pennsylvania, USA) incorporated the 45S5 glass into a Bis-GMA/TEGDMA resin system for use as a bioactive bone cement in 1999 [135]. However, problems were encountered with the high sodium content of the 45S5 glass (Table 1), resulting in swelling and cracking of the resin matrix upon immersion. Consequently, the glass was heat treated to crystallize the glass to combeite ($Na_2Ca_2Si_3O_9$), which solved the problem, but crystallization reduced the reactivity and dissolution of the BAG. Most studies for dental applications in the published literature involve the use of the 45S5 glass without crystallization, with the exception of a patent filed by Rusin from 3M which specifies a partially crystalline glass [136].

Yang *et al.* investigated the capacity of 45S5 glass with a particle size <25 μm in a Bis-GMA/TEGDMA (50/50 ratio) composite with an inert glass filler with up to a 50 wt% loading of the high sodium-containing BAG [137, 138]. These investigators observed a pH rise above 8 with the composite containing 50 wt% BAG over 180 minutes, thereby demonstrating the capacity to neutralize acids produced in bacterial plaque. The water sorption, solubility and FS were measured according to ISO 4049 (2009), which involves storing specimens for 24 hours in distilled water [139]. The FS measured was 76.1 and 45.0 MPa for 0 and 50 wt% BAG content respectively, suggesting a decrease in FS with the incorporation of BAG fillers. The immersion time of 24 hours was however too short to see the influence of the high sodium content glass on the FS, as BAGs degrade over a long period of time. The ISO standard test is therefore not suitable for testing BAG composites especially for BAGs containing

high sodium contents. Therefore, a modified version of ISO 4049 should be implemented considering the behavior of BAG containing dental composites.

Yang *et al.* in a subsequent study also measured lactic acid neutralizing capacity of three types of BAG: 45S5, S53P4 and 45S5F (compositions shown in Table 1) [23, 137]. The investigators reported that the higher the loading of the BAG, the faster the neutralizing capacity. They also recognized the potential for BAGs incorporated into orthodontic adhesives to prevent white spot lesion formation, which is a common problem following fixed orthodontic bracket treatment. The 45S5 glass with a lower NC and higher basicity not surprisingly neutralized the lactic acid more rapidly than the 45S5F and S53P4 for the same BAG loading of 52.5 wt%. Immersion for 24 hours is the standard test condition for shear bond tests but given that orthodontic brackets are applied for typically 18 months, one day is too short and the shear bond strength with BAG filled orthodontic adhesives may decline further with increased immersion time as the BAG particles react further.

Kohda *et al.* investigated the inhibition of enamel demineralization and bond-strength properties of 45S5 BAG (0 and 50 wt% loadings) containing 4-META/MMA-TBB-based resin adhesive [140]. There was extensive ion release and the shear bond strength did not reduce until 50 wt% BAG was used. The time point at which the shear bond strength was measured was not defined. The inclusion of BAG improved the acid neutralization but there was limited inhibition of enamel demineralization. The investigators stated that the addition of fluoride may affect the solubility of the glass.

This reflects again the perceived wisdom at the time that incorporation of fluoride eliminated any bioactivity from composites.

Korkut *et al.* investigated the antibacterial and mechanical properties of a Bis-GMA/TEGDMA (70/30 ratio) based RBC containing BAG [141]. They used the S53P4 BAG composition (Table 1) that has a higher NMO content than 45S5. Compressive and FSs of the composites were measured at 24 hours of immersion in distilled water and decreased significantly with addition of 30 wt% BAG. Antibacterial activity against *S. mutans* was also demonstrated in this study.

Tezvergil-Mutluay *et al.* investigated a very multicomponent RBC system containing 45S5 and a fluoride-containing BAG composition referred to as BAG-F (Table 1). These investigators evaluated the degradation of completely demineralized dentin specimens in contact with either a filler-free or composites containing 45S5 or BAG-F particles. At 30 days of AS storage, the fluoride-containing BAG showed the greatest remineralizing effect of the completely demineralized dentin matrices. The investigators also claimed that the fluoride-containing phosphate-rich BAG may offer greater beneficial effects than the 45S5 in reducing the enzyme-mediated degradation and promoting remineralization of demineralized dentin. It is worth noting that if they had used a higher phosphate glass with a higher fluoride content their results would have been expected to be superior to those reported in this investigation.

Al-eesa *et al.* studied a novel fluoride-containing BAG orthodontic adhesive and observed sufficient ion release and an alkalizing capacity of the BAG [15, 27, 128].

These observations were more pronounced in acidic conditions in comparison to neutral conditions. Apatite formation was clear in the FTIR, XRD, SEM and ssMAS-NMR, especially in AS at pH 7, as apatite formation only forms when the pH is above 5 [32, 142]. It is important to note that the glass synthesized was not completely amorphous to start with and could have aided in the apatite formation as they could have acted as nucleating agents for apatite formation.

