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# The use of bioactive glass (BAG) in dental composites: A critical review

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## ARTICLE INFO

### Article history:

Received 5 May 2020

Received in revised form

23 August 2020

Accepted 21 November 2020

Available online xxxx

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### Keywords:

Bioactive glass

Apatite

Ion release

Melt-quench

Restorative composite

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## ABSTRACT

**Objective.** 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  $\text{Ca}^{2+}$ ,  $\text{PO}_4^{3-}$  and  $\text{F}^-$  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.

**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.

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## Contents

1. Introduction .....	00
2. Bioactivity .....	00
3. Methods .....	00

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<https://doi.org/10.1016/j.dental.2020.11.015>

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4.	Bioactive glasses.....	00
5.	Network connectivity model.....	00
6.	Refractive index of bioactive glass fillers .....	00
7.	Effect of ion substitutions in BAG fillers .....	00
7.1.	Fluoride .....	00
7.2.	Magnesium.....	00
7.3.	Zinc.....	00
7.4.	Strontium .....	00
8.	Effect of silanizing the glass fillers.....	00
9.	Bonding the composite material to the tooth.....	00
10.	Effect of particle size of BAG fillers .....	00
11.	Incorporating BAG fillers into resin matrices .....	00
12.	Conclusion.....	00
	Acknowledgments/funding.....	00
	References .....	00

## 1. 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 (Fig. 1) [2].

When a monomer is converted into a polymer, polymerization shrinkage of 1.7–6 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

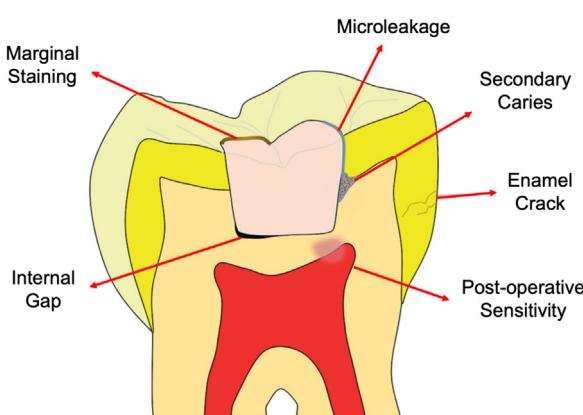
marginal gap providing a marginal seal, prevent acid attack by raising the local pH, reducing the likelihood of failure of the composite. Therefore, bioactive dental composites may increase the longevity and clinical outcomes of restorations [7]. These materials also aim to aid in remineralization of 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.

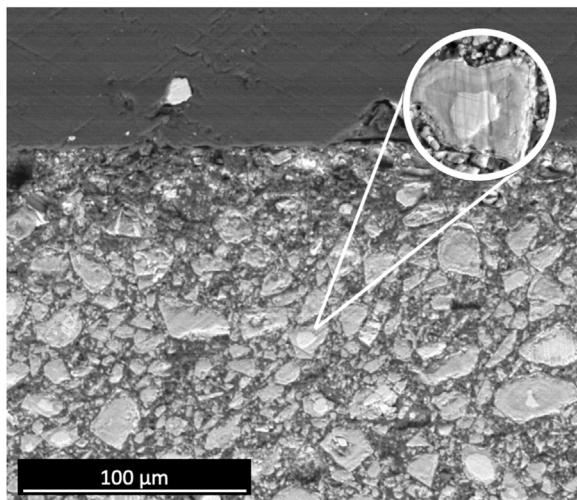
## 2. Bioactivity

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 ( $\text{Ag}^+$ ), tin ( $\text{Sn}^{2+}$ ) and copper ( $\text{Cu}^{2+}$ ), 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  $\text{Ca}^{2+}$  and  $\text{PO}_4^{3-}$ , have a remineralizing capacity and form apatite [14]. However, it is important to note that when they are



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



**Fig. 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].**

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 (Fig. 2) [15]. It is also very difficult to manipulate the refractive indices of crystalline calcium phosphates, which hinders achieving translucency and good final aesthetics.

