Fabrication and in Vitro Characterization of Porous Pmma/Bioglass Scaffolds

K.Sjanani1 , R.Hari1,a)

1Janani Medical Services, Trivandrum, Kerala, India.

**Corresponding Author:** a)[rharipriya09@gmail.com](mailto:rharipriya09@gmail.com)

**Abstract:** Porous scaffolds composed of a blend of polymethyl methacrylate (PMMA) and bioactive glass have emerged as promising materials in the field of bone tissue engineering and regenerative medicine. PMMA is a polymer known for its excellent mechanical properties, including high strength and stiffness. When combined with bioglass, it enhances the structural integrity and load-bearing capacity of the scaffold. This is crucial for bone tissue engineering, as the scaffold should withstand physiological forces and provide mechanical support during the healing process. Bioglass can stimulate osteoblast activity which promotes new bone formation. This bioactivity is attributed to the release of ions, such as Ca, P, and Si from the glass composition, which can initiate and enhance the bone regeneration process. PMMA is a cost-effective material compared to some other biocompatible polymers. This makes PMMA/bioglass scaffolds a potentially economical choice for tissue engineering applications. **Methods-** The TIPS method was used to create scaffolds using PMMA as the polymer. The process involved mixing equal volumes of bioglass and PMMA, and the resulting mixture was added to acetone to form the scaffold material. It's essential to preheat the acetone before adding PMMA. The goal of this method was to produce porous scaffold materials, which are desirable for better integration with bone tissue in applications such as tissue engineering. **Results**-The bioglass-PMMA scaffold exhibits an irregular structure, confirmed by surface morphology and EDAX chemical analysis. Attachment of bioglass onto the PMMA matrix is evident, seen in increased surface roughness (AFM) and shared peaks in FTIR analysis. The scaffold's reduced contact angle signifies higher hydrophilicity, promoting cell binding. With a hemocompatibility value below 5 and a zebrafish study showing less than 10% mortality, the PMMA/bioglass scaffold is deemed biocompatible. **Conclusion-**Porous PMMA/bioglass scaffolds hold great potential for tissue engineering and regenerative medicine applications. The combination of PMMA and bioglass offers a unique balance of mechanical strength and bioactivity, making these scaffolds suitable for bone tissue engineering. These scaffolds have the ability to support cell adhesion, proliferation, and osteogenic differentiation, essential for bone regeneration.

**Keywords-** Polymethyl methacrylate, bioglass, Scaffold, Bone tissue engineering, Porous materials.

# INTRODUCTION

The majority of bone tissue lesions possess the inherent capacity for natural self-regeneration, often necessitating minimal intervention through conservative therapies or traditional surgical methods. This capability is primarily attributed to the ongoing process of bone remodeling that persists throughout human life[(Im et al., 2021)](https://paperpile.com/c/a6ZUVZ/6dsO). However, when confronted with substantial osteochondral defects, complete replacement of the affected area becomes imperative, involving the utilization of artificial prostheses that possess finite lifespans[(Thiripelu et al., 2024)](https://paperpile.com/c/a6ZUVZ/JGnG). Hence, there is a critical need to discover novel materials capable of achieving lasting repairs for such lesions, thereby circumventing the need for subsequent reconstructive surgeries, particularly among younger individuals[(Durgalakshmi & Balakumar, 2015; Sathya et al., 2024)](https://paperpile.com/c/a6ZUVZ/PFt3+Kxx1). Creating three-dimensional microstructural scaffolds that accurately replicate the mechanical characteristics of human bone is of significant importance for implant applications. Hence, researchers have developed a range of biocompatible polymers and bioactive glasses with the specific goal of attaining these desired properties[(“Effect of ZnO Reinforcement on the Compressive Properties, in Vitro Bioactivity, Biodegradability and Cytocompatibility of Bone Scaffold Developed from Bovine Bone-Derived HAp and PMMA,” 2019, “Fabrication and in Vitro Characterization of Electrospun Poly (γ-Glutamic Acid)-Silica Hybrid Scaffolds for Bone Regeneration,” 2016)](https://paperpile.com/c/a6ZUVZ/brH4+IxvU). Extensive focus has been directed towards creating biomaterial-centered synthetic alternatives aimed at restoring impaired musculoskeletal tissue. [(Evaluation Composite Restoration Posterior Teeth Proanthocyanidin Pretreatment Liner Using Fédération Dentaire Internationale Criteria: Split-Mouth Randomized Controlled Trial, n.d.; Pranati et al., 2021; Sakthi, 2021)](https://paperpile.com/c/a6ZUVZ/vtZVr+yWRa5+2MoHV) Particularly in the realm of bone tissue engineering, there has been substantial interest in organic-inorganic composites and hybrids. These materials offer a promising avenue for synergizing and harnessing the characteristics inherent to both organic and inorganic components[(Elakkiya et al., 2023)](https://paperpile.com/c/a6ZUVZ/VBrW). A scaffold serves as a temporary framework within a bioreactor setting for cell growth and cultivation. To fulfill its role effectively, the scaffold needs to possess porosity, allowing for the exchange of nutrients, the diffusion of gasses, and the removal of metabolic waste[(Shanmugam et al., 2013)](https://paperpile.com/c/a6ZUVZ/3j5s). Simultaneously, it must exhibit sufficient mechanical strength to facilitate osteoblast formation and withstand in vivo implantation handling. [(G. & Ganapathy, 2022; Kumar & Ramesh, 2021)](https://paperpile.com/c/a6ZUVZ/Vszit+JdGSo)) As it is challenging to strike a balance between adequate mechanical strength and porous structure, the creation of porous scaffolds with an optimal strength, capable of supporting both osseointegration and cell proliferation, continues to be a critical focal point of research[(Sa et al., 2018)](https://paperpile.com/c/a6ZUVZ/dfmi).Bioglass employed in the creation of synthetic scaffolds for bone regeneration are highly appealing materials. They possess the ability to stimulate in-vitro hydroxyapatite mineralization and exhibit excellent cytocompatibility. Bioglass can be enriched with various functional elements to enhance their biological properties [(Negut et al., 2020)](https://paperpile.com/c/a6ZUVZ/0FSq). Polymers have been the preferred material in the field of tissue engineering. PMMA(Polymethyl methacrylate) acrylic bone cement has found widespread use in joint repair and replacement procedures, as well as in various medical and dental applications[(Floroian et al., 2011)](https://paperpile.com/c/a6ZUVZ/23jD). Polymers are extensively utilized in both in-vivo and in-vitro biomedical applications due to their aesthetic appeal and versatility in injection molding. PMMA is non-toxic, provides compressive strength, and offers versatile processing capabilities[(Atkinson et al., 2021)](https://paperpile.com/c/a6ZUVZ/L38p). Composite scaffolds consisting of polymers and nanostructured bioactive glass show great promise for regenerative applications due to their close resemblance to the composition of natural bone [(Akmal & Duraisamy, 2020)](https://paperpile.com/c/a6ZUVZ/naSb). Poly methyl methacrylate (PMMA), a thermoplastic polymer widely favored for orthopedic applications, offers excellent biocompatibility.[(Venugopalan, 2021)](https://paperpile.com/c/a6ZUVZ/j63m). The incorporation of various bioactive, biodegradable, and biocompatible biomaterials such as Bioglass (BG), Hydroxyapatite (Hap), and Tricalcium phosphate (TCP) into PMMA enhances bioactivity, porosity, and facilitates the regeneration of hard tissues in the human body. Among the bioactive glasses, 60S BG (Bioactive glass with 60% Silica without Sodium ions) stands out as a superior material in comparison to the mentioned systems, primarily due to its mechanical stability and controlled bioactive properties. [(Keerthana & Ramesh, 2021; Murugesan, 2021; Tiwari & Jain, 2021)](https://paperpile.com/c/a6ZUVZ/GwhRT+XCQPI+5DBMT)[(Keerthana & Ramesh, 2021; Murugesan, 2021; Subramanian et al., 2021; Tiwari & Jain, 2021)](https://paperpile.com/c/a6ZUVZ/GwhRT+XCQPI+5DBMT+fC6jw) This makes it a compelling choice for the development of bioactive scaffolds aimed at promoting tissue regeneration in orthopedic and regenerative medicine applications [(Aparna et al., 2021)](https://paperpile.com/c/a6ZUVZ/IZRj). Despite the introduction of novel bone substitutes, poly(methyl methacrylate) (PMMA) cement remains a widely employed biomaterial for bone replacement in orthopedic surgery due to its extensive history[(Chokkattu et al., 2022)](https://paperpile.com/c/a6ZUVZ/dYZx). However, common complications associated with PMMA include aseptic loosening, prosthetic infection, and thermal necrosis of surrounding tissues. [(Kasabwala et al., 2021; Rajeshkumar & Lakshmi, 2021; Varghese et al., 2023)](https://paperpile.com/c/a6ZUVZ/Rxmeb+WVmOJ+MozEh) Consequently, efforts have been made to address these issues by incorporating various additives into PMMA cement[(“Chitosan Based Polymer/bioglass Composites for Tissue Engineering Applications,” 2019; Ravarian et al., 2015)](https://paperpile.com/c/a6ZUVZ/sfGc+cNmW). This chapter provides an overview of different additives aimed at enhancing PMMA cement performance, including, bioceramic, fillers, antibacterial additives, porogens, biological agents, and mixed additives. To enhance both biological and mechanical properties, the incorporation of mixed additives appears to be the most viable approach for creating multifunctional PMMA [(Floroian et al., 2015; Ravarian et al., 2013)](https://paperpile.com/c/a6ZUVZ/XvVt+WLUx).In light of the diverse pathophysiological aspects of the osseointegration process, significant emphasis has been placed on advancing and assessing composite materials to enhance osseointegration and bone regeneration. Composite materials, particularly those incorporating polymers and bioglasses, have garnered heightened interest for their ability to create novel materials with enhanced and synergistic characteristics derived from both components. Certain ceramics and bioglasses, owing to their similarities to bone composition and mineral structure, as well as their ability to promote bone formation, exhibit advantageous properties for applications [(Chung et al., 2016)](https://paperpile.com/c/a6ZUVZ/2Ia2). in scaffolds The CaO-SiO2 binary glass system fosters apatite formation in simulated body fluid (SBF). However, introducing phosphate content into SiO2-CaO-P2O5 glasses induces the creation of orthophosphate nanocrystalline nuclei, promoting the development of carbonate hydroxyapatite. This compound exhibits better compatibility with natural bone. Despite the bioactive glasses' brittleness and limited flexibility, hindering their application as bone implants, the hybridization of key constituents from bioactive glasses and glass-ceramics with polymers, such as PMMA, has the potential to enhance their mechanical properties [(Dhinasekaran & Kumar, 2022)](https://paperpile.com/c/a6ZUVZ/fDmB). Scaffolds designed for cell proliferation typically consist of two primary elements: a porous structure, commonly constructed from polymers, and a bioactive material that envelops the scaffold to promote cell differentiation and growth. The primary application of bioactive glass (BG) in conjunction with polymers is to enhance scaffold efficiency, a purpose well-documented in literature with positive outcomes. Additionally, BG has been reported for other applications, such as coatings for prostheses with functions including bioactive, and anticorrosive properties [(“Impact of Copper on in-Vitro Biomineralization, Drug Release Efficacy and Antimicrobial Properties of Bioactive Glasses,” 2020)](https://paperpile.com/c/a6ZUVZ/5Q6r). The aim of this study is to fabricate and characterize porous scaffolds composed of a blend of polymethyl methacrylate (PMMA) and bioglass for potential applications in bone tissue engineering and regenerative medicine [(Chung et al., 2017)](https://paperpile.com/c/a6ZUVZ/0fhc). Our team has extensive knowledge and research experience that has translated into high quality of publications.