Al-Khafaji *et al.* prepared a novel fluoride and strontium-containing BAG filler to be used in dental varnishes and tested its bioactivity in TB [143]. Results showed that BAG compositions with high SrO substituted for CaO were more likely to crystallize during the melt-quench synthesis. The FTIR results showed split bands that correspond to apatite and an increase in intensity after immersion. The originally amorphous BAGs (with little or no substitution of SrO) were also able to form apatite, concluding that all compositions were able to inhibit demineralization, by raising the pH, and promote remineralization. TB contains no ions and maintains the pH better in comparison to deionized water, so using this solution is an ideal way to test the bioactivity of materials. However, using physiological fluids such as AS would have been preferable in replicating the oral environment. Varnishes are replaced every few months, so measuring the ion release and apatite formation abilities of the varnish for longer than seven days would provide additional information on the materials behavior over time.

Chen *et al.* studied the bioactivity of sodium-free fluoride-containing BAGs in TB and SBF and observed that glasses with low fluoride content formed apatite in TB within

six hours of immersion, which was confirmed to be FAp only, whereas the glasses with higher fluoride content (13.6 to 25.5 mol%) crystallized to form CaF_2, with FAp as a minor phase [144]. The fluoride was present as either SrF_2 or CaF_2. Glasses containing > 4.5 mol% SrF_2 were more likely to crystallize, causing partial crystallization of the glass during the synthesis. However, there was no effect partial crystallization on bioactivity, even though completely amorphous glasses showed a faster dissolution. Glass degradation and apatite formation was significantly slower in SBF solution compared to TB at 24 and six hours respectively, which is suggested to be due to the higher ionic strength of SBF and the fact that it contains magnesium ions, which is known to suppress or slow down apatite formation.

Simila *et al.* investigated the bioactivity and fluoride release of strontium and fluoride modified Biodentine® (Septodont, Saint-Maur-des-Fossés, France) and observed sufficient F^- release and FAp formation when a fluoride-containing BAG was incorporated in Biodentine® [145]. No reference data (non-immersed) was presented using FTIR or XRD, ^{31}P ssMAS-NMR so it cannot be determined if the materials were already crystallized before immersion into phosphate buffered saline. It is not fully possible to compare the FTIR, XRD and ^{31}P ssMAS-NMR, as they all show inconsistent time points: 14 days, one day, and three hours respectively. The ^{19}F and ^{31}P ssMAS-NMR cannot be fully compared as they are performed on different glass compositions. Therefore, it cannot be concluded that FAp has formed with the Biodentine® glass, as no ^{19}F ssMAS-NMR spectrum were provided. Although the original Biodentine® does not contain phosphate, it still appears to have similar apatite forming capacity compared with the BAG containing Biodentine®.

Tiskaya *et al.* investigated the bioactivity of Cention N® (Ivoclar Vivadent, Schaan, Liechtenstein), which contains three glasses: an inert barium boro-alumino-silicate glass an active glass (close to Example 7 in Table 1 from the patent assigned to Ivoclar Vivadent) and an ionomer glass [28, 146, 147]. Cention N® does not contain phosphate in the composition but has been shown to release Ca^{2+} and F^- ions and form small amounts of apatite in an orthophosphate containing AS. FTIR and XRD data showed apatite formation upon immersion into an orthophosphate containing AS. Additional characterization techniques such as ^{31}P and ^{19}F ssMAS-NMR can be performed to completely confirm the apatite formation, and the type of apatite formed. There is also good clinical data for Cention N® preventing secondary caries associated with marginal gaps [148]. This suggests that overall Cention N® potentially forms apatite in the marginal gaps as well as increases the pH, thereby providing an environment that is unfavorable to cariogenic bacteria penetration.

Tiskaya *et al.* also investigated the bioactivity of Activa® by Pulpdent Corporation (Massachusetts, USA), which contains a bioactive ionic resin matrix, reactive ionomer glass fillers and a shock-absorbing rubberized resin component and claims have been made to support its bioactivity [146, 149]. However, the investigators reported no evidence for apatite formation up to six weeks in AS using FTIR and XRD, and the data indicated that CaF_2 may be forming instead of apatite and there was no sufficient Ca^{2+}, PO_4^{3-} or F^- ion release. The clinical trial on Activa® was also abandoned early because of a high incidence of secondary caries [150].

13. Conclusion

BAGs are promising additions to restorative dentistry as they have the capacity to raise the local pH, release beneficial ions (such as Ca^{2+}, PO_4^{3-} and F^-) and facilitate the formation of apatite. Incorporation of fluoride has shown to form FAp, which is more acid resistant than HAp and HCA, and magnesium and zinc substitutions can inhibit crystallization during quenching. Sodium content reduces the melting temperature but reduces the mechanical properties of the composite as it takes up water and is quite soluble.

Silanization of the glass particles should be considered for improving the mechanical properties of the restorative composite, and 4-META to improve the bonding between the tooth and the composite. Mechanical properties of BAG containing composites should not be conducted in dry conditions, as this does not mimic the oral environment, and a standard testing procedure should be established considering the sensitivity of BAGs to moisture.

NC plays a crucial role when designing BAGs and adding phosphate into the glass composition whilst maintaining a fixed NC increases speed and amount of apatite formation of the composite. The apatite formed could potentially form in the marginal gap between the tooth structure and composite restoration caused by polymerization shrinkage.

