

**DEVELOPMENT AND CHARACTERIZATION
OF MISWAK REINFORCED BIOACTIVE GLASS
COMPOSITE FOR DENTAL APPLICATION**

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**DEVELOPMENT AND CHARACTERIZATION OF
MISWAK REINFORCED BIOACTIVE GLASS
COMPOSITE FOR DENTAL APPLICATION**

by

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LIST OF ABBREVIATIONS

Ag-MBG	Ag-loaded mesoporous bioactive glass
Ag-NPs	Silver nanoparticles
BG	Bioactive glass
BITC	Bactericidal benzyl isothiocyanate
BJIs	Bone joint infections
BO	Bridging oxygen
CPP-ACP	Casein phosphopeptide-amorphous calcium phosphate
Cu-MBG	Cu-doped mesoporous glass
DI	Dental implants
DTG	Derivative thermogravimetric analysis
ECM	Extracellular matrix
F-BG	Fluoride-doped bioactive glasses
EDX	Energy dispersive x-ray spectroscopy
FESEM	Field emission scanning electron microscope
FTIR	Fourier transform infrared spectroscopy
GIC	Glass ionomer cement
GP	Gutta percha
HA	Hydroxyapatite
HGF	Human gingival fibroblast
ICP-MS	Inductively coupled plasma mass spectrometry.
MRSA	Methicillin-resistant Staphylococcus aureus
MTA	Mineral trioxide aggregate
NBO	Non-bridging oxygen
M-BG	Miswak-bioactive glass

Nc	Network connectivity
PBS	Phosphate buffer solution
PEEK	Polyetheretherketone
PSA	Particle size analysis
RCT	Randomised controlled trial
rpm	Revolutions per minute
SBF	Simulated body fluid
<i>S. persica</i>	<i>Salvadora persica</i>
TGA	Thermogravimetric analysis
TPE	Thermoplastic elastomer
UPW	Ultra-pure water
w/v	Weight per volume
WHO	World health organization
XRD	X-ray diffraction
XRF	X-ray fluorescence
μ TBS	Micro tensile bond strength
45S5	45SiO ₂ -24.5CaO-24.5Na ₂ O-6P ₂ O ₅ (wt. %)
54S4P	54SiO ₂ -22CaO-20Na ₂ O-4P ₂ O ₅ (wt. %)
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M50BG45	50miswak-50BG45S5 (wt. %)
M75BG45	75miswak-75BG45S5 (wt. %)
M25BG54	25miswak-75BG54S4P (wt. %)
M50BG54	50miswak-50BG54S4P (wt. %)
M75BG54	75miswak-75BG54S4P (wt. %)

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**PEMBANGUNAN DAN PENCIRIAN KOMPOSIT KACA BIOAKTIF
DIPERKUAT MISWAK UNTUK APLIKASI PERGIGIAN**

ABSTRAK

Kayu miswak tradisional (*Salvadora persica*), walaupun terbukti manfaat kesihatan oral dan kelebihannya yang tidak memerlukan ubat gigi, ia masih asing kepada orang ramai dan sering dianggap sukar untuk digunakan kerana bentuknya yang lurus dan tegar. Ketidakbiasaan dan ketidakselesaan yang dirasakan ini menghalang penggunaannya yang meluas sebagai alternatif yang berdaya maju kepada berus gigi moden. Terdapat keperluan untuk membangunkan versi moden miswak yang mengekalkan faedah semula jadi dan menjadi lebih mesra pengguna dan biasa kepada orang ramai. BG telah mendapat perhatian penting dalam aplikasi pergigian kerana keupayaannya yang luar biasa untuk menggalakkan bioaktiviti, memudahkan pemineralan semula dentin, dan mengikat secara berkesan dengan tisu pergigian, disebabkan oleh komposisi kimianya yang menyerupai tisu tulang dan gigi. Oleh itu, kajian ini bertujuan untuk membangunkan dan mencirikan komposit miswak-kaca bioaktif (M-BG) novel. Komposit M-BG telah dihasilkan dengan mengintegrasikan dua komposisi BG (45S5BG dan 54S4PBG) dengan nisbah berat miswak yang berbeza (25%, 50%, 75%) dan menjalani pencirian struktur, kimia, termal dan permukaan morfologi menggunakan difraksi sinar X (XRD), spektroskopi inframerah transformasi Fourier (FTIR), spektroskopi pendarfluor sinar X (XRF), analisis termogravimetrik- termogravimetri derivatif (TGA-DTG), mikroskopi elektron pengimbasan (SEM), dan spektroskopi X-ray penyebaran tenaga (EDX). Bioaktiviti in-vitro dinilai berdasarkan rendaman komposit dalam larutan tubuh tiruan (SBF) dan air ultratulen (UPW) selama 28 hari, dengan analisis lanjutan termasuk XRD, FTIR,

SEM, EDX, pengukuran pH dan spektrometri jisim plasma berganding induktif (ICP-MS). Analisis XRD mendedahkan kehadiran bersama fasa amorfus dan kristal dalam komposit, mewakili komponen fasa amorfus BG dan fasa kristal miswak. Analisis FTIR mengesahkan kehadiran kumpulan bioaktif Si-O-Si manakala analisis SEM dan EDX menunjukkan taburan homogen zarah BG dan miswak pada permukaan komposit. Selepas rendaman, pemendapan hidroksiapatit (HA) dapat diperhatikan, dengan ciri struktur seperti kembang kol, dan peningkatan ion kalsium dan fosfat, membuktikan sifat mineralisasi yang dipertingkatkan bagi biokomposit M-BG dengan peningkatan masa. Kajian ini menyerlahkan komposit M-BG sebagai biomaterial harapan untuk aplikasi pergigian, terutamanya dalam penjanaan semula tisu pergigian dan salutan implan. Keupayaannya untuk menggalakkan pembentukan HA, bersama-sama dengan biokompatibiliti dan sifat antibakterianya, menggariskan potensinya untuk memajukan terapi pergigian pemulihan dan regeneratif. Penemuan ini menyokong penyiasatan lanjut ke dalam komposit inovatif ini untuk aplikasi klinikal.