# MATERIALS AND METHODS

## Calcium Silicate Phosphate (Ca-Si-P) Synthesis

Calcium silica phosphate is synthesized by combining calcium chloride solution (CaCl2) and tetraethyl orthosilicate (TEOS) solution in the presence of a base or catalyst. This reaction forms the desired Ca-Si-P compound along with impurities and unreacted chemicals.The solid Ca-Si-P product is separated from the liquid phase through filtration. Filtration helps remove impurities and unreacted chemicals from the product. The washed Ca-Si-P product is dried using an oven. This step is crucial to remove any remaining moisture and obtain a dry and stable Ca-Si-P compound. The Ca-Si-P compound provides a bioactive material that can promote bone regeneration. It has properties that mimic the natural mineral content of bone, making it suitable for tissue engineering applications.

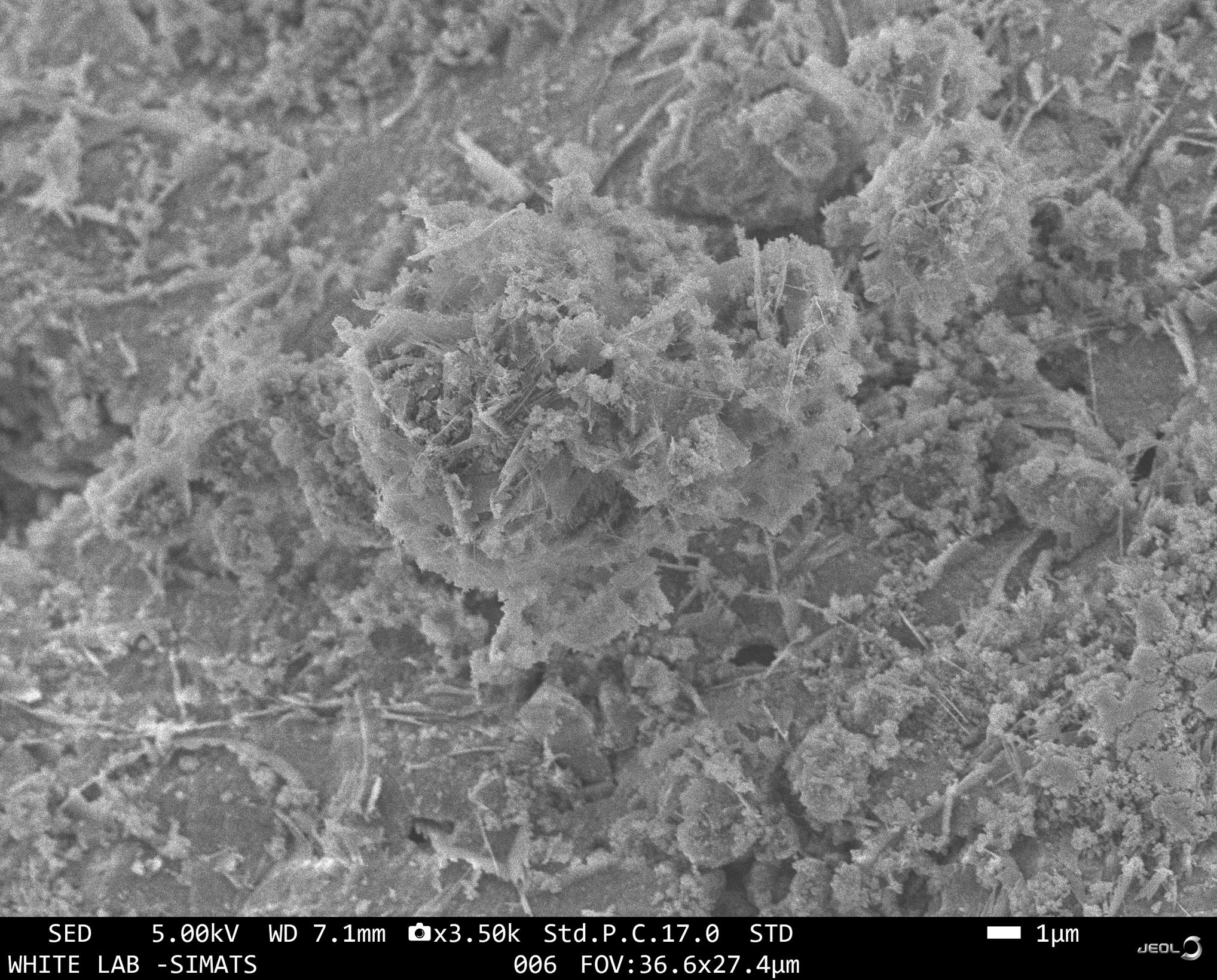
## Preparation of PMMA/bioglass composite

Thermally Induced Phase Separation (TIPS) technique was used for creating porous scaffolds, in this case using PMMA as the polymer matrix material and incorporating bioglass. Procure PMMA from Alfa Aesar, India, which will serve as the polymer matrix material. It's important to note that PMMA has low dissolvability at room temperature. Therefore, the use of preheated acetone is crucial to facilitate the dissolution of PMMA. By heating the acetone, it becomes a more effective solvent for PMMA, resulting in a homogeneous solution without any clumps. This is a critical step to ensure that the PMMA and bioglass are well-distributed throughout the scaffold material. Measure out 3.6 grams of PMMA and 0.3 grams of bioglass. Add these measured quantities to 20 ml of preheated acetone. Stir the mixture continuously to ensure thorough mixing. Continue stirring until the PMMA and bioglass are completely dissolved in acetone.

## Scaffold preparation

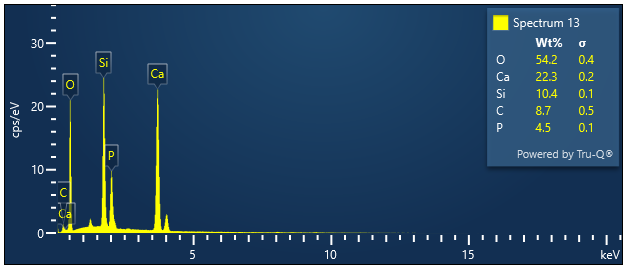
During the heat treatment, the acetone in the solution evaporates. As the solvent evaporates, the dissolved PMMA and bioglass components come together, forming a solid scaffold structure. The heat treatment contributes to the formation of a porous structure within the scaffold. As the solvent evaporates, voids or pores are created within the material. These pores are important for facilitating tissue integration, as they provide space for cells to grow, nutrients to flow, and waste products to be removed. Prepare a mold in the desired shape for the scaffold. The mold will determine the final shape and dimensions of the scaffold. Pour the homogeneous PMMA-bioglass-acetone solution into the mold. Place the mold containing the solution into a hot air oven set at 65°C. Allow the solvent (acetone) to evaporate slowly over the course of 24 hours. As the solvent evaporates, the polymer phase will undergo phase separation and solidify into a porous structure. This is the key principle behind the TIPS method. The resulting scaffold should have a porous microstructure. After 24 hours, remove the scaffold from the oven. Carefully detach the solidified scaffold from the mold. The scaffold may undergo additional processing steps, such as further drying, sterilization, or surface modification, depending on the intended application.

# RESULTS



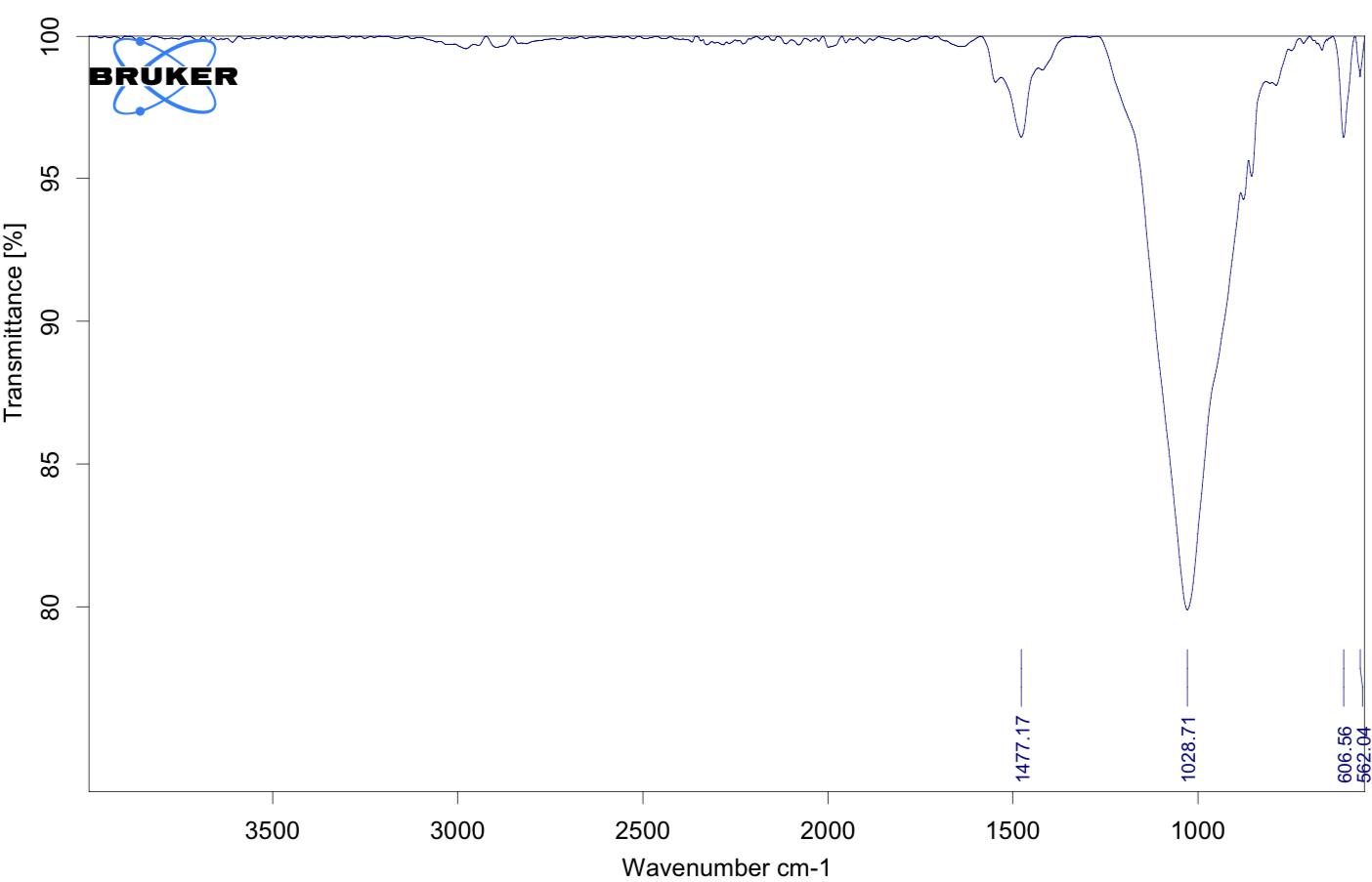
**Fig1**- Scanning Electron Microscope (SEM) of Bioglass Surface Morphology

Bioglass consists of calcium (Ca), silicon (Si), and phosphate (P). When examining the surface morphology of bioglass, it's evident that it is an irregular composite material. This irregularity can be observed at the micro or nanoscale, where the surface may appear rough, porous, or non-uniform. Such irregularities are often intentionally designed in bioglass scaffolds to promote better integration with natural bone tissue. The irregular surface texture can enhance cell adhesion, proliferation, and the formation of a stable interface between the scaffold and the surrounding tissue.