14. Acknowledgements/funding

The authors would like to thank BioMin Technologies Ltd, UK for funding this project.

15. Bibliography

1. Minamata convention on mercury—text and annexes. United Nations Environment Programme, 2013:1-61.
2. Soares CJ, Rodrigues MDP, Vilela ABF, Pfeifer CS, Tantbirojn D, Versluis A. Polymerization shrinkage stress of composite resins and resin cements–What do we need to know? Brazilian oral research. 2017;31.
3. Deliperi S, Bardwell DN. An alternative method to reduce polymerization shrinkage in direct posterior composite restorations. The Journal of the American Dental Association. 2002;133(10):1387-98.
4. Spiller MS. Dental composites: a comprehensive review. Albany, NY. 2012;12212.
5. Forss H, Widström E. From amalgam to composite: selection of restorative materials and restoration longevity in Finland. Acta Odontologica Scandinavica. 2001;59(2):57-62.
6. Maas MS, Alania Y, Natale LC, Rodrigues MC, Watts DC, Braga RR. Trends in restorative composites research: what is in the future? Brazilian Oral Research. 2017;31.
7. Jefferies S, Fuller A, Boston D. Preliminary evidence that bioactive cements occlude artificial marginal gaps: bioactive cements occlude artificial marginal gaps. Journal of Esthetic and Restorative Dentistry. 2015;27.
8. Vallittu P, Boccaccini A, Hupa L, Watts D. Bioactive dental materials—do they exist and what does bioactivity mean? Dental Materials. 2018;34.
9. Hench LL, Splinter RJ, Allen WC, Greenlee TK. Bonding mechanisms at the interface of ceramic prosthetic materials. Journal of Biomedical Materials Research. 1971;5(6):117-41.
10. Hench LL. Bioceramics. Journal of the American Ceramic Society. 1998;81(7):1705-28.
11. Sonarkar S, Purba R. Bioactive materials in conservative dentistry. International Journal of Contemporary Dental and Medical Reviews. 2015;2015.
12. Roulet J-F, Price RB. The value of consensus conferences: peer review by 50 key opinion leaders! Dent. 2018;3(2):218-21.
13. Lawson N. Bioactive restorative materials in dentistry2019:[1-7 pp.].
14. Liang K, Wang S, Tao S, Xiao S, Zhou H, Wang P, et al. Dental remineralization via poly (amido amine) and restorative materials containing calcium phosphate nanoparticles. International journal of oral science. 2019;11(2):15.
15. Al-eesa NA, Karpukhina N, Hill RG, Johal A, Wong FSL. Bioactive glass composite for orthodontic adhesives — Formation and characterisation of apatites using MAS-NMR and SEM. Dental Materials. 2019;35(4):597-605.
16. Hill R, Alan W. Some structural aspects of glasses used in ionomer cements. Glass Technology. 1988;29:150-8.
17. Hench L. The Story of Bioglass®. Journal of materials science Materials in medicine. 2006;17:967-78.
18. Gillam DG, Tang JY, Mordan NJ, Newman HN. The effects of a novel Bioglass dentifrice on dentine sensitivity: a scanning electron microscopy investigation. J Oral Rehabil. 2002;29(4):305-13.
19. Earl JS, Ward MB, Langford RM. Investigation of dentinal tubule occlusion using FIB-SEM milling and EDX. J Clin Dent. 2010;21(2):37-41.