DEVELOPMENT AND CHARACTERIZATION OF MISWAK REINFORCED BIOACTIVE GLASS COMPOSITE FOR DENTAL APPLICATION

ABSTRACT

The traditional miswak stick (*Salvadora persica*), despite its proven oral health benefits and the advantage of not requiring toothpaste, remains unfamiliar to the public and is often perceived as difficult to use due to its straight and rigid form. This unfamiliarity and perceived inconvenience hinder its widespread adoption as a viable alternative to modern toothbrushes. There is a need to develop a modernized version of the miswak that retains its natural benefits while being more user-friendly and familiar to the public. BG has gained significant attention in dental applications due to its exceptional ability to promote bioactivity, facilitate dentin remineralisation, and bind effectively with dental tissues, attributed to its chemical composition resembling that of bone and dental tissues. Hence, this study aims to develop and characterise a novel miswak-bioactive glass (M-BG) composite. The M-BG composite was developed by incorporating two BG compositions (45S5BG and 54S4PBG) with varying weight ratios of miswak (25%, 50%, 75%) and subjected to structural, chemical, thermal, and morphological characterisations using X-Ray Diffraction (XRD), Fourier Transform Infrared Spectroscopy (FTIR), X-Ray Fluorescence (XRF), Thermogravimetric Analysis-Derivative Thermogravimetry (TGA-DTG), Scanning Electron Microscopy (SEM), and Energy-Dispersive X-Ray Spectroscopy (EDX). In-vitro bioactivity was evaluated by immersing the composite in simulated body fluid (SBF) and ultrapure water (UPW) for 28 days, with subsequent analyses including XRD, FTIR, SEM, EDX, pH measurements, and Inductively Coupled Plasma Mass Spectrometry (ICP-MS). The XRD results indicated the coexistence of amorphous and

crystalline phases within the composite, derived from the amorphous nature of BG and the crystalline structure of miswak. FTIR analysis confirmed the presence of bioactive Si-O-Si groups, while SEM and EDX demonstrated a homogeneous distribution of BG and miswak particles across the composite surface. Following immersion, hydroxyapatite (HA) deposition was observed, characterised by cauliflower-like structures and an increased concentration of calcium and phosphate ions, evidencing enhanced mineralization properties of the M-BG bio-composite over time. This study highlights the M-BG composite as a promising biomaterial for dental applications, particularly in dental tissue regeneration and implant coatings. Its ability to promote HA formation, along with its biocompatibility and antibacterial properties, underscores its potential to advance restorative and regenerative dental therapeutics. The findings support further investigation into this innovative composite for clinical applications.

CHAPTER 1

INTRODUCTION

1.1 Background of the study

A composite material is composed of two distinct stages, typically involving a combination of components with different structures and properties (Radzi et al., 2020). Dental composites represent a significant advancement in biomaterials, offering an effective alternative to biological tissue in dental restoration procedures. Initially introduced in the late 1950s, dental composite resins have become a staple in modern dentistry, serving various applications such as liners, sealants, inlays, onlays, veneers, core build-up, endodontic posts, and sealers (German, 2022). In comparison to traditional materials like amalgam, composite resins offer distinct advantages including superior aesthetic properties, enhanced bonding to tooth surfaces facilitated by adhesive systems, and the preservation of remaining tooth structure. Ongoing research endeavours are primarily focused on optimising dental composites, with particular attention to filler content. Notably, recent trends underscore a shift towards exploring natural bioresources for dental applications, leading to the emergence of eco-friendly composite resins. Incorporating natural products into composite resins is gaining traction among researchers due to its potential to reduce costs, toxicity, and environmental impact while promoting sustainability and offering comparable mechanical performance.

Bioactive materials, a subset of biomaterials, induce a biological response by forming bonds between them and the tissues. These materials are classified as Class A and Class B, with Class A materials, such as osteopductive materials, stimulating both intracellular and extracellular responses (Jones, 2015). Bioactive glass (BG) is a

Class A biomaterial renowned for its ability to bond with both hard and soft tissues. The pioneering work of Professor Larry Hench and colleagues in 1969 led to the development of 45S5 Bioglass®, which consists of silicon dioxide (SiO₂), calcium oxide (CaO), sodium oxide (Na₂O), and phosphorus pentoxide (P₂O₅) in specific proportions (Hench, 2006). This discovery marked a significant milestone in medical material production, as BG compositions were found to form solid interfacial bonds with bone, aided by the formation of a hydroxyapatite (HA) layer on the material's surface in biological environments (Hench, 2006; Hench & Jones, 2015; Jones, 2015).

BG's unique properties, including its osteoconductive and osteostimulative capabilities through the release of inorganic ions, make it an attractive material for various medical and dental applications (Hench & Jones, 2015; Hoppe & Boccaccini, 2015). In dentistry, BG has been utilised for remineralising dentin, disinfecting root canals, restorative dental procedures, alveolar ridge augmentation, and treating periodontal issues and dentin hypersensitivity. Moreover, BG is incorporated into dental composites to enhance radiopacity, bioactivity, antibacterial properties, and mechanical strength.

Recent studies have expanded the scope of BG applications in dentistry, including its use as a desensitising agent, promoting dentine mineralisation, combating bacterial infections, and serving as inorganic fillers. Furthermore, research has investigated BG's biocompatibility, its effects on cell viability, differentiation, proliferation, and its potential osteoinductive properties, highlighting its promising role in dental therapies and regenerative medicine (Jafari et al., 2022).

Miswak is an ancient chewing stick derived from the Arak Tree (*Salvadora Persica L (S. Persica)*), also known by various names such as Miswak, Meswak, Miswaki, Siwaki, and Sewak, belonging to the family Salvadoraceae. This shrub has been utilised for centuries as a traditional chewing stick and is native to regions spanning Asia, the Middle East, and Africa (Sher et al., 2011).

S. Persica holds significant cultural and historical importance, particularly among Muslim populations. This has prompted researchers to conduct phytochemical and biological investigations into extracts and isolated compounds from *S. Persica*, aiming to uncover potential therapeutic agents from indigenous plants. Various phytoconstituents present in *S. Persica* have shown promising results in maintaining oral hygiene. Its composition includes flavonoids, glycosides, benzyl isothiocyanate, resins, mineral salts, silica, terpenes, and volatile oils (Mohammed et al., 2014; Ahmad & Rajagopal, 2014; Abdel-Kader et al., 2014; Albabtain et al., 2017). These constituents have been linked to numerous therapeutic benefits such as antibacterial, antifungal (Al-Ayed et al., 2016; Alili et al., 2014), antiplaque (Amoian et al., 2010; Abdulbaqi et al., 2016), and anti-cariogenic properties (Khunkar et al., 2021), targeting oral pathogens effectively. In modern medicine, miswak is used as dental care instead of chewing sticks. Commercially available options such as miswak toothpaste, mouthwashes, irrigates, and chewing gums incorporate this ingredient to enhance oral hygiene and overall healthcare management.