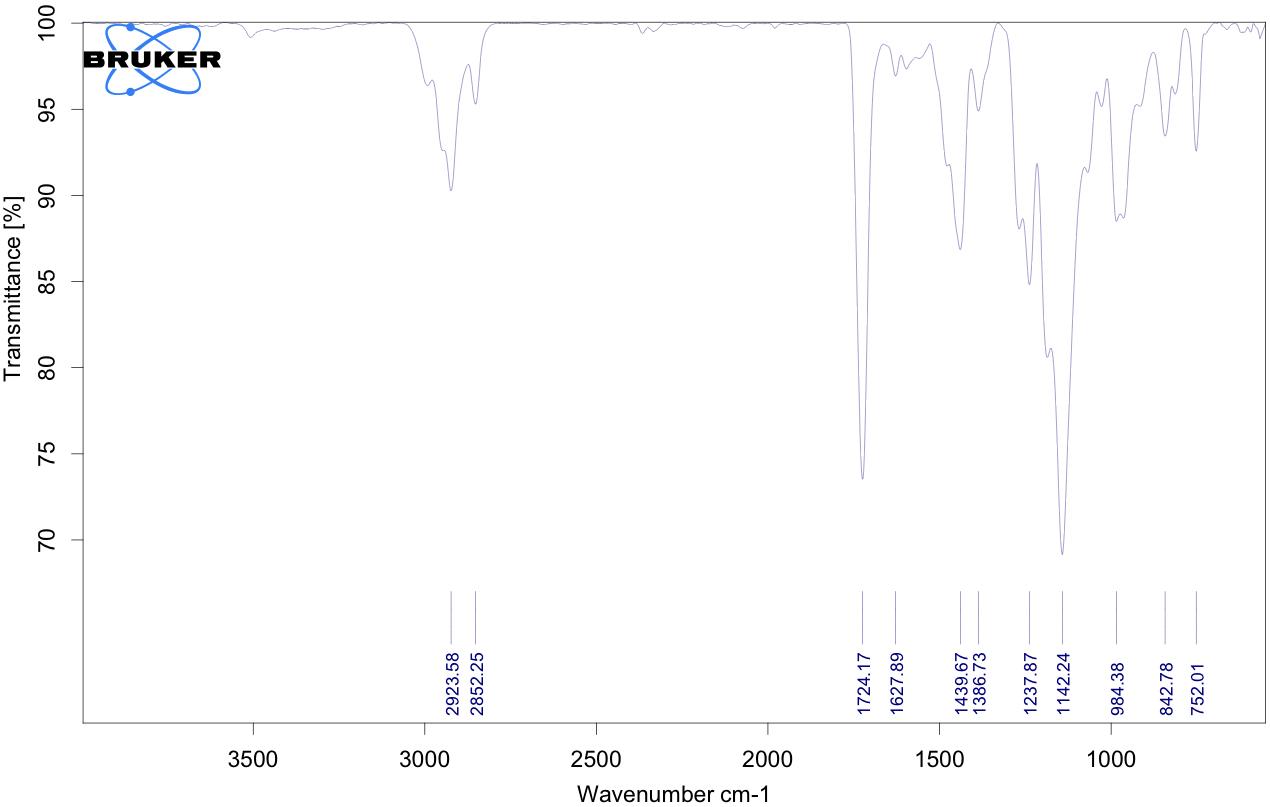


**Fig2-** Energy-Dispersive X-ray Analysis (EDAX) of Bioglass

EDAX is a powerful technique employed for elemental composition analysis in materials. When applied to bioglass, EDAX allows for the identification of key components such as calcium (Ca), silicon (Si), and phosphate (P), integral to the composition of bioglass. This chemical confirmation through EDAX not only reinforces the composite nature of the material but also furnishes valuable insights into its elemental makeup. The presence of these specific elements, as revealed by EDAX analysis, aligns with the expected composition of bioglass and enhances our understanding of its chemical structure.