20. Greenspan D. NovaMin and tooth sensitivity- an overview. The Journal of clinical dentistry. 2010;21:61-5.
21. Earl JS, Leary RK, Muller KH, Langford RM, Greenspan DC. Physical and chemical characterization of dentin surface following treatment with NovaMin technology. J Clin Dent. 2011;22(3):62-7.
22. Earl JS, Topping N, Elle J, Langford RM, Greenspan DC. Physical and chemical characterization of the surface layers formed on dentin following treatment with a fluoridated toothpaste containing NovaMin. J Clin Dent. 2011;22(3):68-73.
23. Hench LL, Spilman DB, Hench JWl, Fluoride-containing Bioglass™ compositions, 1988. Patent Number 4775646.
24. Andersson Ö, Liu G, Karlsson K, Niemi L, Miettinen J, Juhanoja J. In vivo behaviour of glasses in the SiO2-Na2O-CaO-P2O5-Al2O3-B2O3 system. Journal of Materials Science: Materials in Medicine. 1990;1(4):219-27.
25. Tezvergil-Mutluay A, Seseogullari-Dirihan R, Feitosa V, Cama G, Brauer D, Sauro S. Effects of Composites Containing Bioactive Glasses on Demineralized Dentin. Journal of dental research. 2017;96:999-1005.
26. Bakry A, Abbassy M, Alharkan H, Basuhail S, Al-Ghamdi K, Hill R. A novel fluoride containing bioactive glass paste is capable of re-mineralizing early caries lesions. Materials. 2018;11:1636.
27. Al-eesa NA, Johal A, Hill RG, Wong FSL. Fluoride containing bioactive glass composite for orthodontic adhesives — Apatite formation properties. Dental Materials. 2018;34(8):1127-33.
28. Fischer UK, Grabher K, Höland W, Moszner N, Rheinberger V, Salz ARD, et al.l, Polymerisable composite material, 1997. Patent Number 6353039.
29. Brauer D, Karpukhina N, Law R, Hill R. Structure of fluoride-containing bioactive glasses. Journal of Materials Chemistry. 2009;19:5629-36.
30. Pajor K, Pajchel L, Kolmas J. Hydroxyapatite and fluorapatite in conservative dentistry and oral implantology- a review. Materials (Basel). 2019;12(17):2683.
31. Mneimne M, Hill RG, Bushby AJ, Brauer DS. High phosphate content significantly increases apatite formation of fluoride-containing bioactive glasses. Acta Biomaterialia. 2011;7(4):1827-34.
32. Goldstep F. Proactive intervention dentistry: a model for oral care through life. Compendium of continuing education in dentistry (Jamesburg, NJ: 1995). 2012;33(6):394-6, 8-402; quiz 4, 16.
33. Hill R. An alternative view of the degradation of bioglass. Journal of Materials Science Letters. 1996;15:1122-5.
34. Edén M. The split network analysis for exploring composition–structure correlations in multi-component glasses: I. Rationalizing bioactivity-composition trends of bioglasses. Journal of Non-Crystalline Solids. 2011;357(6):1595-602.
35. Yu Y, Mathew R, Edén M. Quantitative composition–bioactivity relationships of phosphosilicate glasses: Bearings from the phosphorus content and network polymerization. Journal of Non-Crystalline Solids. 2018;502:106-17.
36. O'Donnell MD, Watts SJ, Hill RG, Law RV. The effect of phosphate content on the bioactivity of soda-lime-phosphosilicate glasses. J Mater Sci Mater Med. 2009;20(8):1611-8.
37. O'Donnell MD, Watts SJ, Law RV, Hill RG. Effect of P2O5 content in two series of soda lime phosphosilicate glasses on structure and properties – part I: NMR. Journal of Non-Crystalline Solids. 2008;354(30):3554-60.

38. O'Donnell MD, Watts SJ, Law RV, Hill RG. Effect of P2O5 content in two series of soda lime phosphosilicate glasses on structure and properties – part II: physical properties. Journal of Non-Crystalline Solids. 2008;354(30):3561-6.
39. Hill RG, Brauer DS. Predicting the bioactivity of glasses using the network connectivity or split network models. Journal of Non-Crystalline Solids. 2011;357(24):3884-7.
40. Hadis M, Tomlins P, Shortall A, Palin W. Dynamic monitoring of refractive index change through photoactive resins. Dental materials. 2010;26(11):1106-12.
41. Appen AA. Chemistry of glass. 1974;10.
42. Duminis T, Shahid S, Karpukhina N, Hill R. Predicting refractive index of fluoride containing glasses for aesthetic dental restorations. Dental materials : official publication of the Academy of Dental Materials. 2018;34.
43. Shortall AC, Palin WM, Burtscher P. Refractive index mismatch and monomer reactivity influence composite curing depth. J Dent Res. 2008;87(1):84-8.
44. Fujita K, Nishiyama N, Nemoto K, Okada T, Ikemi T. Effect of base Monomer's refractive index on curing depth and polymerization conversion of photo-cured resin composites. Dental materials journal. 2005;24:403-8.
45. Habib E, Wang R, Wang Y, Zhu M, Zhu XX. Inorganic fillers for dental resin composites: present and future. ACS Biomaterials Science & Engineering. 2016;2(1):1-11.
46. Li Y, Swartz ML, Phillips RW, Moore BK, Roberts TA. Effect of filler content and size on properties of composites. J Dent Res. 1985;64(12):1396-401.
47. Morrell A. Matching the refractive index between di-methacrylate polymers and bioactive glasses: University of Birmingham; 2015.
48. Gan F. Optical properties of fluoride glasses: a review. Journal of Non-Crystalline Solids. 1995;184:9-20.
49. Chen X, Chen X, Brauer DS, Wilson RM, Law RV, Hill RG, et al. Sodium is not essential for high bioactivity of glasses. Int J Appl Glass Sci. 2017;8(4):428-37.
50. Stamboulis A, Law RV, Hill RG. Characterisation of commercial ionomer glasses using magic angle nuclear magnetic resonance (MAS-NMR). Biomaterials. 2004;25(17):3907-13.
51. Hill RG, Law RV, O'Donnell MD, Hawes J, Bubb NL, Wood DJ, et al. Characterisation of fluorine containing glasses and glass-ceramics by 19F magic angle spinning nuclear magnetic resonance spectroscopy. Journal of the European Ceramic Society. 2009;29(11):2185-91.
52. Hill RG, Stamboulis A, Law RV. Characterisation of fluorine containing glasses by 19F, 27Al, 29Si and 31P MAS-NMR spectroscopy. J Dent. 2006;34(8):525-32.
53. Hill RG, Costa ND, Law RV. Characterization of a mould flux glass. Journal of Non-Crystalline Solids. 2005;351(1):69-74.
54. Hill RG, Stamboulis A, Law RV, Clifford A, Towler MR, Crowley C. The influence of strontium substitution in fluorapatite glasses and glass-ceramics. Journal of Non-Crystalline Solids. 2004;336(3):223-9.
55. Hill R, Calver A, Skinner S, Stamboulis A, Law R. A MAS-NMR and combined Rietveldt study of mixed calcium/strontium fluorapatite glass-ceramics. In Key Engineering Materials. 2006;309-311:305-8.
56. Hill R, Stamboulis A, Law R, J H, J H. MAS-NMR study of the crystallisation process of barium fluorphlogopite glass ceramics. Physics and Chemistry of Glasses - European Journal of Glass Science and Technology Part B. 2004;45:121-6.