Resin-based composites have served as prominent materials for dental restorations over the course of several decades. While numerous studies have concentrated on enhancing the strength of acrylic resin to mitigate breakages, achieved through reinforcement with fibres such as glass, carbon/graphite, calcium oxide nanoparticles, and ultrahigh-modulus polyethylene fibres, limited research has delved

into the realm of antibacterial properties within dental resin-based materials. These materials hold potential in effectively curtailing the formation of oral biofilms and preventing bacterial microleakage. BG has undergone extensive exploration due to its remarkable bioactivity, biocompatibility, and bonding qualities with bone and dental tissues. Similarly, miswak has exhibited desirable characteristics, including antiplaque, antibacterial, anticariogenic, and non-toxic properties. Hence, there is theoretical merit in exploring the incorporation of these two beneficial materials into the manufacturing of oral or dental care products, with the aim of harnessing their inherent advantages for human benefit. Therefore, this study aimed to develop a composite material miswak-BG (M-BG) comprising miswak and BG, investigate its potential applications in dental care products, with the ultimate goal of improving oral health and well-being.

1.2 Problem Statement

Dental composites have traditionally been developed for restorative applications, with extensive research focusing on enhancing their mechanical properties. However, the integration of bioactive and antibacterial functionalities in dental materials remains relatively underexplored, despite their critical role in preventing bacterial biofilm formation, microleakage, and dental diseases such as caries and periodontitis (Argueta-Figueroa et al., 2014; Wu et al., 2015).

Recent advances in biomaterials have demonstrated the potential of incorporating antimicrobial agents into dental composites, yet natural plant-derived components with inherent antibacterial and remineralisation properties have received limited attention.

Salvadora persica (miswak) has long been recognized for its oral health benefits due to its rich bioactive composition, including flavonoids, tannins, silica, and calcium salts, which contribute to antimicrobial activity, anti-inflammatory effects, and enamel remineralisation (Ahmad, 2012; Ibrahim et al., 2015). Despite its advantages, the traditional miswak stick is not widely adopted due to its rigid form and unfamiliar usage. A more modern and user-friendly application of miswak could enhance its accessibility while preserving its natural benefits.

Similarly, BG particularly 45S5BG and the newer 54S4PBG, has gained significant attention in dental applications due to its ability to promote bioactivity and facilitate dentin remineralisation (Jones, 2015). However, BG lacks intrinsic antibacterial and anti-inflammatory properties, which are crucial for preventing bacterial colonization in oral environments. The combination of miswak and BG presents an opportunity to develop a novel bio-composite with enhanced antibacterial and remineralisation capabilities.

This study aims to develop and characterise an M-BG composite integrating miswak with 45S5BG and 54S4PBG, specifically for application in toothbrush bristles. By bridging traditional oral hygiene practices with contemporary dental materials, this composite seeks to create an innovative, biodegradable alternative to conventional toothbrush bristles, eliminating the need for toothpaste while enhancing dental hygiene efficacy. The development of this sustainable bio-composite could revolutionize oral care by offering a practical and eco-friendly solution to modern dental health challenges.

1.3 Objective of the Study

1.3.1 General Objective

This study aimed to develop and characterise novel M-BG bio-composite for potential application in toothbrush bristles.

1.3.2 Specific Research Objectives (RO)

RO1. To synthesise and characterise 45S5BG and 54S4PBG powder particles.

RO2. To determine the components in miswak extract by using Gas chromatography-mass Spectrometry (GCMS) analysis.

RO3. To synthesise and characterise miswak-BG (M-BG) composite.

RO4. To investigate the bioactivity of miswak-BG composite by immersing the miswak-BG pellet into simulated body fluid (SBF) solution.

1.4 Research Questions (RQ)

The research questions of the study are listed below:

RQ1. What are the structural, chemical and morphological characteristics of synthesised 45S5 and 54S4P BG powders ?

RQ2. What are the components of miswak?

RQ3. What are the characteristics of M-BG composite?

RQ4. Does the M-BG composite exhibit bioactivity when immersed in SBF, and what ions are released during the immersion process?

1.5 Research Hypothesis

H_A: It is possible to develop M-BG composite and the M-BG composite suitable for dental care application.

H_O: It is not possible to develop M-BG composite and the M-BG composite is not a suitable for dental care application.

1.6 Significance of the Study

BG and miswak both exhibit promising individual properties that have gained significant attention in the field of dentistry. However, the synergistic potential of combining these two materials in a composite form remains largely unexplored. Therefore, this study endeavours to capitalise on the complementary benefits of miswak and BG to develop a novel bioactive dental composite material. The principal objective is to augment the bioactivity, antibacterial effectiveness, anticariogenic characteristics, anti-inflammatory properties, enamel remineralisation capacity, and mechanical strength of the dental composite. This enhancement aims to broaden the potential applications of the composite in diverse dental care products, with the overarching aim of fostering enhanced oral health and overall well-being.

Furthermore, it's noteworthy to mention that this study on the miswak-BG composite is part of a broader project focused on fabricating a novel toothbrush bristle composed of miswak-BG composite integrated with polymer. This endeavour aimed to transform dental hygiene practices by introducing a biodegradable product that reduces the need for additional toothpaste, enhances enamel remineralisation, and promotes overall oral health. By diminishing the reliance on additional toothpaste and promoting biodegradability, this initiative contributes to minimising environmental

waste and reducing carbon emissions, aligning with the sustainable development goal of responsible consumption and production.

CHAPTER 2

LITERATURE REVIEW

2.1 Bioactive Materials

Biomaterials are fundamentally used to replace damaged or diseased tissues (Maçon et al., 2017). An important characteristic of biomaterials is their ability to form bonds with host tissues, which in turn produces specific biological reactions at the interface between the material and the tissue (Polymeris et al., 2017). Currently, considerable research is being conducted on the commercialisation and utilisation of biomaterials, especially in the area of biomedical applications, with widespread utilisation observed in dental and medical fields.