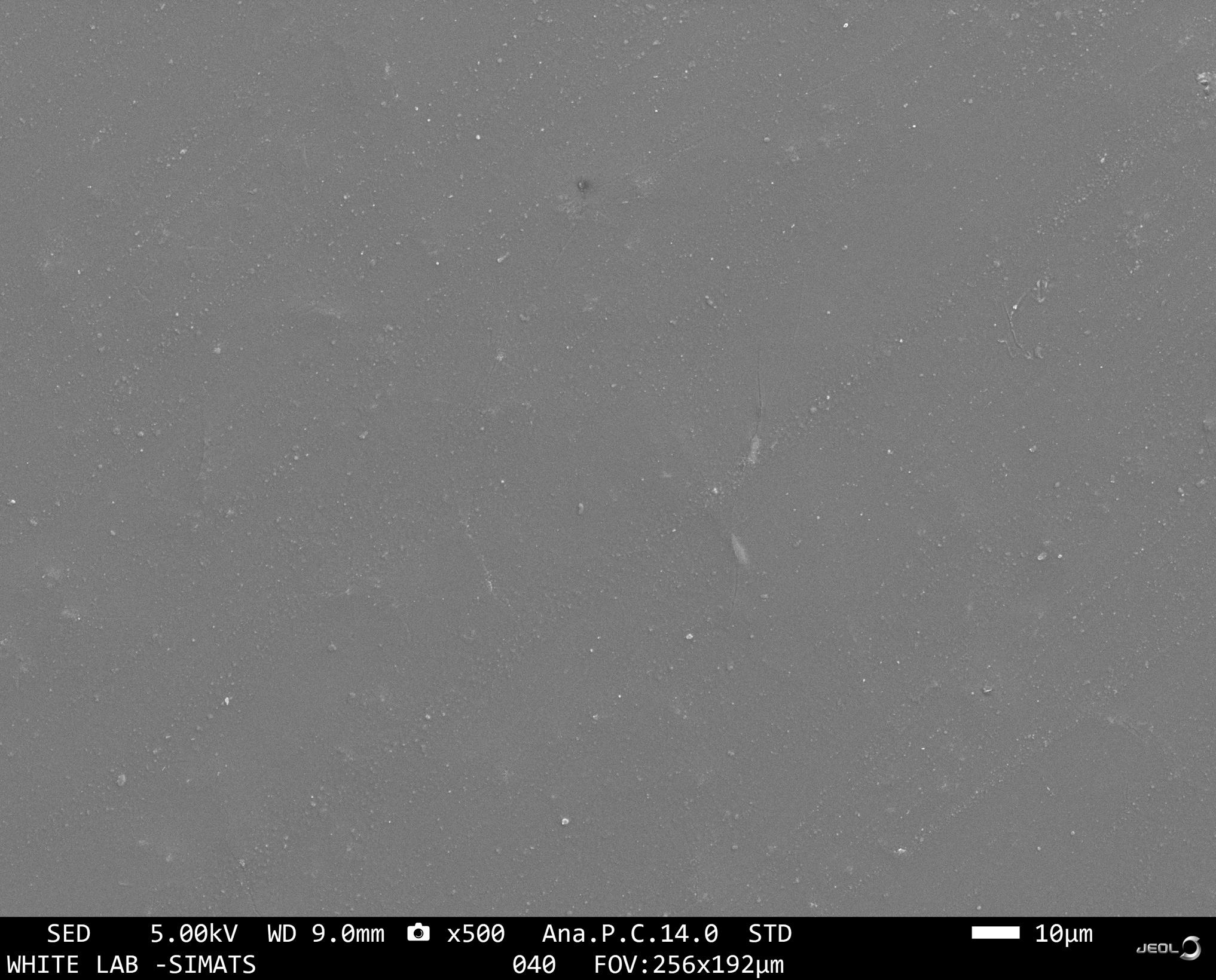


**Fig3**- Fourier Transform Infrared (FTIR) Analysis of bioglass.

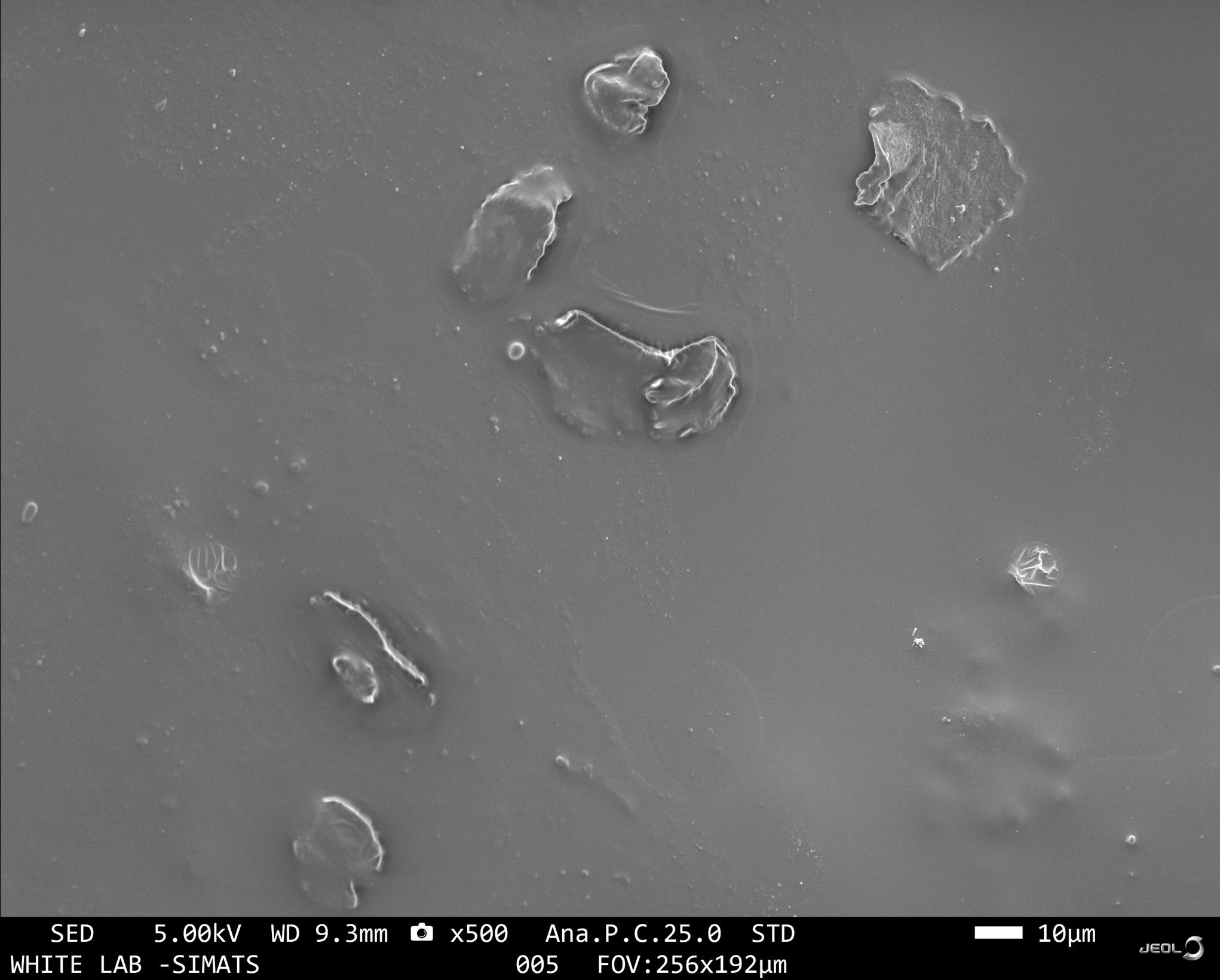


**Fig 4-** Fourier Transform Infrared (FTIR) Analysis of PMMA Scaffold

FTIR analysis conducted on the scaffolds yielded noteworthy findings, as the peaks associated with the bioglass material were also discernible in the PMMA scaffolds. This observation suggests a successful integration or interaction between the bioglass and PMMA components within the scaffolds(Nikalje et al., 2024). The shared peaks in the FTIR spectra indicate the presence of similar chemical functionalities or bonds in both materials, possibly indicating a degree of compatibility or interaction between the polymer matrix (PMMA) and the bioglass(Chehelgerdi et al., 2023). This insight is crucial for understanding the composite nature of the scaffolds and hints at potential synergistic effects between the two components, contributing to the overall properties and performance of the composite material.

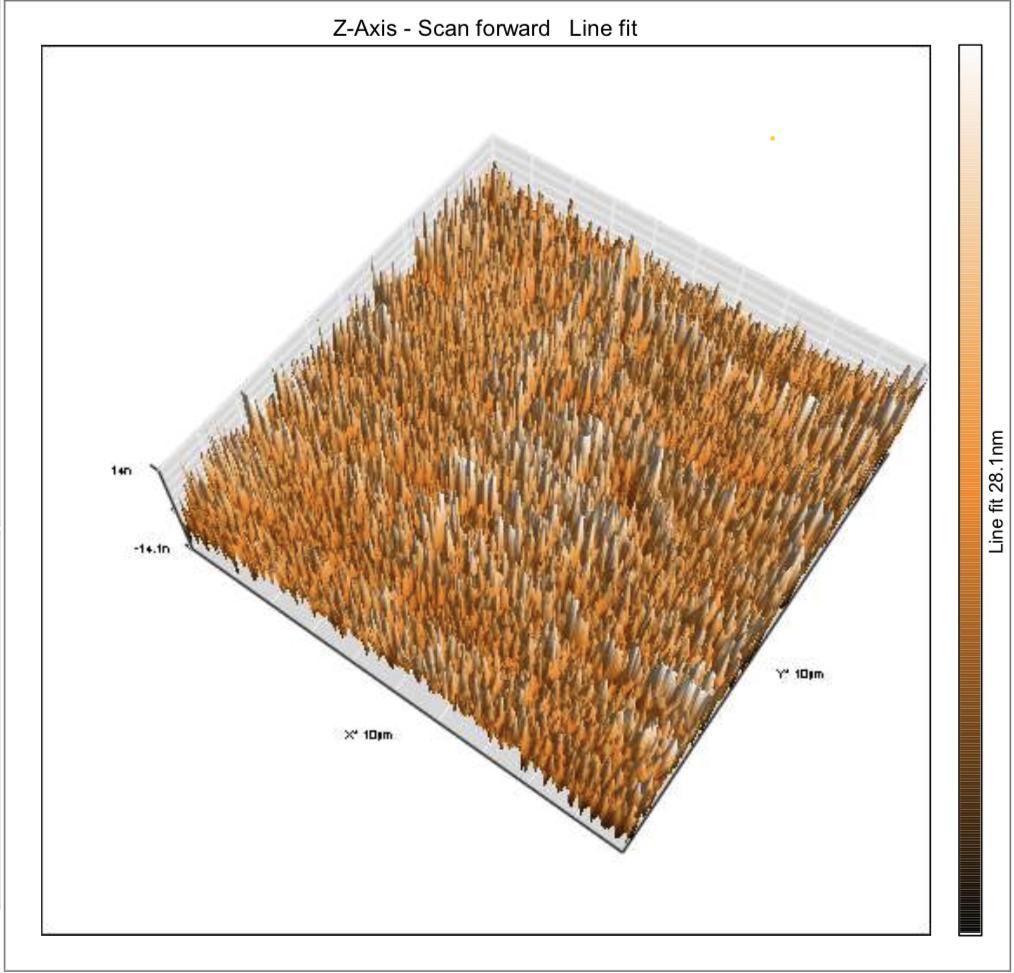
****

**Fig 5-** Scanning Electron Microscope (SEM) of Pristine PMMA Surface Morphology

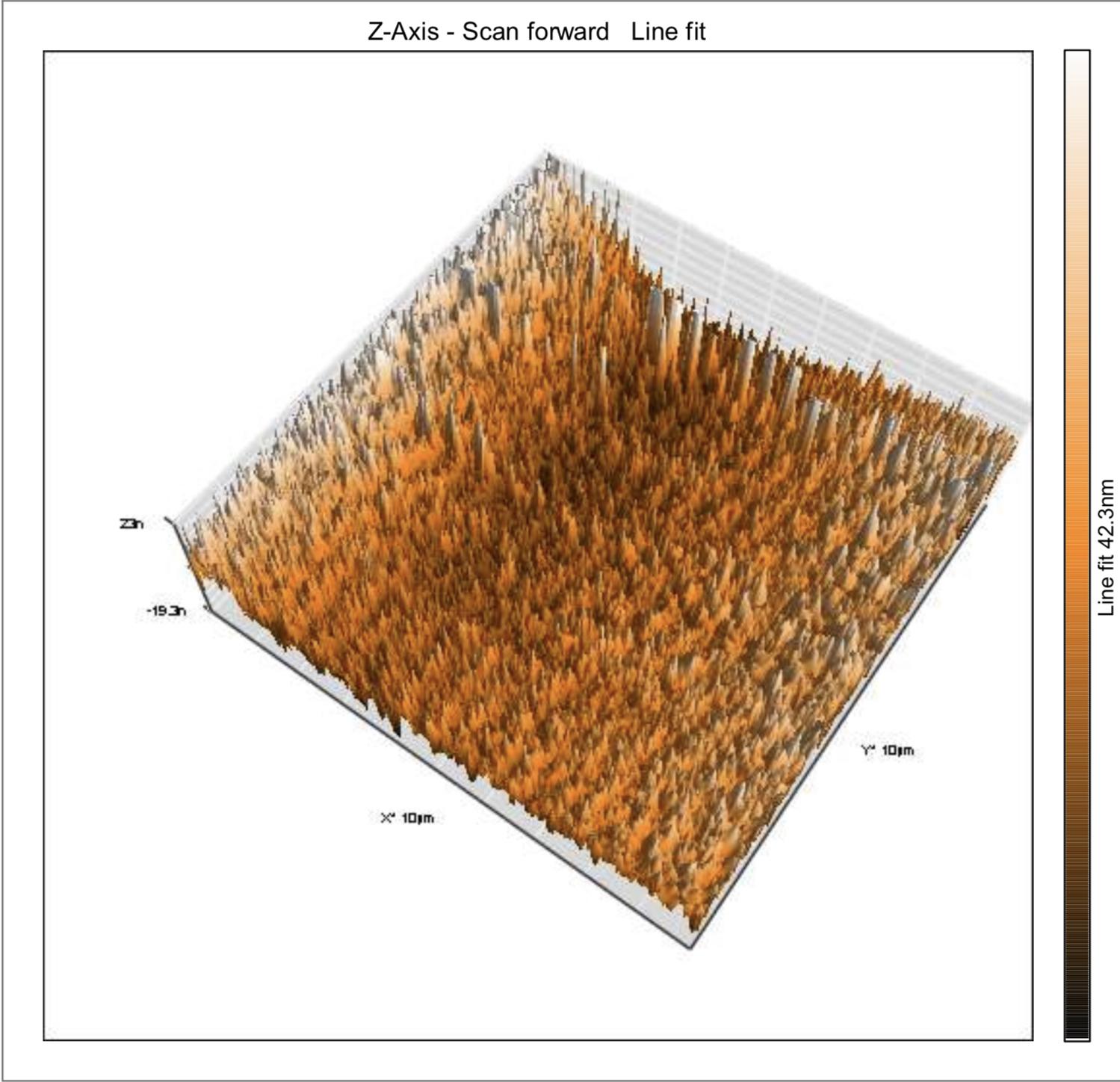


**Fig 6-** Scanning Electron Microscope (SEM) of PMMA Scaffold Surface Morphology

The examination of pristine PMMA samples revealed a smooth and plain surface. In contrast, the scaffolds exhibited a distinct transformation, indicating the successful attachment of bioglass onto the PMMA matrix. This alteration in surface morphology suggests effective integration between the PMMA polymer and the bioglass component, reinforcing the composite nature of the material. The observed changes in the scaffold surface provide visual evidence of the presence and attachment of bioglass, signifying a modified and potentially enhanced material compared to the pristine PMMA

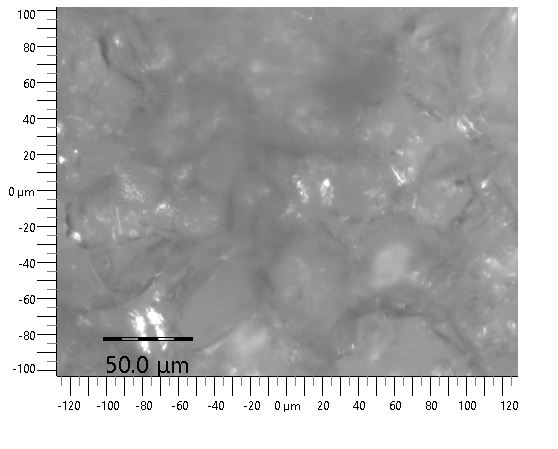


**Fig 7**- Atomic Force Microscopy (AFM) of Pristine PMMA Surface (Sa=3.4546 nm)

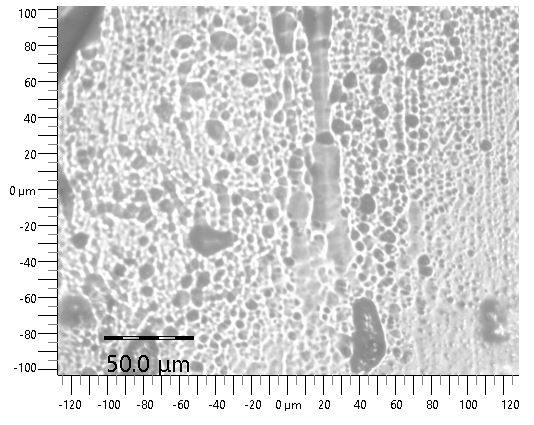


**Fig 8**- Atomic Force Microscopy (AFM) of PMMA Scaffold Surface (Sa=4.2382 nm)

The AFM analysis revealed a rise in surface roughness from 3 to 4, signifying the incorporation of bioglass onto the PMMA surface. This increase in roughness provides clear evidence of the presence and successful integration of bioglass with the PMMA matrix, highlighting the modification of the surface characteristics. The observed change in surface roughness is indicative of the altered topography resulting from the addition of bioglass, a crucial aspect in applications where surface properties play a significant role, such as in biomaterials for tissue engineering.