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.

### 3. 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.

### 4. 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.

Hench explained the mechanism of dissolution and apatite formation (Fig. 3) in many stages [17]. However, stages 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 5). 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.

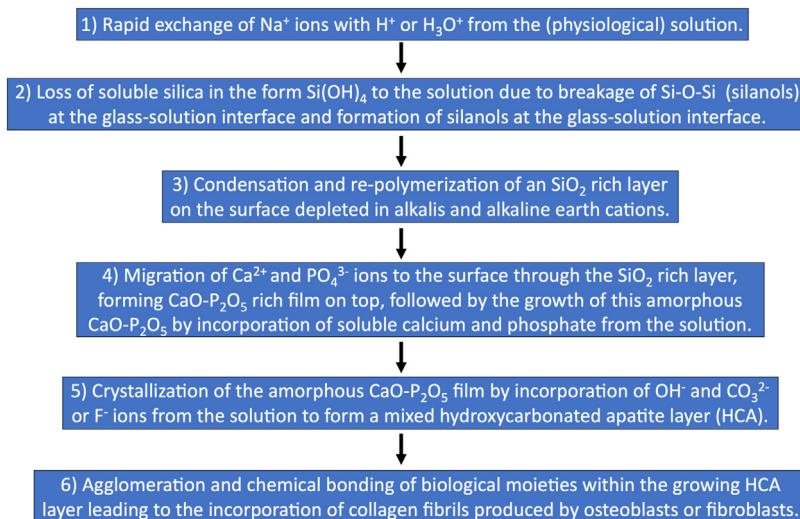
FAP,  $Ca_5(PO_4)_3F$ , is more acid resistant and less degradable than both HCA and HAp as the  $OH^-$  ion in apatite distorts the lattice slightly due to its large ionic radius, whereas the  $F^-$  ion has a smaller ionic radius, and fits perfectly in the hexagonal apatite lattice perfectly, thus 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].

### 5. Network connectivity model

Hill et al. questioned the BAG degradation mechanism in Fig. 3 and developed a network connectivity (NC) model ( $NC_{old}$ ) for predicting the dissolution and apatite forming capability of BAG fillers (Eq. (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

**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 <sub>2</sub>	P <sub>2</sub> O <sub>5</sub>	CaO	Na <sub>2</sub> O	CaF <sub>2</sub>		
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

**Fig. 3 – The mechanism of degradation/dissolution and apatite formation of BAGs by Hench et al. [17].**

the NC of the silicate network. In a pure SiO<sub>2</sub> glass, each silicon is linked via a bridging oxygen (a Si–O–Si) to four other silicons, providing a NC of 4.0 (Q<sup>4</sup>). When network modifying oxides (NMOs) are introduced (such as Na<sup>+</sup> Ca<sup>2+</sup>, Sr<sup>2+</sup> or Mg<sup>2+</sup>), the glass network is disrupted, giving rise to non-bridging oxygens (NBOs). In a calcium metasilicate glass containing equimolar ratios of CaO and SiO<sub>2</sub>, each CaO introduces two NBOs (O<sup>−</sup>–Si–O<sup>−</sup>), breaking up the three-dimensional network. Each silicon becomes linked to two other oxygens and the NC = 2.0 (Q<sup>2</sup> glass). The glass corresponds to a linear silicate chain and may be considered as a silicate polymer of [SiO<sub>3</sub><sup>2−</sup>]<sub>n</sub>. Reducing the CaO content results in the NC increasing beyond 2.0 and the polymeric chains become increasingly cross-linked.

$$NC_{old} = \frac{4[\text{SiO}_2] - 2[\sum \text{NMO}]}{[\text{SiO}_2]} \quad (1)$$