Bioceramics like hydroxyapatite (HA), bioactive glass (BG), and BG composites hybrid materials combining BG with polymers, ceramics, or other components—are bioactive materials that closely resemble the mineral composition of natural bone, enabling them to bond with bone and stimulate biological responses such as hydroxyapatite layer formation. In addition, the materials are divided into two classes, A and B (Cao & Hench, 1996). Materials in class A, called osteoprotective materials, elicit both intracellular and extracellular responses. In contrast, Class B biomaterials, called osteoconductive materials, stimulate only extracellular responses. A BG is classified as a Class A biomaterial because it can form bonds with both soft and hard tissues (Cao & Hench 1996).

2.2 Bioactive Glass

BG is classified among Class A bioactive materials due to its ability to promote osteoconductive and osteoinductive properties. With its compatibility with the human

body and ability to stimulate tissue regeneration, BG has been widely utilised as implant devices for repairing and replacing damaged bones (Boccaccini et al., 2017). Notably, BG primarily consists of silicate-based materials that release healing ions, such as calcium, phosphate, silicon, and sodium, into bodily fluids, aiding in the healing process; what sets BG apart from other synthetic bone grafting materials like HA and calcium sulfate are its unique anti-infective and angiogenic properties (Boccaccini et al., 2017).

2.2.1 Development and Discovery of Bioactive Glass

The initial development of BG, specifically the 45S5 Bioglass[®], was undertaken by Professor Hench in 1969. Subsequently, his research team at Imperial College London, alongside scientists worldwide, have continued to the development of BG (Sawant, 2020). Professor Hench's pioneering work was grounded in the hypothesis, that the body would reject metallic or polymeric material unless it could form a coating of the mineral HA found in bone. The development began with submission of a proposal hypothesis to the United States Army Medical Research and Development command in 1968. Following approval and funding for a year, Hench and his colleagues initiate their investigations, leading to the discovery of the first composition of 45S5BG, which was subsequently trademarked as "Bioglass[®]" by the University of Florida (Hench, 2006). 45S5BG is composed of 46.1% SiO₂, 26.9% CaO, 24.4% Na₂O, and 2.5% P₂O₅ in mole percentages (mol.%).

The first batch of BG was synthesised via melt-derived method and implanted into the femoral bone of rats for a duration of six weeks. The promising results indicated firm bonding of the ceramic implants with the bone, contrasting with the control substance, which easily slid off the bone. This breakthrough marked the first

in vitro experiment demonstrating the development of HA when exposed to a biological environment which was later validated in an in vivo study by Dr. Greenlee, who reported similar findings of HA formation and strong bonding with bone tissue (Hench, 2006).

In subsequent studies, in 1986, a scientist in Amsterdam, Netherlands, implanted BG cubes into the tibias of guinea pigs. After 8 to 16 weeks post-implantation, the tibias were harvested and subjected to shear strength testing (Vogel et al., 1986). The analysis revealed a shear strength of 5 N/mm², with electron microscopy confirming tight bonding, bone cell presence, and blood vessel development within the implant area, indicative of biocompatibility between the bone and implants (Vogel et al., 1986). This marked the initial discovery of BG, capable of forming a solid link with living bone tissue, (Baino, 2018).

2.2.2 Types of Bioactive Glass

BG exhibit diverse compositions, as indicated by Abbasi et al. (2015). They are categorised based on their constituents: silicate-based glass (SiO₂), phosphate-based glass (P₂O₅), and borate-based glass (B₂O₃) (Tabatabaei et al., 2020). Despite decades of extensive research, only a select few glass compositions have garnered approval for clinical use. Notably, the FDA has sanctioned clinical trials involving 45S5 and S53P4 BG. The composition of S53P4 glass closely resembles that of 45S5, comprising four core oxides: SiO₂, Na₂O, CaO, and P₂O₅. However, a distinguishing factor between S53P4 and 45S5 BG lies in their specific oxide ratios; S53P4 consists of 53SiO₂, 20CaO, 23Na₂O, and 4P₂O₅ (wt.%) (Fagerlund et al., 2012).

In recent years, numerous studies have endeavoured to develop novel glass compositions rooted in silicate glass networks to enhanced properties. For instance, substituting strontium within BG has been shown to increase osteoblast proliferation in high-density glass, that sintered without crystallisation (Gentleman et al., 2010). Moreover, copper has demonstrated superior efficacy in stimulating angiogenesis compared to zinc, owing to its release of bone-stimulating ions (Zhao et al., 2015), while zinc enhances bioactivity by promoting bone formation (Goh et al., 2013). Furthermore, it has been proposed that the degradation rate of BG could be augmented by modifying the composition of 45S5BG, potentially by replacing or eliminating silicon dioxide, which contributes to the formation of borosilicate BG (Rahaman, 2007).

Glass materials are classified into three main types, Type I, Type II, Type III, Type IV and Type V based on their surface reactions and interactions in biological environments (Hench, 1988; Ylänen, 2017). Type I glasses exhibit minimal surface reactivity, forming a stable hydrous layer that renders them biologically inert. In biological environments, they develop non-adherent fibrous capsules, which limit their utility in applications requiring bioactivity. Type II glasses, exemplified by commercial soda lime glass, undergo surface leaching in solutions with a pH below nine, leading to the formation of a protective layer. However, like Type I glasses, their reactivity is insufficient to induce bioactivity, and they also tend to become biologically inert due to fibrous capsule formation. In contrast, Type III first described by Prof. Hench, are unique for their ability to form a protective bioactive layer when exposed to water or bodily fluids (Hench, 1988). This layer, composed of silica and calcium phosphate, strongly adheres to tissue and promotes bonding with bone. While in neutral solutions, high-silica Type III glass may develop a thin hydrous layer similar to Type I reactions,

they retain their bioactive properties, enabling them to stimulate bone regeneration and integrate effectively with biological tissues. Unlike the biologically inert behaviour of Type I and Type II glasses, Type III glasses stand out for their exceptional bioactivity, making them highly suitable for advanced biomedical applications. Resorbable glass compositions, which exhibit type IV and V surface reactions, typically dissipate within one to three weeks after they have been inserted into living organisms. Type IV glass exhibits a thick silica-rich layer lacking protective properties. The glass gradually dissolves over time if the depolymerised silica-rich layer is not sufficient to shield the surface from further reaction. BG surfaces may be subject to type V reactions if they encounter solutions with a pH greater than nine to ten (Hench, 1988; Ylänen, 2017).