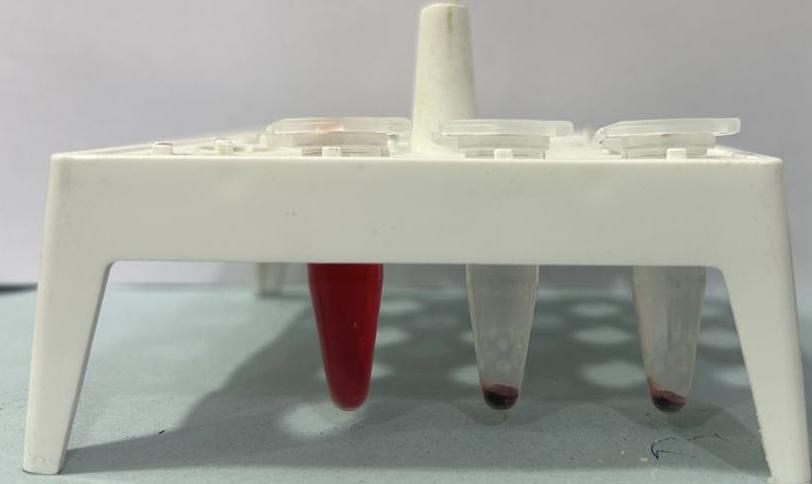


**Fig 9-** Light microscopy of pristine PMMA

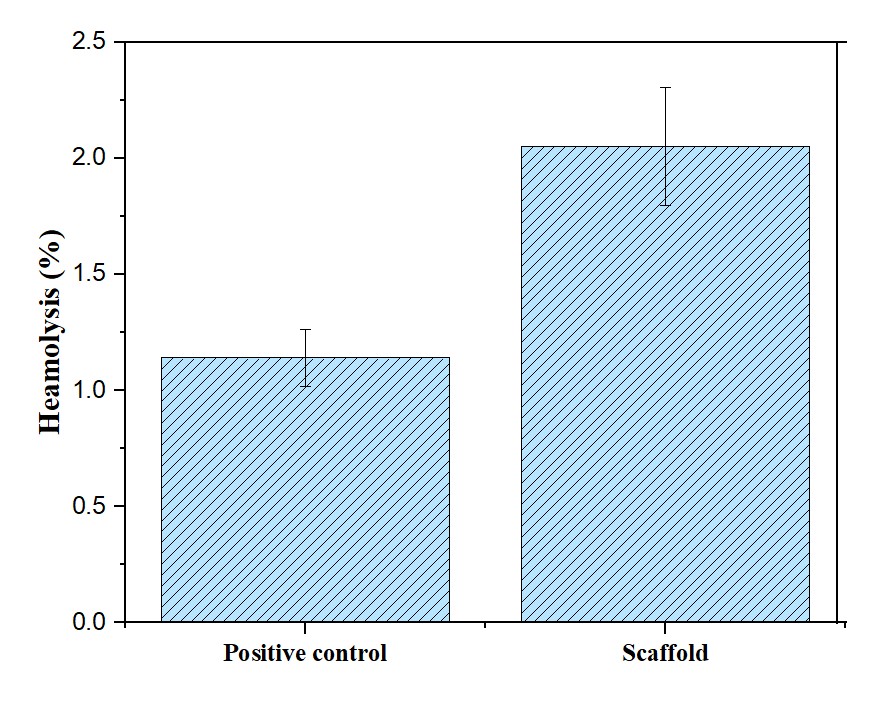
****

**Fig 10**- Light microscopy of PMMA scaffold

Light microscopy images comparing the pristine polymethyl methacrylate (PMMA) and the PMMA scaffold. The images provide a macroscopic view, allowing for the visual assessment of structural differences and modifications resulting from the incorporation of additional components, such as bioglass, into the PMMA matrix. The comparison aids in understanding the overall morphology and composition of the pristine and scaffolded PMMA, providing insights into the impact of modifications on the material's macroscopic appearance.

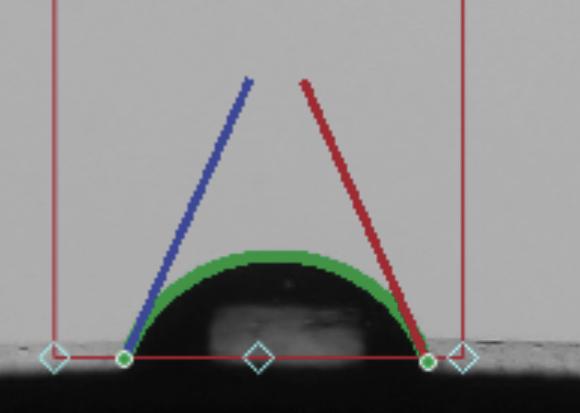


**Fig 11-** Hemocompatibility Assessment of PMMA/Bioglass Scaffold

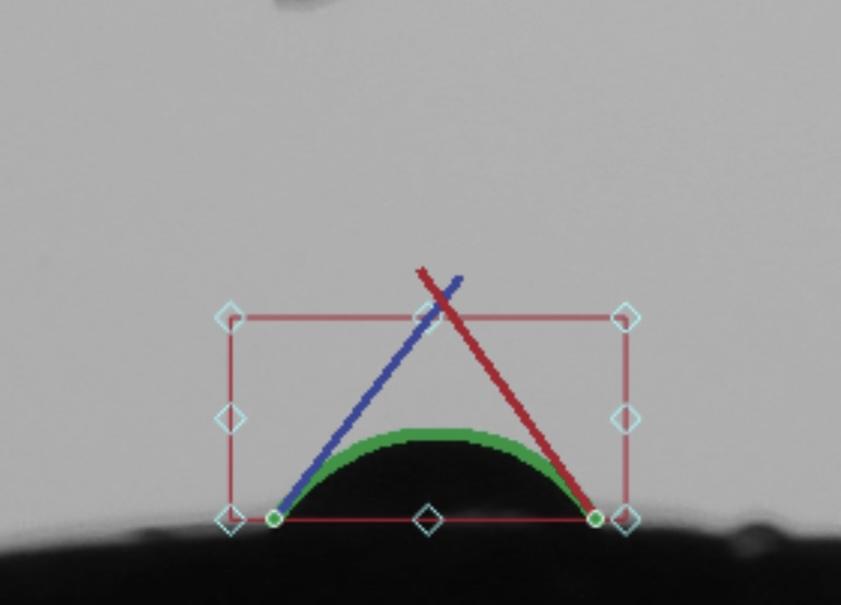
****

**Fig 12:** Comparing the hemocompatibility of a control sample with that of the scaffold material.

Hemocompatibility value less than 5 indicates the biocompatibility of the PMMA/Bioglass scaffold. The assessment demonstrates that the interaction between the scaffold and blood components falls within an acceptable range, suggesting minimal adverse effects on blood elements. A hemocompatibility value below 5 is indicative of the scaffold's ability to maintain compatibility with blood, a critical parameter for considering its suitability in biomedical applications.