57. Matsuya S, Stamboulis A, Hill RG, Law RV. Structural characterization of ionomer glasses by multinuclear solid state MAS-NMR spectroscopy. Journal of Non-Crystalline Solids. 2007;353(3):237-43.
58. Lusvardi G, Malavasi G, Tarsitano F, Menabue L, Menziani MC, Pedone A. Quantitative structure-property relationships of potentially bioactive fluoro phospho-silicate glasses. J Phys Chem B. 2009;113(30):10331-8.
59. Brauer DS, Karpukhina N, O'Donnell MD, Law RV, Hill RG. Fluoride-containing bioactive glasses: Effect of glass design and structure on degradation, pH and apatite formation in simulated body fluid. Acta Biomaterialia. 2010;6(8):3275-82.
60. Pedone A, Charpentier T, Menziani MC. The structure of fluoride-containing bioactive glasses: new insights from first-principles calculations and solid state NMR spectroscopy. J Mater Chem. 2012;22:12599-608.
61. Christie J, Pedone A, Menziani MC, Tilocca A. Fluorine environment in bioactive glasses: ab initio molecular dynamics simulations. The journal of physical chemistry B. 2011;115:2038-45.
62. Prasad S, Ganisetti S, Jana A, Kant S, Sinha P, Tripathy S, et al. Elucidating the effect of CaF2 on structure, biocompatibility and antibacterial properties of S53P4 glass. Journal of Alloys and Compounds. 2020:154704.
63. Lynch E, Brauer DS, Karpukhina N, Gillam DG, Hill RG. Multi-component bioactive glasses of varying fluoride content for treating dentin hypersensitivity. Dent Mater. 2012;28(2):168-78.
64. Liu J, Rawlinson S, Hill R, Fortune F. Fluoride incorporation in high phosphate containing bioactive glasses and in vitro osteogenic, angiogenic and antibacterial effects. Dental Materials. 2016;32.
65. Farooq I, Tylkowski M, Müller S, Janicki T, Brauer D, Hill R. Influence of sodium content on the properties of bioactive glasses for use in air abrasion. Biomedical materials (Bristol, England). 2013;8.
66. De Caluwe T, Vercruysse CWJ, Declercq H, Schaubroeck D, Verbeeck R, Martens L. Bioactivity and biocompatibility of two fluoride containing bioactive glasses for dental applications. Dental Materials. 2016;32:1414-28.
67. Watts SJ, Hill RG, O'Donnell MD, Law RV. Influence of magnesia on the structure and properties of bioactive glasses. Journal of Non-Crystalline Solids. 2010;356(9):517-24.
68. Souza MT, Crovace MC, Schröder C, Eckert H, Peitl O, Zanotto ED. Effect of magnesium ion incorporation on the thermal stability, dissolution behavior and bioactivity in Bioglass-derived glasses. Journal of Non-Crystalline Solids. 2013;382:57-65.
69. Watts S. Composition structure property relationships in bioactive glasses [Doctor of Philosophy]: Imperial College London; 2010.
70. Al-Noaman A. Novel bioactive glass coating for dental implant 2012.
71. Araujo M, Miola M, Baldi G, Perez J, Verne E. Bioactive Glasses with Low Ca/P Ratio and Enhanced Bioactivity. Materials (Basel). 2016;9(4).
72. Jallot E. Role of magnesium during spontaneous formation of a calcium phosphate layer at the periphery of a bioactive glass coating doped with MgO. Applied surface science. 2003;211(1-4):89-95.
73. Boskey A, Posner A. Magnesium stabilization of amorphous calcium phosphate: a kinetic study. Materials Research Bulletin. 1974;9(7):907-16.