The distinctive characteristics of BG render it suitable for a multitude of biological applications. The bioactivity of glass is contingent upon its chemical composition. BG, with its specific ratio of oxides, falls within the optimal range for promoting bone bonding. Figure 2.1 depicts the dissolution rate of glass and delineates the compositions that exhibit bioactive properties. Since the advent of BG, numerous other glass formulations have been developed, aligning with the criteria outlined in Figure 2.1. Each material exhibits distinct properties, encompassing degradation kinetics and the capacity to fabricate scaffolds with varying porosity and mechanical attributes (Fu et al., 2011).

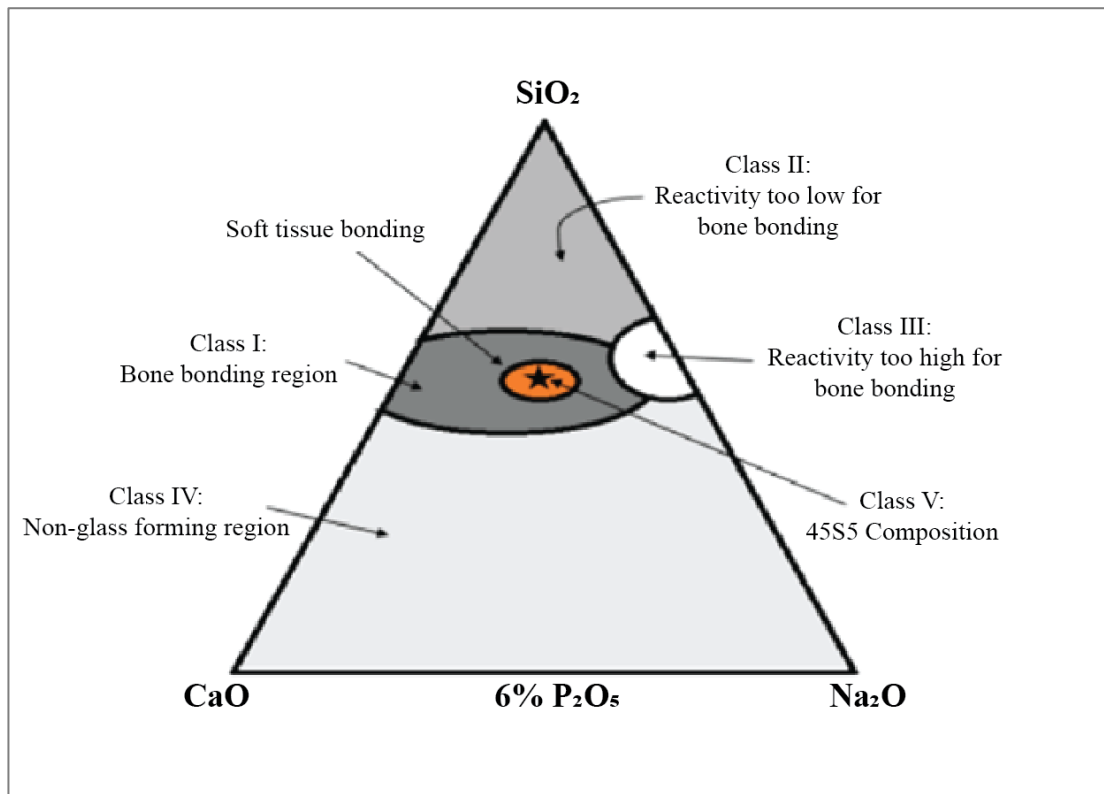


Figure 2.1 Schematic composition map showing the degree of bioactivity in different composition. (Adapted from Hench, 2006).

2.2.3 The Structure of Bioactive Glass

Glass, inherently amorphous, is characterised by its glass transition temperature and lack of long-range atomic order (Shelby, 2020). Typically, the atoms constituting glass are categorised based on their roles within the structure, primarily as network formers or network modifiers. Network formers comprise the oxide components forming the glass networks, such as silica, borate, and phosphate. These materials can create glass independently without additional components. Meanwhile, network modifiers, predominantly calcium, sodium, and strontium oxides, are incorporated into the network, altering its structure through the addition of supplementary oxides. By breaking oxygen bonds with cations, these modifiers can integrate into the network (Shelby, 2020). This process involves a network modifier breaking bridging oxygen atoms, resulting in the formation of two non-bridging

oxygen atoms. The non-bridging oxygen atoms acquire a negative charge, with the oxide cation typically dispersed randomly to balance the charge (Zarzycki, 1991). This mechanism is depicted in Figure 2.2.

Several oxides exhibit intermediate behaviour, acting either as network formers or network modifiers based on their concentration or the presence of other oxides within the glass structure. Common examples include cobalt oxide and magnesium oxide (Zarzycki, 1991). The Q^n structure of a glass refers to the number of bridging oxygens surrounding the cations interconnected by the network. For instance, in a Q^3 structure, one non-bridging oxygen surrounds the network-forming cation, along with three bridging oxygens. Network connectivity (N_c) is utilised to identify glasses and predict their probable Q^n structures, offering insights into properties such as glass transition temperature, surface reactivity, and solubility (Hill, 1996).