Eq. (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<sub>old</sub> 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<sub>old</sub> 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<sub>4</sub><sup>3−</sup>), was locally charge balanced by Ca<sup>2+</sup> and Na<sup>+</sup> ions and was therefore not part of the silicate network. This lead to the modification of the NC model (NC<sub>new</sub>) in Eq. (2), considering that phosphate is present as orthophosphate (by Eq. (1)) [39]. Note that when NC is discussed from this point on, it refers to NC<sub>new</sub>. Increasing the NMOs at the expense of SiO<sub>2</sub> decreases the NC, thus making the glass more degradable.

$$NC_{new} = \frac{(4[\text{SiO}_2] - 2[\sum \text{NMO}] + 6[\text{P}_2\text{O}_5])}{[\text{SiO}_2]} \quad (2)$$

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

**Table 2 – Appen factors for the different components commonly used in BAG [41,42].**

Compound	Appen factor
SiO <sub>2</sub>	1.46
Al <sub>2</sub> O <sub>3</sub>	1.52
Na <sub>2</sub> O	1.58
ZnO	1.71
MgO	1.61
K <sub>2</sub> O	1.58
CaO	1.73
SrO	1.78
P <sub>2</sub> O <sub>5</sub>	1.31
SrF <sub>2</sub>	1.47
CaF <sub>2</sub>	1.42

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<sub>2</sub>O, 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.

## 6. 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 (Eq. (3)) using Appen factors (Table 2), which are empirically derived factors calculated based on previous measurements of RI.

$$RI = \frac{\sum_{i=1}^n n_{d,i} c_i}{100} \quad (3)$$

Eq. (3): The equation used to calculate the RI, where n<sub>d,i</sub> is the Appen factor (Table 2) for the respective oxide component and C<sub>i</sub> 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<sub>2</sub> 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 Eq. (3) and Table 2 (shown in Table 1).

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<sub>2</sub> 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 ( $\approx$ 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.

## 7. 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<sub>2</sub> 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<sup>-</sup>, Mg<sup>2+</sup>, Zn<sup>2+</sup> and Sr<sup>2+</sup> are common in BAGs, and all contribute to the final properties, such as the NC, RI and opacity, of the dental composite.

### 7.1. Fluoride

Hill et al. studied the structure of a wide range of fluorine containing glasses including fluorosilicate and fluoro-alumino-silicate glasses using <sup>19</sup>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  $\text{CaF}_2$  for  $\text{CaO}$  in the original Hench et al. studies and patent [23].

Substituting  $\text{CaO}$  for  $\text{CaF}_2$  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  $\text{CaF}_2$  to the composition without substituting for  $\text{CaO}$  or  $\text{Na}_2\text{O}$  does not affect the NC. Hill et al. did not substitute  $\text{CaF}_2$  for  $\text{CaO}$ , but instead added  $\text{CaF}_2$  to the composition of the glass, keeping the ratios of all other components fixed in a low  $\text{P}_2\text{O}_5$  content glass [29]. The silicon speciation, analyzed using  $^{29}\text{Si}$  ssMAS-NMR, remained constant, verifying no change in the NC and the fluorine was complexed largely by calcium/sodium and formed  $\text{F}-\text{M}(\text{n})$  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  $\text{F}^-$  release. Lusvardi et al. substituted  $\text{CaF}_2$  for  $\text{Na}_2\text{O}$  in the 45S5 BAG and observed enhanced chemical durability, but observed a reduction in chemical durability when  $\text{CaF}_2$  was substituted for  $\text{CaO}$  [58]. This may be due to water sorption by  $\text{NaF}$ , 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  $\text{CaF}_2$  [59]. The glasses formed FAp when the  $\text{CaF}_2$  content was  $\leq 5$  mol% and released fluoride in addition to  $\text{Ca}^{2+}$  and  $\text{PO}_4^{3-}$  ions. However above 5 mol%, the glasses formed fluorite ( $\text{CaF}_2$ ) 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  $\text{Ca}^{2+}$ ,  $\text{PO}_4^{3-}$  and  $\text{F}^-$  ions together in appropriate ratios to form FAp and avoid the formation of  $\text{CaF}_2$  [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  $\text{CaF}_2$  for  $\text{CaO}$  in S53P4 and observed a delay in apatite formation due to the increase in NC with increasing substitutions of  $\text{CaF}_2$ , emphasizing the effect of NC on bioactivity [62]. S53P4 has a low  $\text{P}_2\text{O}_5$  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  $^{29}\text{Si}$  ssMAS-NMR spectrum and recalculating the NC, to determine if the experimental NC is the same. The NC equation assumes that  $\text{F}-\text{Ca}(\text{n})$  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%  $\text{CaF}_2$  formed FAp in under six hours. Lynch et al. [63] showed a similar behavior in multicomponent glasses containing strontium. The optimum  $\text{CaF}_2$  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  $\text{CaF}_2$  content (3 mol%) compared to the 9 mol%  $\text{CaF}_2$  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 De 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.