74. Boulet M, Marier J, Rose D. Effect of magnesium on formation of calcium phosphate precipitates. Archives of biochemistry and biophysics. 1962;96(3):629-36.
75. Ding H, Pan H, Xu X, Tang R. Toward a detailed understanding of magnesium ions on hydroxyapatite crystallization inhibition. Crystal growth & design. 2014;14(2):763-9.
76. Amjad Z, Koutsoukos P, Nancollas G. The crystallization of hydroxyapatite and fluorapatite in the presence of magnesium ions. Journal of colloid and interface science. 1984;101(1):250-6.
77. LeGeros R, Taheri M, Quirolgico G, LeGeros J, editors. Formation and stability of apatites: effects of some cationic substituents. Proc 2nd International Congress on Phosphorus Compounds, Boston; 1980.
78. Salinas AJ, Shruti S, Malavasi G, Menabue L, Vallet-Regí M. Substitutions of cerium, gallium and zinc in ordered mesoporous bioactive glasses. Acta Biomaterialia. 2011;7(9):3452-8.
79. Balamurugan A, Balossier G, Sanjeevi K, Michel J, Rebelo A, Ferreira J. Development and in vitro characterization of sol-gel derived CaO-P2O5-SiO2-ZnO bioglass. Acta biomaterialia. 2007;3:255-62.
80. Bini M, Grandi S, Capsoni D, Saino E, Visai L. SiO2−P2O5−CaO glasses and glass-ceramics with and without ZnO: relationships among composition, microstructure, and bioactivity. J Phys Chem C. 2009;113.
81. Oki A, Parveen B, Hossain S, Adeniji S, Donahue H. Preparation and in vitro bioactivity of zinc containing sol-gel-derived bioglass materials. J Biomed Mater Res A. 2004;69(2):216-21.
82. Shahrabi S, Hesaraki S, Moemeni S, Khorami M. Structural discrepancies and in vitro nanoapatite formation ability of sol–gel derived glasses doped with different bone stimulator ions. Ceramics International. 2011;37(7):2737-46.
83. Aina V, Malavasi G, Fiorio Pla A, Munaron L, Morterra C. Zinc-containing bioactive glasses: surface reactivity and behaviour towards endothelial cells. Acta Biomater. 2009;5(4):1211-22.
84. Malavasi G, Cortada M, Menabue L, Menziani MC, Pedone A, Segre U. Elucidation of the structural role of fluorine in potentially bioactive glasses by experimental and computational investigation. The Journal of Physical Chemistry B. 2008;112:12730-9.
85. Balasubramanian P, Strobel L, Kneser U, Boccaccini A. Zinc-containing bioactive glasses for bone regeneration, dental and orthopedic applications. Biomedical Glasses. 2015;1.
86. Chen X, Brauer DS, Karpukhina N, Waite RD, Barry M, McKay IJ, et al. ‘Smart’ acid-degradable zinc-releasing silicate glasses. Materials Letters. 2014;126:278-80.
87. Du RL, Chang J, Ni SY, Zhai WY, Wang JY. Characterization and in vitro bioactivity of zinc-containing bioactive glass and glass-ceramics. J Biomater Appl. 2006;20(4):341-60.
88. Huang M, Hill RG, Rawlinson SCF. Zinc bioglasses regulate mineralization in human dental pulp stem cells. Dental Materials. 2017;33(5):543-52.
89. Courtheoux L, Lao J, Nedelec J-M, Jallot E. Controlled bioactivity in zinc-doped sol−gel-derived binary bioactive glasses. The Journal of Physical Chemistry C. 2008;112.

90. Sánchez-Salcedo S, Saxena S, Salinas A, Malavasi G, Menabue L, Vallet-Regí M. In vitro antibacterial capacity and cytocompatibility of SiO2–CaO–P2O5 meso-macroporous glass scaffolds enriched with ZnO. J Mater Chem B. 2014;2.
91. Zaffe D, Menabue L, Bertoldi C, Malavasi G, Consolo U. In vitro and in vivo behaviour of zinc-doped phosphosilicate glasses. Acta biomaterialia. 2009;5:419-28.
92. Singh R, Srinivasan A. Bioactivity of SiO2–CaO–P2O5–Na2O glasses containing zinc–iron oxide. Applied Surface Science. 2010;256:1725-30.
93. Beyth N, Farah S, Domb AJ, Weiss EI. Antibacterial dental resin composites. Reactive and Functional Polymers. 2014;75:81-8.
94. Baghbani F, Moztarzadeh F, Hajibaki L, Mozafari M. Synthesis, characterization, antibacterial activity and bioactivity evaluation of quinary glass system SiO2-CaO-P2O5-MgO-ZnO: An in vitro study. Bulletin of Materials Science. 2014;36:1339-46.
95. Blochberger M, Hupa L, Brauer DS. Influence of zinc and magnesium substitution on ion release from Bioglass 45S5 at physiological and acidic pH. Biomedical glasses. 2015;1(open-issue).
96. Fredholm YC, Karpukhina N, Brauer DS, Jones JR, Law RV, Hill RG. Influence of strontium for calcium substitution in bioactive glasses on degradation, ion release and apatite formation. J R Soc Interface. 2012;9(70):880-9.
97. Fredholm YC, Karpukhina N, Law RV, Hill RG. Strontium containing bioactive glasses: Glass structure and physical properties. Journal of Non-Crystalline Solids. 2010;356(44):2546-51.
98. Gentleman E, Fredholm YC, Jell G, Lotfibakhshaiesh N, O'Donnell MD, Hill RG, et al. The effects of strontium-substituted bioactive glasses on osteoblasts and osteoclasts in vitro. Biomaterials. 2010;31(14):3949-56.
99. Gentleman E, Hill R, Stevens M. Strontium-substituted bioactive glass coatings for bone tissue engineering. Clinical Biochemistry - CLIN BIOCHEM. 2011;44.
100. Shahid S, Hassan U, Billington R, Hill R, Anderson P. Glass ionomer cements: effect of strontium substitution on esthetics, radiopacity and fluoride release. Dental Materials. 2014;30(3):308-13.
101. Curzon ME, Spector PC, Iker HP. An association between strontium in drinking water supplies and low caries prevalence in man. Arch Oral Biol. 1978;23(4):317-21.
102. O'Donnell MD, Fredholm Y, de Rouffignac A, Hill RG. Structural analysis of a series of strontium-substituted apatites. Acta Biomaterialia. 2008;4(5):1455-64.
103. Thuy TT, Nakagaki H, Kato K, Hung PA, Inukai J, Tsuboi S, et al. Effect of strontium in combination with fluoride on enamel remineralization in vitro. Arch Oral Biol. 2008;53(11):1017-22.
104. Massera J, Hupa L. Influence of SrO substitution for CaO on the properties of bioactive glass S53P4. Journal of Materials Science: Materials in Medicine. 2014;25(3):657-68.
105. Martin R, Twyman H, Rees G, Barney E, Moss R, Smith J, et al. An examination of the calcium and strontium site distribution in bioactive glasses through isomorphic neutron diffraction, X-ray diffraction, EXAFS and multinuclear solid state NMR. Journal of Materials Chemistry. 2012;22.
106. Xiang Y, Du J. Effect of strontium substitution on the structure of 45S5 bioglasses. Chemistry of Materials. 2011;23(11):2703-17.