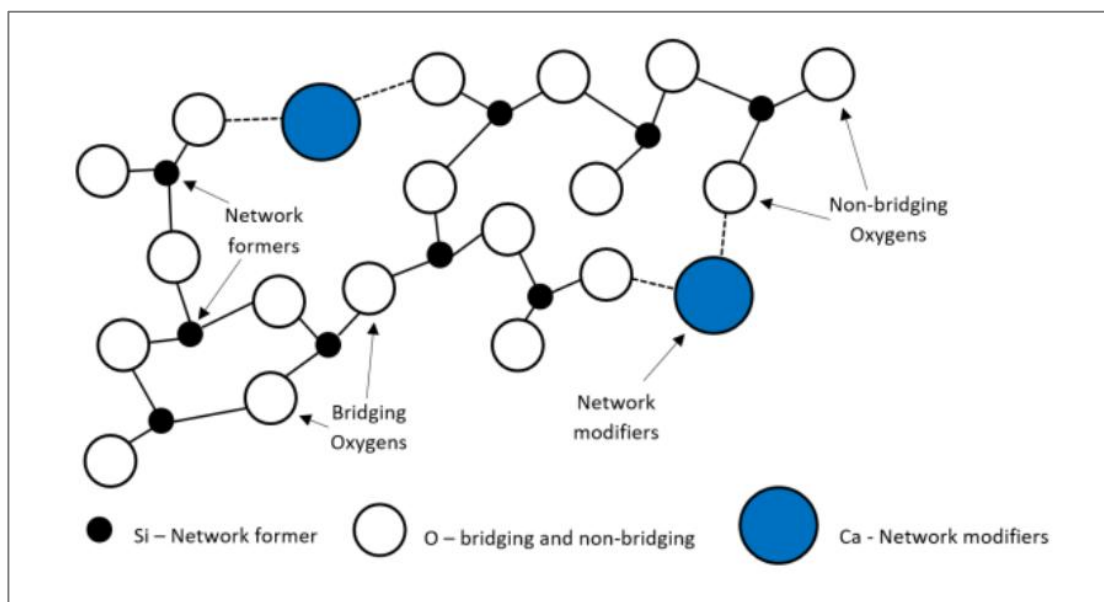


Figure 2.2 Schematic representation of the structure of glass. (Adapted from Shelby, 2020).

2.2.4 Sol-Gel and Melt-Derived Route Bioactive Glass

In the early stages of BG ceramics and glass-ceramics development, the melt-derived route was predominantly employed for synthesis. This process involves melting phases at high temperatures, followed by casting them as bulk implants or quenching them into powders. In contrast, the sol-gel process operates at lower temperatures and offers greater control over the material's surface chemistry, thereby directly influencing its biological properties (Sepulveda et al., 2001). Sol-gel derived BGs exhibit intrinsic nano-porosity, leading to enhanced bioactivity attributed to significantly larger surface areas compared to melt-derived glasses, enabling them to contain biologically active levels of silica up to 88 mol.% (Sepulveda et al., 2001). However, enhanced bioactivity cannot solely be attributed to surface area and pore size. Protons act as additional network modifiers in sol-gel glasses due to their OH groups. Increasing the processing temperature reduces the OH content, thus altering the actual composition of the product compared to its nominal composition. Consequently, the lower OH content and N_c result in higher dissolution rates and increased bioactivity (Lin et al., 2009).

Sol-gel processing entails longer synthesis times due to the occurrence of cracks during drying, posing challenges in producing large monoliths. As water molecules evaporate through the pore network, capillary pressure develops, leading to crack formation. This phenomenon hampers the production of large monoliths via the sol-gel process. However, sol-gel processing finds application in the fabrication of particles, fibres, foams, porous scaffolds, coatings, and net-shaped monoliths (Lin et al., 2009). Figure 2.3 illustrates the conventional steps involved in both processes, while Table 2.1 provides a comparison of BGs derived from these two processing methods.

Table 2.1 Properties of melt-derived BG and sol-gel derived.

Property	Melt-derived BG	Sol-gel-derived BG	References
Processing temperature	Higher processing temperatures	Lower processing temperatures, more energy-efficient	(Fiume et al., 2020)
Surface Area	Lower specific surface area around 2-3 m ² /g	Higher specific surface area (80-300 m ² /g) due to inherent nanoporosity	(Fiume et al., 2020; Barrioni et al., 2017)
Bioactivity	Good bioactivity with slower ion release	Enhanced bioactivity due to faster ion release and bone bonding	(Barrioni et al., 2017; Bejarano et al., 2015)
Porosity	Generally lower porosity	High porosity which can be tailored for specific applications	(Fiume et al., 2020)
Structural and textural properties	More homogeneous structure	Nanomaterials with improved cellular responses	(Fiume et al., 2020; Barrioni et al., 2017)
Synthesis Complexity	Relatively simpler synthesis process	Complex synthesis process, especially for multicomponent systems	(Fiume et al., 2020)
Economic Efficiency	Cost-effective for large scale production	More expensive due to the complexity of the process	(Shoushtari et al., 2024)

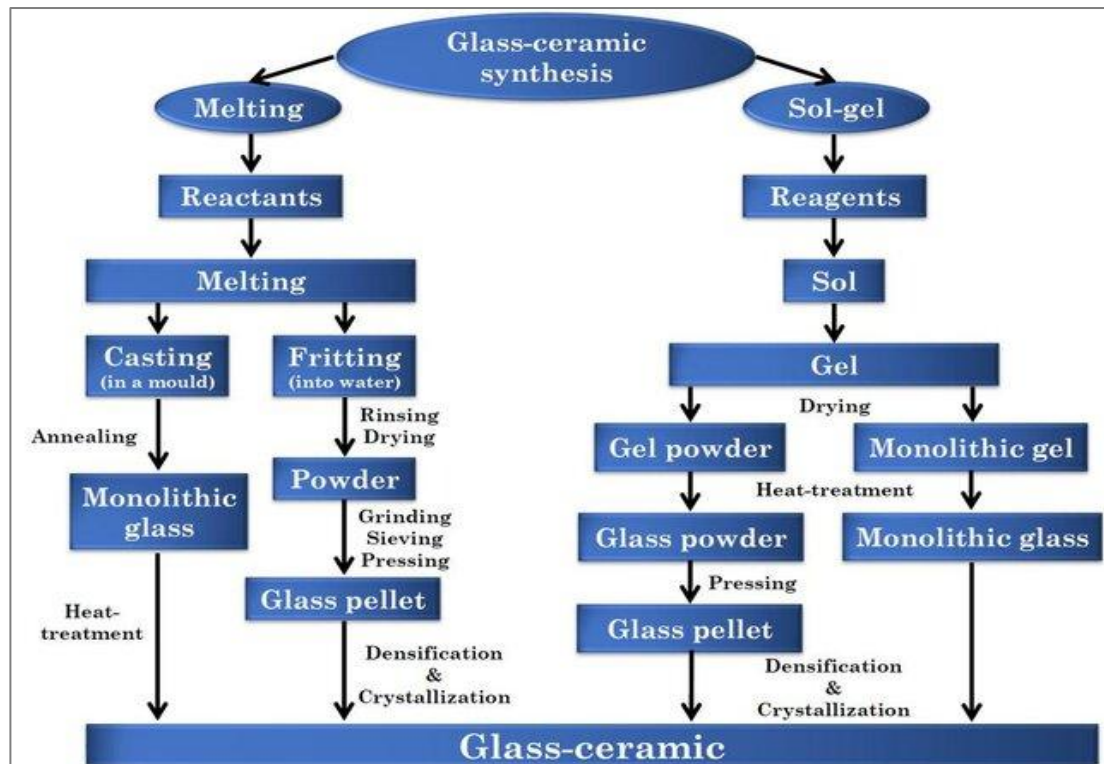


Figure 2.3 Diagram of main stages in the melting (a) and sol-gel (b) process to obtain BG. (Adapted from Kaur et al., 2016)