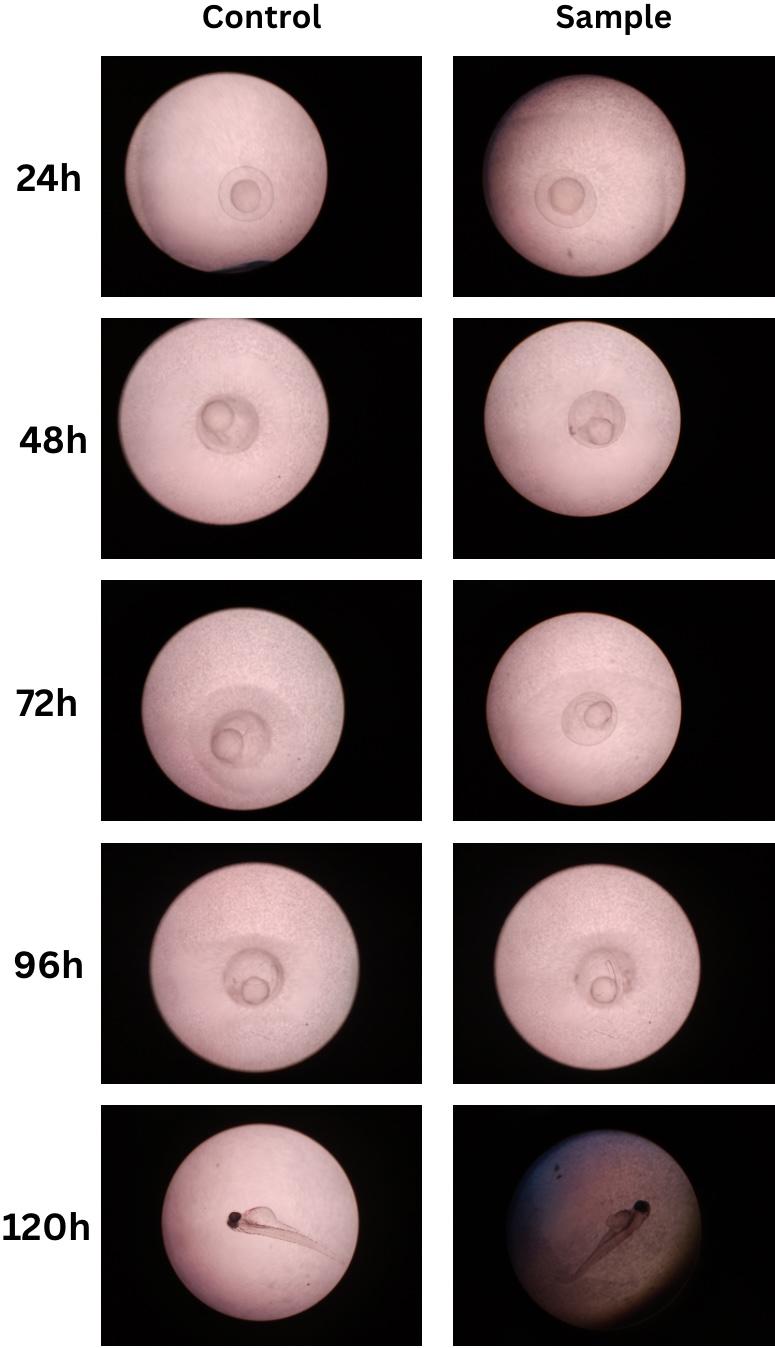


**Fig 13**- Contact Angle Measurement of Pristine PMMA (θ = 79.8°)

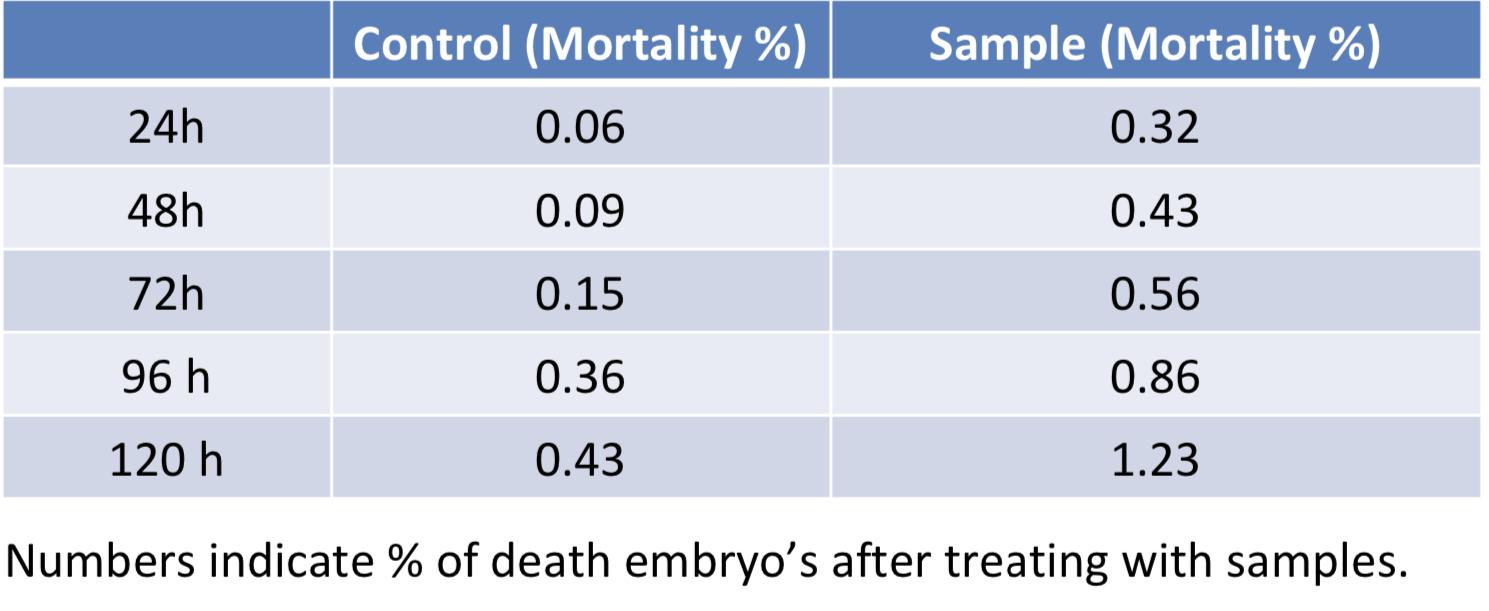


**Fig 14-** Contact Angle Measurement of PMMA Scaffold (θ = 66.0°)

A decreased contact angle signifies heightened hydrophilicity, rendering the scaffold more conducive to binding with blood cells. A reduced contact angle indicates an increased affinity for water, suggesting enhanced interactions between the scaffold's surface and aqueous environments. In the context of hemocompatibility, a more hydrophilic surface is favorable as it promotes better adhesion and interactions with blood cells, facilitating biocompatibility. This property is essential for biomaterials intended for applications involving blood contact, ensuring a favorable environment for biological processes without undesirable effects on blood components.

****

**Fig 15-** Zebrafish Embryological Assay for control and PMMA/Bioglass Scaffold

****

**Fig 16:**  Zebrafish Study - Mortality Percentages Over Time for Control and PMMA/Bioglass Scaffold Treatments

An observed mortality rate of under 10% in a zebrafish study indicates the biocompatibility of the PMMA/bioglass scaffold. This finding implies that the presence of the scaffold has minimal adverse effects on the zebrafish, suggesting a high degree of compatibility between the material and the living organisms. Biocompatibility is a critical factor in assessing the suitability of biomaterials for medical applications. In this context, a mortality rate below 10% signifies that the PMMA/bioglass scaffold is well-tolerated by the zebrafish, supporting its potential for use in biomedical and tissue engineering applications.

# DISCUSSION

Current composite scaffolds often use collagen as the polymer, which can lead to allergic reactions and pathogen transmission. An alternative natural polymer, chitosan, has been utilized to create scaffolds with bioglass, avoiding the issues associated with collagen. Chitosan possesses desirable properties like biocompatibility, biodegradability, and antibacterial qualities. Chitosan is a positively charged, linear polysaccharide derived from chitin, the second most abundant natural polysaccharide after cellulose. Chitin is found in the exoskeletons of insects, crabs, lobsters, and fungal cell walls. Since chitin is a byproduct in the food industry, chitosan production is economically feasible and environmentally advantageous[(Kachhara et al., 2020)](https://paperpile.com/c/a6ZUVZ/CedB). The problem of nonuniform degradation in physical mixtures of organic-inorganic biomaterials was addressed by establishing a chemical bond between chitosan and bioglass. To create a homogeneous composite material, chitosan was modified with γ-glycidoxypropyl trimethoxysilane and chemically linked with bioglass using the sol-gel method. [(Ramakrishnan et al., 2023; Shenoy & Maiti, 2023; J. S. Sindhu et al., 2023)](https://paperpile.com/c/a6ZUVZ/dyeiv+ehCVm+1BTCA) The gelation time of these hybrid samples was optimized by adjusting parameters like chitosan composition and temperature. The in vitro results revealed that the presence of nanoscale interactions significantly improved the bioactivity of chitosan. Hybrid scaffolds were manufactured with pore sizes ranging from 200 to 400 µm. These scaffolds were created by incorporating sodium bicarbonate as a gas foaming agent. The hybrids exhibit superior characteristics compared to pure chitosan, as well as physical mixtures of chitosan and bioglass. This makes them highly promising alternatives for applications in bone tissue engineering [(“Chitosan Based Polymer/bioglass Composites for Tissue Engineering Applications,” 2019)](https://paperpile.com/c/a6ZUVZ/sfGc). Bioglasses are favorable biomaterials for bone tissue engineering; however, their applications are limited due to their brittleness. In addition, the early failure in the interface is a common problem of composites of bioglass and a polymer with high mechanical strength. This effect is due to the phase separation, nonhomogeneous mixture, nonuniform mechanical strength, and different degradation properties of two compounds. To address these issues, in this study a nanoscale interaction between poly(methyl methacrylate) (PMMA) and bioactive glass was formed via silane coupling agent (3-trimethoxysilyl)propyl methacrylate (MPMA)[(Ravarian et al., 2015)](https://paperpile.com/c/a6ZUVZ/cNmW).The proposed deposition strategy can also be used for co-deposition of PMMA with other functional materials. The PMMA and composite films were tested for biomedical implant applications. The PMMA-alumina films showed statistically improved metabolic results compared to both the bare stainless steel substrate and pure PMMA films.[(Dharman et al., 2023; S. Sindhu et al., 2023; Sreenivasagan et al., 2023)](https://paperpile.com/c/a6ZUVZ/thhxB+zon0M+jjZKi) Alkaline phosphatase (ALP) activity affirmed the bioactivity and osteoconductive potential of PMMA and composite films. PMMA-alumina films showed greater ALP activity than both the PMMA-coated and uncoated stainless steel [(“Impact of Copper on in-Vitro Biomineralization, Drug Release Efficacy and Antimicrobial Properties of Bioactive Glasses,” 2020)](https://paperpile.com/c/a6ZUVZ/5Q6r). A hemocompatibility value of less than 5 indicates that the PMMA/bioglass scaffold is considered biocompatible. Hemocompatibility refers to the ability of a material to interact with blood components without causing adverse reactions or hemolysis. A hemocompatible material is crucial in biomedical applications to ensure that it does not trigger harmful responses when it comes into contact with blood. By achieving a hemocompatibility value of less than 5, the PMMA/bioglass scaffold demonstrates its compatibility with blood and suggests that it can be safely used in contact with blood or within the circulatory system. This finding further supports the biocompatibility of the scaffold and suggests its potential suitability for tissue engineering and regenerative medicine applications, particularly in bone replacement therapy where it may come into contact with blood vessels[(Ravarian et al., 2013)](https://paperpile.com/c/a6ZUVZ/XvVt). The selection of the polymer in hybrid structures significantly influences their structure and properties through chemical interactions between organic and inorganic components. However, incorporating many biodegradable polymers into the sol is challenging due to poor solubility and phase incompatibility. In this study, poly(γ-glutamic acid) (γ-PGA), a microbial polyamino acid derived from D- and l-glutamic acid units, was chosen for its biocompatibility, enzymatic degradability, and non-immunogenic properties. γ-PGA's side group contains a reactive carboxylic acid (COOH), allowing for functionalization. Notably, the degradation product, glutamic acid, is a collagen component and facilitates hydroxyapatite nucleation during bone formation. Thus, employing γ-PGA in hybrid systems holds significant promise for bone regeneration applications[(Atkinson et al., 2021)](https://paperpile.com/c/a6ZUVZ/L38p).Bioglass, the pioneering synthetic biomaterial that establishes a chemical bond with bone, exhibits brittleness despite its ability to mimic the porous structure of bone. This brittleness can be addressed by utilizing sol–gel derived hybrids, which offer nanoscale co-networks of silica and organic polymer.[(Ajay et al., 2023; Chokkattu et al., 2023; Padarthi et al., 2023)](https://paperpile.com/c/a6ZUVZ/sFSw4+KkvJg+xnNCy) These hybrids present the potential for unique physical properties and controlled, homogeneous biodegradation. In the quest to enhance these properties, copolymers of methyl methacrylate (MMA) and 3-(trimethoxysilyl)propyl methacrylate (TMSPMA) have been employed due to their self-hardening characteristics. However, the impact of a well-defined poly(MMA-co-TMSPMA) architecture within the hybrid system remains unexplored. In this study, copolymers with linear, randomly branched, and star-shaped structures were synthesized using reversible addition–fragmentation chain transfer (RAFT) polymerization. These copolymers were then utilized to fabricate hybrids, revealing that the three-dimensional polymer structure significantly influenced mechanical properties. The resulting hybrids exhibited a higher strain to failure while maintaining a compressive strength similar to sol–gel glass[(Chung et al., 2016)](https://paperpile.com/c/a6ZUVZ/2Ia2) Silicate-based [(Delia et al., 2020)](https://paperpile.com/c/a6ZUVZ/wLGY). bioactive glasses, valued for their versatile chemical composition and favorable osteoconductive and osteoinductive properties, find potential applications in orthopedic and dental fields. Initially produced through the melt-derived method, they are now predominantly synthesized using the sol–gel technique. This method offers advantages such as homogenous composition, low sintering temperature, and the ability to tailor gel structure. The sol–gel approach is highly adaptable, allowing the development of nanoparticles, mesoporous structures, electrospun fibers, 3D printable scaffolds, and template-assisted 3D structures. This flexibility aligns with the "Lab-to-product" concept, enabling the rapid realization of diverse applications. Notably, combining sol–gel bioactive glass with 3D printing hydrogel techniques has facilitated the creation of futuristic, customized scaffolds [(Chung et al., 2017)](https://paperpile.com/c/a6ZUVZ/0fhc). Molecular-scale co-network hybrids, integrating organic and inorganic components, present promising biomaterials that address the brittleness of bioactive glass and enhance the strength of polymers [(Chung et al., 2016)](https://paperpile.com/c/a6ZUVZ/2Ia2). Methacrylate polymers are particularly advantageous as the organic component due to their potential to be tailored through controlled polymerization, resulting in intricate architectures capable of bonding to silicate networks. Prior investigations have indicated that the mechanical properties of hybrids can be altered by the polymer's architecture and molar mass (MM). However, for these hybrids to be employed as tissue engineering scaffolds, ensuring biodegradability is crucial. The templates must undergo remodeling by host tissue, and degradation by-products should either completely biodegrade or be eliminated through renal excretion [(Dhinasekaran & Kumar, 2022)](https://paperpile.com/c/a6ZUVZ/fDmB).