107. Sriranganathan D, Kanwal N, Hing KA, Hill RG. Strontium substituted bioactive glasses for tissue engineered scaffolds: the importance of octacalcium phosphate. J Mater Sci Mater Med. 2016;27(2):39.
108. Brown W, Eidelman N, Tomazic BB. Octacalcium phosphate as precursor in biomineral formation. Advances in dental research. 1988;1:306-13.
109. Sriranganathan D, Chen X, Hing KA, Kanwal N, Hill RG. The effect of the incorporation of fluoride into strontium containing bioactive glasses. Journal of Non-Crystalline Solids. 2017;457:25-30.
110. Wang L, Nancollas GH. Calcium orthophosphates: crystallization and dissolution. Chem Rev. 2008;108(11):4628-69.
111. Featherstone JD, Shields CP, Khademazad B, Oldershaw MD. Acid reactivity of carbonated apatites with strontium and fluoride substitutions. J Dent Res. 1983;62(10):1049-53.
112. O'Donnell MD, Hill RG. Influence of strontium and the importance of glass chemistry and structure when designing bioactive glasses for bone regeneration. Acta Biomaterialia. 2010;6(7):2382-5.
113. Hesaraki S, Gholami M, Vazehrad S, Shahrabi S. The effect of Sr concentration on bioactivity and biocompatibility of sol–gel derived glasses based on CaO–SrO–SiO2–P2O5 quaternary system. Materials Science and Engineering: C. 2010;30(3):383-90.
114. Lao J, Jallot E, Nedelec J-M. Strontium-delivering glasses with enhanced bioactivity: a new biomaterial for antiosteoporotic applications? Chemistry of Materials. 2008;20.
115. Lao J, Jallot E, Nedelec J-M. New strontium-based bioactive glasses: physicochemical reactivity and delivering capability of biologically active dissolution products. Journal of Materials Chemistry. 2009;19.
116. Mousavinasab SM. Effects of filler content on mechanical and optical properties of dental composite resin. 2011.
117. El Zohairy A, Feilzer A. Bonding in prosthodontics with cements. Dental Hard Tissues and Bonding: Springer; 2005. p. 155-73.
118. Oral O, Lassila LV, Kumbuloglu O, Vallittu PK. Bioactive glass particulate filler composite: Effect of coupling of fillers and filler loading on some physical properties. Dental Materials. 2014;30(5):570-7.
119. Nicolae LC, Shelton RM, Cooper PR, Martin RA, Palin WM. The effect of UDMA/TEGDMA mixtures and bioglass incorporation on the mechanical and physical properties of resin and resin-based composite materials. Conference Papers in Science. 2014;2014:5.
120. Par M, Spanovic N, Bjelovucic R, Skenderovic H, Gamulin O, Tarle Z. Curing potential of experimental resin composites with systematically varying amount of bioactive glass: Degree of conversion, light transmittance and depth of cure. Journal of Dentistry. 2018;75:113-20.
121. Par M, Tarle Z, Hickel R, Ilie N. Polymerization kinetics of experimental bioactive composites containing bioactive glass. Journal of Dentistry. 2018;76:83-8.
122. Par M, Tarle Z, Hickel R, Ilie N. Mechanical properties of experimental composites containing bioactive glass after artificial aging in water and ethanol. Clin Oral Investig. 2019;23(6):2733-41.
123. Chang JC, Hurst TL, Hart DA, Estey AW. 4-META use in dentistry: A literature review. The Journal of Prosthetic Dentistry. 2002;87(2):216-24.