2.2.5 Composition of Bioactive Glass

BG typically comprises SiO_2 , Na_2O , CaO , and P_2O_5 . To enhance the properties and processability of 45S5 Bioglass®, various alternative compositions have been extensively investigated. Among these, a bioactive silicate glass containing 53 wt.% SiO_2 has garnered significant attention due to its superior mechanical properties (Brown et al., 2008). Furthermore, glass compositions specifically designed for bone regeneration often incorporate magnesium oxide (MgO) and potassium oxide (K_2O) as glass modifiers, which distinguish them from the traditional formulation of 45S5BG (Hupa et al., 2016). An additional widely studied composition is S53P4BG, which has demonstrated clinical utility comparable to that of 45S5 (Rahaman, 2007). Previous studies have successfully synthesised a novel BG composition, 50S8P, using a melt-derived approach (Ibrahim et al., 2017; Lucas-Girot et al., 2011). This composition boasts the highest phosphorus content among tested formulations and exhibits favourable biological responses comparable to those of 45S5. The bioactivity of the 50S8P compositions has been demonstrated in research studies (Ibrahim et al., 2017; Lucas-Girot et al., 2011). Table 2.2 presents a summary of the diverse BG compositions available for laboratory investigations.

A new composition BG, designed as 54S4P, has been successfully synthesised via the melt-derived route by Ibrahim et al. (2017). Notably, this variant exhibits a reduced melting temperature compared to the traditional 45S5BG. Remarkably, the properties of this new BG variant are on par with those of the esteemed 45S5BG, suggesting promising prospects particularly in dental treatments and tissue regeneration applications. Notably, HA is facilitated to form on the surface of the BG powder, it enhances its efficacy in these applications (Aishah et al., 2020; Ibrahim et al., 2017). Aishah et al. (2020) have effectively fabricated the 54S4PBG using the sol-

gel method, achieving stabilisation at a temperature of 700°C. Analysis reveals the predominant crystalline structure to be combeite ($\text{Ca}_4\text{Na}_4\text{O}_{18}\text{Si}_6$). Noteworthy observations indicate that elevating the aging temperature induces the generation of larger and coarser particles, thereby facilitating nucleation and fostering increased crystal growth. Particularly, lower temperatures favour the formation of needle-like crystals characteristic of the combeite high phase. Subsequent immersion for 14 days in physiological fluid revealed a homogeneous coverage of the glass particles by precipitated apatite crystals.

Table 2.2 Different composition of BG (wt.%).

Composition	SiO ₂	Na ₂ O	CaO	P ₂ O ₅	MgO	B ₂ O ₃	Al ₂ O ₃	SrO
45S5	45.0	24.5	24.5	6.0	-	-	-	-
42S5	42.1	26.3	29.0	2.6	-	-	-	-
S53P4	52.0	23.0	20.0	4.0	-	-	-	-
54S4P	54.0	22.0	20.0	4.0	-	-	-	-
55S4	52.1	21.5	23.8	2.6	-	-	-	-
58S	60.0	0	36.0	4.0	-	-	-	-
70S30C	70.0	30.0	0	0	-	-	-	12.5
40S5B5	40.0	24.5	24.5	6.0	-	5.0	-	-
H12	7.5	8.0	40.0	2.5	-	40.0	2.0	-
6P44	44.2	17.0	18.0	6.0	10.2	-	-	-

2.2.6 Utilisation of Bioactive Glass in Dentistry

BG is frequently utilised in restorative materials alongside other substances due to the comparatively lower bioactivity of materials such as glass ionomer cements (GIC) (DeCaluwé et al., 2017), sealants (Yang et al., 2016), and gutta-percha (GP) (Alhashimi et al., 2017). Among commercial BG variants, 45S5 Bioglass® is widely utilised due to its superior bone regeneration capabilities compared to commercial HA.

Notably, BG exhibits biocompatible properties and contributes to tooth remineralisation and demineralisation (Yang et al., 2013).

Typically, BG is manufactured in powder form and added to other dental materials to enhance their properties. It is employed as fillers in pastes (Bakry et al., 2014; Wang et al., 2016b), root canal filling materials (Alhashimi et al., 2017), and fillers in glass ionomer cements (De Caluwé et al., 2017; Kanjevac et al., 2012). Moreover, BG serves as an additive in composite resins (Aguilar-Pérez et al., 2016; Chatzistavrou et al., 2015; Schickle et al., 2011) and dental adhesives (Fu et al., 2014; Rizk et al., 2017). BG finds widespread application in caries treatment, early caries lesion management, mineralisation, desensitisation, and root canal procedures. The BG utilised in the present study is in powdered form, and the subsequent sections delve into the role of BG powder in dental applications within the realm of dentistry.

2.2.6(a) Oral Care

Various dental products, particularly toothpaste formulations, have incorporated BG (Tai et al., 2006; Farooq et al., 2012) owing to their ability to release antibacterial agents, facilitate remineralisation, and alleviate hypersensitivity. BG has demonstrated efficacy in toothpaste formulations (Skallevold et al., 2019). One commercially available BG variant, NovaMin, is added to toothpaste formulations to enhance tooth remineralisation and reduce sensitivity. NovaMin (calcium-sodium-phosphate silicate) releases calcium and phosphate ions upon use. These ions elevate the pH level, facilitate calcium phosphate deposition, and foster the transformation of calcium phosphate into HA (Burwell et al., 2009). Notably, NovaMin exhibits a sustained release of calcium ions following an initial burst, distinguishing it from other calcium-based products (Burwell et al., 2010).

Another commercially accessible BG product, Biomin F, contains phosphate and fluoride, promoting the synthesis of fluorapatite (FAP) (Brauer et al., 2010). In a significant development, the FDA approved the first toothpaste containing fluoride and BG in 2021. This toothpaste fosters the formation of acid-resistant fluorapatite on the tooth surface and within exposed dentine tubules by gradually releasing calcium, phosphate, and fluoride ions for several hours post-brushing.