# CONCLUSION

Porous PMMA/bioglass scaffolds emerge as highly promising materials for applications in tissue engineering and regenerative medicine. The synergistic combination of PMMA and bioglass imparts a distinctive equilibrium between mechanical strength and bioactivity, rendering these scaffolds particularly well-suited for use in bone tissue engineering. The porous structure of the scaffolds is instrumental in facilitating crucial biological processes such as cell adhesion, proliferation, and osteogenic differentiation. This means that the scaffolds not only provide a supportive framework for cells to adhere and proliferate but also create an environment conducive to the development of bone-forming cells. In essence, porous PMMA/bioglass scaffolds have the potential to play a pivotal role in promoting bone regeneration by fostering the essential cellular activities required for the restoration of damaged or lost bone tissue.

# SCOPE OF FUTURE RESEARCH

* Animal models can be used to assess the scaffold's biocompatibility, degradation behavior, and tissue regeneration potential. Combining the scaffold with biomaterials that possess antibacterial properties can provide an enhanced environment for tissue regeneration. Studies can focus on adjusting the scaffold composition, porosity, or incorporating reinforcing materials to enhance strength, elasticity, and load-bearing capacity.
* Explore the incorporation of drug delivery systems within PMMA cement to provide localized and controlled release of therapeutic agents. This can aid in preventing infections, promoting tissue regeneration, and addressing inflammation.
* Facilitate the translation of research findings into clinical practice by conducting well-designed clinical trials, addressing safety concerns, and evaluating the long-term performance of PMMA cement with innovative additives in human patients.