124. da Silva EM, de Sá Rodrigues CUF, de Oliveira Matos MP, de Carvalho TR, dos Santos GB, Amaral CM. Experimental etch-and-rinse adhesive systems containing MMP-inhibitors: physicochemical characterization and resin-dentin bonding stability. Journal of dentistry. 2015;43(12):1491-7.
125. Moszner N, Salz U, Zimmermann J. Chemical aspects of self-etching enamel–dentin adhesives: a systematic review. Dental Materials. 2005;21(10):895-910.
126. Takeyama M, Kashibuchi S, Nakabayashi N, Masuhara E. Adhesion of PMMA with bovine enamel or dental alloys. Journal of the Japan Society for Dental Apparatus and Materials. 1978;19(47):179-85.
127. Yasuda N, Sasaki M, Mogi T, Ai M, NAKABAYASHI N. Interface between metal and resin on the finishing line of Co-Cr denture. J Jpn Prosthet Dent. 1978;22:525.
128. Al-eesa NA, Wong FSL, Johal A, Hill RG. Fluoride containing bioactive glass composite for orthodontic adhesives – ion release properties. Dental Materials. 2017;33(11):1324-9.
129. Gupta S, Pradesh M. Dentin bonding agents: an overview. J Adv Med Dent Sci. 2014;2(1):82-4.
130. Perdigao J, Swift E, Walter R. Fundamental concepts of enamel and dentin adhesion. Sturdevant's Art and Science of Operative Dentistry. 2014:114-40.
131. Carvalho R, Chisini L, Ferrúa C, Guiraldo R, Gonini-Junior A, Moura S, et al. The influence of concentration of HEMA on degree of conversion and cytotoxicity of a dental bonding resin. Minerva stomatologica. 2016;65:65-71.
132. Marghalani HY. Effect of filler particles on surface roughness of experimental composite series. Journal of Applied Oral Science. 2010;18(1):59-67.
133. Faqhiri H, Hannula M, Kellomäki M, Calejo MT, Massera J. Effect of melt-derived bioactive glass particles on the properties of chitosan scaffolds. J Funct Biomater. 2019;10(3):38.
134. Agea-Blanco B, Reinsch S, Müller R. Sintering and Foaming of Barium Silicate Glass Powder Compacts. Frontiers in Materials. 2016;3(45).
135. Erik M. Erbe Bl, Bioactive load bearing bone bonding compositions, 1999. Patent Number 5914356.
136. Rusin RP, Cummings KM, Mitra SB, Burgio PA, Tzou T-Z, Arney DSl, Dental compositions with calcium phosphorus releasing glass, 2015. Patent Number 8957126.
137. Yang s-y, Kim S-H, Choi S, Kim K-M. Acid neutralizing ability and shear bond strength using orthodontic adhesives containing three different types of bioactive glass. Materials. 2016;9:125.
138. Yang S-Y, Piao Y-Z, Kim S-M, Lee Y-K, Kim K-N, Kim K-M. Acid neutralizing, mechanical and physical properties of pit and fissure sealants containing melt-derived 45S5 bioactive glass. Dental Materials. 2013;29(12):1228-35.
139. International Standard Organization (2009). Dentistry-polymer-based restorative materials, ISO 4049.
140. Kohda N, Iijima M, Kawaguchi K, Toshima H, Muguruma T, Endo K, et al. Inhibition of enamel demineralization and bond-strength properties of bioactive glass containing 4-META/MMA-TBB-based resin adhesive. Eur J Oral Sci. 2015;123(3):202-7.
141. Korkut E, Torlak E, Altunsoy M. Antimicrobial and mechanical properties of dental resin composite containing bioactive glass. Journal of applied biomaterials & functional materials. 2016;14.

142. Kanwal N, Brauer DS, Earl J, Wilson RM, Karpukhina N, Hill RG. In-vitro apatite formation capacity of a bioactive glass - containing toothpaste. Journal of Dentistry. 2018;68:51-8.
143. Al-Khafaji TJ, Wong F, Fleming PS, Karpukhina N, Hill R. Novel fluoride and strontium-containing bioactive glasses for dental varnishes-design and bioactivity in Tris buffer solution. Journal of Non-Crystalline Solids. 2019;503-504:120-30.
144. Chen X, Chen X, Brauer D, Wilson R, Hill R, Karpukhina N. Bioactivity of sodium free fluoride containing glasses and glass-ceramics. Materials. 2014;7(8):5470-87.
145. Simila HO, Karpukhina N, Hill RG. Bioactivity and fluoride release of strontium and fluoride modified Biodentine. Dental Materials. 2018;34(1):e1-e7.
146. Tiskaya M, Al-eesa NA, Wong FSL, Hill RG. Characterization of the bioactivity of two commercial composites. Dental Materials. 2019;35(12):1757-68.
147. Scientific documentation. Ivoclar Vivadent, 2016:1-58.
148. Dodiya P, Parekh V, Gupta M, Patel N, Shah M. Clinical evaluation of Cention–N and nano hybrid composite resin as a restoration of non-carious cervical lesion. Journal of Dental Specialities. 2019;7:3-5.
149. Activa bioactive: a closer look at bioactive materials. Pulpdent, 2016:1-12.
150. van Dijken JWV, Pallesen U, Benetti A. A randomized controlled evaluation of posterior resin restorations of an altered resin modified glass-ionomer cement with claimed bioactivity. Dent Mater. 2019;35(2):335-43.