2.2.6(b) Filler Materials in Glass Ionomer Cement

In contemporary restorative dentistry, glass ionomer cements (GIC) have emerged as a popular alternative to traditional amalgam fillings. GIC offers numerous advantages, such as direct bonding with teeth and biocompatibility properties. Recently, researchers have investigated the incorporation of BG into GIC to assess its mechanical, bioactivity, and biocompatible properties (De Caluwé et al., 2016; Kim et al., 2017). The addition of BG has been shown to enhance the bioactivity of GIC, particularly with BG CF9 (a sodium free composition of BG) (De Caluwé et al., 2017). A study by De Caluwé et al. (2017) compared the addition of CaF_2 into BG compositions with BG CF9, which lacked the Na_2O compound, in disc form. It was observed that the particle size of both BG variants did not significantly affect their properties, but their N_c differed. Specifically, CF9, with a lower N_c (2.08), exhibited a higher dissolution rate compared to BG 45S5F (N_c 2.68). Furthermore, the increased release of calcium ions from BG influenced osteoblast differentiation, proliferation, and gene expression (De Caluwé et al., 2017).

BG CF9 demonstrated the highest bioactivity rate, with apatite formation on the discs and superior cell viability and adhesion capabilities. Therefore, BG as fillers in GIC holds promise for future applications, although further investigations,

especially regarding biocompatibility with cells to prevent toxicity, are warranted (De Caluwé et al., 2017). Additionally, BG in the form of nanoparticles (BGN) has been incorporated into GIC due to its higher surface area and bioactivity, thereby enhancing the mechanical and biological properties (Kim et al., 2017). BGNs were synthesised via the sol-gel method and fabricated into disc specimens with the addition of GIC and chitosan as a binder. The inclusion of BGNs improved the mechanical properties of GIC and exhibited higher cell viability in cytotoxicity tests with dental pulp stem cells. Nevertheless, further investigations are necessary for in vivo studies on the incorporation of BGNs into GIC (Kim et al., 2017).

2.2.6(c) Application in Endodontics

Gutta percha (GP) is commonly utilised as a root canal filling material; however, it lacks the ability to adhere to the root canal system. To address this limitation, conventional root canal sealers are often employed in conjunction with GP to facilitate adhesion to dentin (Setya et al., 2014). GP's inability to adhere to the canal wall, coupled with susceptibility to setting shrinkage, poses challenges that may lead to root canal infections (Alhashimi et al., 2017). In response, novel bioceramic root canal filling materials have been developed to mitigate GP's shrinkage issue and enhance the sealing of the root canal. The incorporation of BG within polymer matrices has been explored to create root filling systems with improved sealing capabilities, particularly at the end of root canals (Alhashimi et al., 2017).

Effective root canal therapy, or endodontic treatment, hinges on the thorough elimination of bacterial biofilms from the root canal system, which are implicated in pulpal and periapical diseases (Fan et al., 2015). Current research endeavours aim to develop new canal disinfectants with sustained antibacterial effects, devoid of bacterial

resistance or tolerance, and conducive to apical tissue regeneration (Fan et al., 2015). Mineral trioxide aggregate (MTA) or BG are potential candidates for novel canal disinfectants, given their demonstrated antibacterial properties and potential for bone defect regeneration (Fan et al., 2015).

Fan et al. (2015) synthesised Ag-loaded mesoporous bioactive glass (Ag-MBG) powders and assessed their antibacterial efficacy. Human single-rooted mandibular premolars with mature apices were procured from native Chinese patients for the study. Ag-MBGs exhibited a highly ordered mesoporous structure with silver nanoparticles deposited within the mesopores, facilitating the release of Ag ions. The results demonstrated that Ag-MBG possessed potent antibacterial effects against *Enterococcus faecalis*, attributable to the release of Ag ions from the material (Fan et al., 2015).

2.2.6(d) Dental Implant

Dental implants, also known as endosseous implants, are screw-shaped devices inserted into the alveolar bone to support prosthodontic constructions to improve function and appearance (Vaddamanu et al., 2024). Direct contact between the implant surface and bone tissue is required for adequate osseointegration and retention in bone (Vaddamanu et al., 2024). Titanium-based alloys are the most commonly used dental implants materials. They are bioinert but highly biocompatible and osteoconductive (Ahmed et al., (2024). However, they provide attachment for osteoprogenitor cells and osteoblasts while being toxic to microorganisms (Yeo et al., 2012). There have also been reports of Titanium-dental implant osseointegration failures (Kate et al., 2016; Petersen, 2014). BG implants that actively bond to the bone may provide antimicrobial protection and reduce total treatment time (Talreja et al., 2013; Civantos et al., 2017;

Mistry et al., 2011). No BG coating for dental implants has been commercialised for clinical use.

Dental implants carry a risk of developing infections such as peri-implantitis (PI) or periprosthetic joint diseases (PJI). These infections increase morbidity and mortality, causing the surrounding bone tissue to resorb and the implant to eventually become loose. The weighted mean prevalence estimate for PI was 22% (Derks and Tomasi, 2015). Each artificial joint is susceptible to PJI. PJI affects 0.2 to 9% of prostheses and accounts for 15% of hip prostheses and 25% of knee prostheses, as one of the most common causes of revision and replacement of the joint prosthesis (Bozic et al., 2010). The development of a bacterial biofilm on the surface of an implant can lead to infection, as biofilms are highly resistant to antibiotic (AB) therapy. A biofilm is a structured layer of microbial populations that adhere to a surface using a robust polysaccharide matrix, providing protection to the bacteria and facilitating their persistence in hostile environments. This matrix strengthens the attachment to the surface and shields the bacterial colonies from immune responses and antimicrobial agents, making infections difficult to treat. Developing a bacterial biofilm on the implant's surface leads to infection. As such, in dentistry, bacterial infections are relevant, mainly because the treatment of bacterial infection is rendered ineffective due to the rise in the incidence of bacteria resistant to antibiotics, particularly multidrug-resistant bacteria.

However, S53P4BG has demonstrated broad-spectrum antibacterial activities, with no resistance so far observed (Drago et al., 2015). The BG was effective against the most implicated bacteria and biofilm in PJI and bone infections. In fact, S53P4BG significantly reduced the biofilm mass in-vitro settings (Bortolin et al., 2015; Coraca-Huber et al., 2014). Anti-biofilm effect of BG is enhanced by incorporating