## 7.2. Magnesium

Watts et al. investigated the substitution of  $\text{CaO}$  by  $\text{MgO}$  on the BAG structure and observed that the  $T_g$  decreased when the  $\text{MgO}$  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  $\text{MgO}$  contributed to the silica network, and 86% acted as a network modifier.

Souza et al. substituted  $\text{MgO}$  for  $\text{CaO}$  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  $\text{MgO}$  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  $\text{MgO}$  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  $\text{MgO}$  could be a solution.

Araujo et al. studied the bioactivity of  $\text{MgO}$ -containing BAGs with low  $\text{Ca}/\text{P}$  ratio and reported that BAGs with a higher  $\text{MgO}$  content formed apatite slower than BAGs with a lower  $\text{MgO}$  content [71]. This suggests that high contents of  $\text{MgO}$  can inhibit apatite layer formation, thus bioactivity. Jallot et al. investigated the role of  $\text{Mg}^{2+}$  during spontaneous formation of a calcium phosphate layer and observed that *in vivo*,  $\text{Mg}^{2+}$  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  $\text{Mg}^{2+}$  stabilizes the intermediate amorphous calcium phosphate, delaying apatite formation especially at high concentrations [72–76].

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

### 7.3. Zinc

Incorporating  $\leq 0.4$  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<sub>2</sub>O<sub>5</sub> 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<sub>2</sub>O<sub>3</sub> 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<sup>-1</sup> and 600 cm<sup>-1</sup>, 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 *Pseudomonas 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 forma-

tion, 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 Zn<sup>2+</sup> will be released in an acidic environment that is favored by bacterial.

### 7.4. 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 Group II of the periodic table and exhibits complete solid substitution for calcium in allapatites [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<sup>2+</sup> and F<sup>-</sup>, almost all of the available Sr<sup>2+</sup> and F<sup>-</sup> 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<sup>2+</sup> and F<sup>-</sup> 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<sup>2+</sup> 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<sub>2</sub>O<sub>5</sub>–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.  $^{29}\text{Si}$  ssMAS-NMR and FTIR spectra have shown very little change in the glass network, and no change in the  $^{31}\text{P}$  ssMAS-NMR spectrum, regardless of strontium substitution. FTIR showed that with a higher content of SrO, there were more intense carbonate signals, suggesting incorporating  $\text{Sr}^{2+}$  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  $\text{Ca}^{2+}$ , 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.

## 8. 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 (Fig. 4) [117]. The most commonly used silanizing agent is  $\gamma$ -methacryloxypropyl trimethoxysilane ( $\gamma$ -MPS).

Oral et al. investigated the effect of silanization and filler loading on physical properties [118] and reported that silanizing the BAG fillers with  $\gamma$ -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.

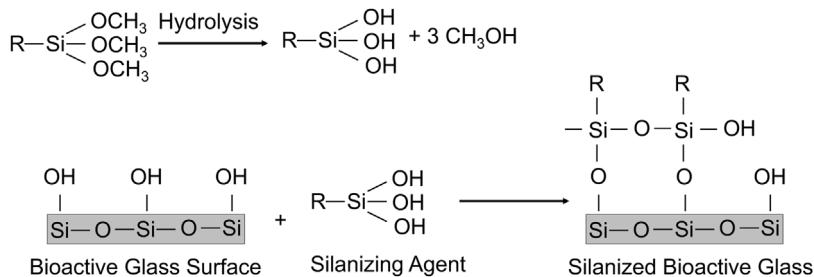
Studies by Par et al. have reported that adding 45S5 as a BAG filler to a composite material still presented significant curing, and that non-silanized BAG fillers can diminish the depth of cure [120–122]. Water present on the non-silanized glass surface may inhibit the polymerization process as well 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.

## 9. Bonding the composite material to the tooth

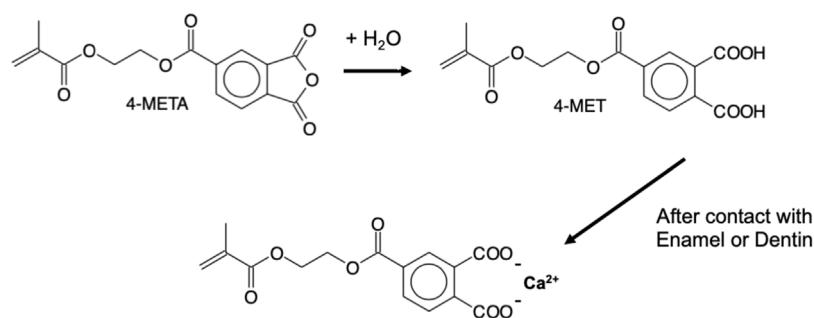
4-Methacryloyloxyethyl trimellitate anhydride (4-META) is used to improve the adhesion of the material to the dentin, reducing the need for a bonding agent [123]. It is added to the composition of the resin, so that an additional bonding agent is not required. 4-META contains both hydrophobic and hydrophilic 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  $\text{Ca}^{2+}$  in dentin or enamel to provide a chemical bond (Fig. 5) [124,125].

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 tech-



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



**Fig. 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].**

nique 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].

## 10. 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  $\mu\text{m}$ ) gives rise to problems such as the large surface area increasing the degradation rate of the BAG [133] as well as  $\text{CO}_2$  and  $\text{H}_2\text{O}$  pick up from the atmosphere [134]. On the other hand, using a larger particle size (i.e., above 100  $\mu\text{m}$ ) 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 5–45  $\mu\text{m}$  can

ensure that there is degradation of the BAG fillers and apatite is formed within 28 days.

## 11. 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 ( $\text{Na}_2\text{Ca}_2\text{Si}_3\text{O}_9$ ), 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  $<25 \mu\text{m}$  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 min, 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 h 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 h 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 h 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 h of immersion in distilled water and decreased significantly with addition of 30 wt% BAG. Antibacterial activity against *Streptococcus 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 alkalinizing 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 (13.6–25.5 mol%) crystallized to form CaF<sub>2</sub>, with FAp as a minor phase [144]. The fluoride was present as either SrF<sub>2</sub> or CaF<sub>2</sub>. Glasses containing >4.5 mol% SrF<sub>2</sub> 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<sup>-</sup> 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, <sup>31</sup>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 <sup>31</sup>P ssMAS-NMR, as they all show inconsistent time points: 14 days, one day, and three hours respectively. The <sup>19</sup>F and <sup>31</sup>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 <sup>19</sup>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 Biobentine®.

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<sup>2+</sup> and F<sup>-</sup> 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 <sup>31</sup>P and <sup>19</sup>F ssNMR 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<sub>2</sub> may be forming instead of apatite and there was no sufficient Ca<sup>2+</sup>, PO<sub>4</sub><sup>3-</sup> or F<sup>-</sup> ion release. The clinical trial on Activa® was also abandoned early because of a high incidence of secondary caries [150].

## 12. Conclusion

BAGs are promising additions to restorative dentistry as they have the capacity to raise the local pH, release beneficial ions (such as Ca<sup>2+</sup>, PO<sub>4</sub><sup>3-</sup> and F<sup>-</sup>) 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.

## Acknowledgments/funding

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

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