# REFERENCEs

1. [Ajay, R., JafarAbdulla, M. U., Sivakumar, J. S., Baburajan, K., Rakshagan, V., & Eyeswarya, J. (2023). Dental alloy adhesive primers and bond strength at alloy-resin interface: A systematic review and meta-analyses. The Journal of Contemporary Dental Practice, 24(8), 521–544. https://doi.org/](http://paperpile.com/b/a6ZUVZ/KkvJg)[10.5005/jp-journals-10024-3514](http://dx.doi.org/10.5005/jp-journals-10024-3514)
2. [Akmal, N. L. H. B., & Duraisamy, R. (2020). Evaluation of the Marginal Fit of Implant-Supported Crowns. Journal of Long-Term Effects of Medical Implants, 30(3). https://doi.org/](http://paperpile.com/b/a6ZUVZ/naSb)[10.1615/JLongTermEffMedImplants.2020035935](http://dx.doi.org/10.1615/JLongTermEffMedImplants.2020035935)
3. [Aparna, J., Maiti, S., & Jessy, P. (2021). Polyether ether ketone - As an alternative biomaterial for Metal Richmond crown-3-dimensional finite element analysis. Journal of Conservative Dentistry: JCD, 24(6), 553–557. https://doi.org/](http://paperpile.com/b/a6ZUVZ/IZRj)[10.4103/jcd.jcd\_638\_20](http://dx.doi.org/10.4103/jcd.jcd_638_20)
4. [Atkinson, I., Seciu-Grama, A. M., Mocioiu, O. C., Mocioiu, A. M., Predoana, L., Voicescu, M., Cusu, J. P., Grigorescu, R. M., Ion, R. M., & Craciunescu, O. (2021). Preparation and Biocompatibility of Poly Methyl Methacrylate (PMMA)-Mesoporous Bioactive Glass (MBG) Composite Scaffolds. Gels (Basel, Switzerland), 7(4). https://doi.org/](http://paperpile.com/b/a6ZUVZ/L38p)[10.3390/gels7040180](http://dx.doi.org/10.3390/gels7040180)
5. [Chitosan based polymer/bioglass composites for tissue engineering applications. (2019). Materials Science and Engineering: C, 96, 955–967. https://doi.org/](http://paperpile.com/b/a6ZUVZ/sfGc)[10.1016/j.msec.2018.12.026](http://dx.doi.org/10.1016/j.msec.2018.12.026)
6. Chehelgerdi M., Chehelgerdi, M., Allela, O. Q. B., Pecho, R. D. C., Jayasankar, N., Rao, D. P. & Akhavan-Sigari, R. (2023). Progressing nanotechnology to improve targeted cancer treatment: overcoming hurdles in its clinical implementation. Molecular cancer, 22(1), 169.
7. [Chokkattu, J. J., Mary, D. J., Shanmugam, R., & Neeharika, S. (2022). Embryonic Toxicology Evaluation of Ginger- and Clove-mediated Titanium Oxide Nanoparticles-based Dental Varnish with Zebrafish. The Journal of Contemporary Dental Practice, 23(11), 1157–1162. https://doi.org/](http://paperpile.com/b/a6ZUVZ/dYZx)[10.5005/jp-journals-10024-3436](http://dx.doi.org/10.5005/jp-journals-10024-3436)
8. [Chokkattu, J. J., Mary, D. J., Shanmugam, R., & Neeharika, S. (2023). Evaluation clove ginger-mediated titanium oxide nanoparticles-based dental varnish against Streptococcus mutans Lactobacillus Species: vitro study. World J Dent, 14(3), 233–237.](http://paperpile.com/b/a6ZUVZ/xnNCy)
9. [Chung, J. J., Fujita, Y., Li, S., Stevens, M. M., Kasuga, T., Georgiou, T. K., & Jones, J. R. (2017). Biodegradable inorganic-organic hybrids of methacrylate star polymers for bone regeneration. Acta Biomaterialia, 54, 411–418. https://doi.org/](http://paperpile.com/b/a6ZUVZ/0fhc)[10.1016/j.actbio.2017.03.008](http://dx.doi.org/10.1016/j.actbio.2017.03.008)
10. [Chung, J. J., Li, S., Stevens, M. M., Georgiou, T. K., & Jones, J. R. (2016). Tailoring Mechanical Properties of Sol–Gel Hybrids for Bone Regeneration through Polymer Structure. https://doi.org/](http://paperpile.com/b/a6ZUVZ/2Ia2)[10.1021/acs.chemmater.6b01941](http://dx.doi.org/10.1021/acs.chemmater.6b01941)
11. [Delia, A., Deering, J., Clifford, A., Lee, B., Grandfield, K., & Zhitomirsky, I. (2020). Electrophoretic deposition of polymethylmethacrylate and composites for biomedical applications. Colloids Surf B Biointerfaces, 188.](http://paperpile.com/b/a6ZUVZ/wLGY)
12. [Dharman, S., Maragathavalli, G., Shanmugam, R., & Shanmugasundaram, K. (2023). Curcumin mediated gold nanoparticles analysis its antioxidant, anti-inflammatory, antimicrobial activity against oral pathogens. Pesquisa Brasileira Em Odontopediatria E Clínica Integrada, 23.](http://paperpile.com/b/a6ZUVZ/zon0M)
13. [Dhinasekaran, D., & Kumar, A. (2022). Fabrication of Bioactive Structures from Sol-Gel Derived Bioactive Glass. In Bioactive Glasses and Glass-Ceramics (pp. 87–117). John Wiley & Sons.](http://paperpile.com/b/a6ZUVZ/fDmB)
14. [Durgalakshmi, D., & Balakumar, S. (2015). Analysis of solvent induced porous PMMA-Bioglass monoliths by the phase separation method--mechanical and in vitro biocompatible studies. Physical Chemistry Chemical Physics: PCCP, 17(2), 1247–1256. https://doi.org/](http://paperpile.com/b/a6ZUVZ/PFt3)[10.1039/c4cp03515a](http://dx.doi.org/10.1039/c4cp03515a)
15. [Effect of ZnO reinforcement on the compressive properties, in vitro bioactivity, biodegradability and cytocompatibility of bone scaffold developed from bovine bone-derived HAp and PMMA. (2019). Ceramics International, 45(16), 20331–20345. https://doi.org/](http://paperpile.com/b/a6ZUVZ/IxvU)[10.1016/j.ceramint.2019.07.006](http://dx.doi.org/10.1016/j.ceramint.2019.07.006)
16. [Elakkiya, K., Bargavi, P., & Balakumar, S. (2023). 3D interconnected porous PMMA scaffold integrating with advanced nanostructured CaP-based biomaterials for rapid bone repair and regeneration. Journal of the Mechanical Behavior of Biomedical Materials, 147, 106106. https://doi.org/](http://paperpile.com/b/a6ZUVZ/VBrW)[10.1016/j.jmbbm.2023.106106](http://dx.doi.org/10.1016/j.jmbbm.2023.106106)
17. [Evaluation Composite Restoration Posterior Teeth Proanthocyanidin Pretreatment Liner Using Fédération Dentaire Internationale Criteria: Split-mouth Randomized Controlled Trial. (n.d.).](http://paperpile.com/b/a6ZUVZ/2MoHV)
18. [Fabrication and in vitro characterization of electrospun poly (γ-glutamic acid)-silica hybrid scaffolds for bone regeneration. (2016). Polymer, 91, 106–117. https://doi.org/](http://paperpile.com/b/a6ZUVZ/brH4)[10.1016/j.polymer.2016.03.056](http://dx.doi.org/10.1016/j.polymer.2016.03.056)
19. [Floroian, L., Popescu, A., Serban, N., & Mihailescu, I. (2011). Polymer-Bioglass Composite Coatings: A Promising Alternative For Advanced Biomedical Implants. In Metal, Ceramic and Polymeric Composites for Various Uses. IntechOpen. https://doi.org/](http://paperpile.com/b/a6ZUVZ/23jD)[10.5772/18339](http://dx.doi.org/10.5772/18339)
20. [Floroian, L., Samoila, C., Badea, M., Munteanu, D., Ristoscu, C., Sima, F., Negut, I., Chifiriuc, M. C., & Mihailescu, I. N. (2015). Stainless steel surface biofunctionalization with PMMA-bioglass coatings: compositional, electrochemical corrosion studies and microbiological assay. Journal of Materials Science. Materials in Medicine, 26(6), 195. https://doi.org/](http://paperpile.com/b/a6ZUVZ/WLUx)[10.1007/s10856-015-5527-y](http://dx.doi.org/10.1007/s10856-015-5527-y)
21. [G., K. E. V., & Ganapathy, D. (2022). Operator errors in failed composite restoration-A review. Int J Dent Oral Sci, 8(7), 2941–2944.](http://paperpile.com/b/a6ZUVZ/JdGSo) <https://www.academia.edu/download/73121996/IJDOS_2377_8075_08_702.pdf>
22. [Impact of copper on in-vitro biomineralization, drug release efficacy and antimicrobial properties of bioactive glasses. (2020). Materials Science and Engineering: C, 109, 110598. https://doi.org/](http://paperpile.com/b/a6ZUVZ/5Q6r)[10.1016/j.msec.2019.110598](http://dx.doi.org/10.1016/j.msec.2019.110598)
23. [Im, S. B., Tripathi, G., Le, T. T. T., & Lee, B. T. (2021). Early-stage bone regeneration of hyaluronic acid supplemented with porous 45s5 bioglass-derived granules: an injectable system. Biomedical Materials , 16(4). https://doi.org/](http://paperpile.com/b/a6ZUVZ/6dsO)[10.1088/1748-605X/ac058f](http://dx.doi.org/10.1088/1748-605X/ac058f)
24. [Kachhara, S., Nallaswamy, D., Ganapathy, D. M., Sivaswamy, V., & Rajaraman, V. (2020). Assessment of intraoral scanning technology for multiple implant impressions - A systematic review and meta-analysis. Journal of Indian Prosthodontic Society, 20(2), 141–152. https://doi.org/](http://paperpile.com/b/a6ZUVZ/CedB)[10.4103/jips.jips\_379\_19](http://dx.doi.org/10.4103/jips.jips_379_19)
25. [Kasabwala, H., Nallaswamy, D., Subhashree, R., & Ahmed, N. (2021). Evaluation Of Overall Marginal Accuracy Of DMLS Copings Fabricated Using 3 Different DMLS Printing Machines. Int J Dentistry Oral Sci, 8(7), 3335–3340.](http://paperpile.com/b/a6ZUVZ/WVmOJ) <https://www.academia.edu/download/73133070/IJDOS_2377_8075_08_7085.pdf>
26. [Keerthana, T., & Ramesh, S. (2021). Knowledge, attitude and practice survey on awareness of the association between diet and dental erosion. International Journal of Dentistry and Oral Science, 8(2), 1533–1540.](http://paperpile.com/b/a6ZUVZ/XCQPI) <https://www.academia.edu/download/72505812/IJDOS_2377_8075_08_2026.pdf>
27. [Kumar, I. L., & Ramesh, S. (2021). Knowledge, Attitude and Practices (KAP) survey of shade selection for indirect veneers. Int J Dent Oral Sci, 26, 2856–2864.](http://paperpile.com/b/a6ZUVZ/Vszit) <https://www.researchgate.net/profile/Sindhu-Ramesh/publication/353259903_Knowledge_Attitude_And_Practices_KAP_Survey_Of_Shade_Selection_For_Indirect_Veneers/links/60efe4d60859317dbde2f353/Knowledge-Attitude-And-Practices-KAP-Survey-Of-Shade-Selection-For-Indirect-Veneers.pdf>
28. [Murugesan, A. (2021). Saravana Dinesh SP evaluation of shear bond strength of ceramic brackets with two different base designs: An in-vitro study. Int J Dentistry Oral Sci.](http://paperpile.com/b/a6ZUVZ/5DBMT) <https://www.academia.edu/download/72981941/IJDOS_2377_8075_08_304.pdf>
29. Nikalje, A. V., Tajane, S. T., Kocharekar, A., Vekariya, D., & Patil, H. (2024, April). Detecting Cancer through Analysis of Histopathological Images. In 2024 International Conference on Expert Clouds and Applications (ICOECA) (pp. 579-585). IEEE.
30. [Negut, I., Floroian, L., Ristoscu, C., Mihailescu, C. N., Mirza Rosca, J. C., Tozar, T., Badea, M., Grumezescu, V., Hapenciuc, C., & Mihailescu, I. N. (2020). Functional Bioglass-Biopolymer Double Nanostructure for Natural Antimicrobial Drug Extracts Delivery. Nanomaterials (Basel, Switzerland), 10(2). https://doi.org/](http://paperpile.com/b/a6ZUVZ/0FSq)[10.3390/nano10020385](http://dx.doi.org/10.3390/nano10020385)
31. [Padarthi, L. C., Anumula, L., Chinni, S. K., Sannapureddy, S., & Govula, K. (2023). Evaluation Composite Restoration Posterior Teeth Proanthocyanidin Pretreatment Liner Using Fédération Dentaire Internationale Criteria: Split-mouth Randomized Controlled Trial. International Journal Prosthodontics Restorative Dentistry, 13(4), 191–200.](http://paperpile.com/b/a6ZUVZ/sFSw4)
32. [Pranati, T., Ranjan, M., & Sandeep, A. H. (2021). Marginal adaptability custom made cast post made different techniques-a literature review. Int J Dentistry Oral Sci, 8(8), 3954–3959.](http://paperpile.com/b/a6ZUVZ/vtZVr)
33. [Rajeshkumar, S., & Lakshmi, T. (2021). Biomedical potential of zinc oxide nanoparticles synthesized using plant extracts. Int J Dent Oral Sci, 8, 4160–4163.](http://paperpile.com/b/a6ZUVZ/MozEh) <https://www.academia.edu/download/73182974/IJDOS_2377_8075_08_8120.pdf>
34. [Ramakrishnan, M., Shanmugam, R., Neeharika, S., Chokkattu, J. J., Thangavelu, L., & Khanna, N. (2023). Anti-inflammatory activity and cytotoxic effect of ginger and Rosemary-mediated titanium oxide nanoparticles-based dental varnish. World Journal of Dentistry, 14(9), 761–765. https://doi.org/](http://paperpile.com/b/a6ZUVZ/ehCVm)[10.5005/jp-journals-10015-2299](http://dx.doi.org/10.5005/jp-journals-10015-2299)
35. [Ravarian, R., Craft, M., & Dehghani, F. (2015). Enhancing the biological activity of chitosan and controlling the degradation by nanoscale interaction with bioglass. Journal of Biomedical Materials Research. Part A, 103(9), 2898–2908. https://doi.org/](http://paperpile.com/b/a6ZUVZ/cNmW)[10.1002/jbm.a.35423](http://dx.doi.org/10.1002/jbm.a.35423)
36. [Ravarian, R., Zhong, X., Barbeck, M., Ghanaati, S., Kirkpatrick, C. J., Murphy, C. M., Schindeler, A., Chrzanowski, W., & Dehghani, F. (2013). Nanoscale chemical interaction enhances the physical properties of bioglass composites. ACS Nano, 7(10), 8469–8483. https://doi.org/](http://paperpile.com/b/a6ZUVZ/XvVt)[10.1021/nn402157n](http://dx.doi.org/10.1021/nn402157n)
37. [Sakthi, S., (2021). Thymus vulgaris mediated selenium nanoparticles, characterization and its antimicrobial activity - an in vitro study. International Journal of Dentistry and Oral Science, 3516–3521. https://doi.org/](http://paperpile.com/b/a6ZUVZ/yWRa5)[10.19070/2377-8075-21000718](http://dx.doi.org/10.19070/2377-8075-21000718)
38. [Sathya, I., Pitchai, A., Subhapradha, N., & Ramasamy, P. (2024). Chitosan from gladius of Doryteuthis sibogae and their capability to inhibit the blood clotting and its antibacterial effect against human pathogens. Process Biochemistry (Barking, London, England), 146, 109–114. https://doi.org/](http://paperpile.com/b/a6ZUVZ/Kxx1)[10.1016/j.procbio.2024.07.016](http://dx.doi.org/10.1016/j.procbio.2024.07.016)
39. [Sa, Y., Yang, F., Wang, Y., Wolke, J. G. C., & Jansen, J. A. (2018). Modifications of Poly(Methyl Methacrylate) Cement for Application in Orthopedic Surgery. Advances in Experimental Medicine and Biology, 1078, 119–134. https://doi.org/](http://paperpile.com/b/a6ZUVZ/dfmi)[10.1007/978-981-13-0950-2\_7](http://dx.doi.org/10.1007/978-981-13-0950-2_7)
40. [Shanmugam, V., Subhapradha, N., Ramasamy, P., Raveendran, S., Srinivasan, A., & Shanmugam, A. (2013). Physico-chemical characteristics and antioxidant efficacy of chitosan from the internal shell of spineless cuttlefish Sepiella inermis. Preparative Biochemistry and Biotechnology, 43, 696–716.](http://paperpile.com/b/a6ZUVZ/3j5s)
41. [Shenoy, N. D., & Maiti, S. (2023). Evaluation marginal fit CAD/CAM crowns using CBCT digital scanners. Annals Dental Specialty, 11(3-2023), 37–44.](http://paperpile.com/b/a6ZUVZ/dyeiv)
42. [Sindhu, J. S., Maiti, S., & Nallaswamy, D. (2023). Comparative analysis on efficiency and accuracy of parallel confocal microscopy and three-dimensional in motion video with triangulation technology-based intraoral scanner under influence of moisture and mouth opening - A crossover clinical trial. Journal of Indian Prosthodontic Society, 23(3), 234–243. https://doi.org/](http://paperpile.com/b/a6ZUVZ/1BTCA)[10.4103/jips.jips\_65\_23](http://dx.doi.org/10.4103/jips.jips_65_23)
43. [Sindhu, S., Maiti, S., & Nallaswamy, D. (2023). Factors affecting accuracy intraoral scanners-a systematic review. Annals Dental Specialty, 11(1-2023), 40–52.](http://paperpile.com/b/a6ZUVZ/thhxB)
44. [Sreenivasagan, S., Subramanian, A. K., Mohanraj, K. G., & Kumar, R. S. (2023). Assessment of toxicity of Green Synthesized Silver Nanoparticle-coated Titanium Mini-implants with Uncoated Mini-implants: Comparison in an Animal Model Study. The Journal of Contemporary Dental Practice, 24(12), 944–950. https://doi.org/](http://paperpile.com/b/a6ZUVZ/jjZKi)[10.5005/jp-journals-10024-3577](http://dx.doi.org/10.5005/jp-journals-10024-3577)
45. [Subramanian, E., Ravindran, V., & Jeevanandan, G. (2021). Comparison of amount of tooth reduction in primary first molar for stainless steel, zirconia and fibre-glass crowns–in-vitro study. International Journal of Dentistry and Oral Science, 8(7), 3427–3430.](http://paperpile.com/b/a6ZUVZ/fC6jw) <https://www.academia.edu/download/73139190/IJDOS_2377_8075_08_7103.pdf>
46. [Thiripelu, P., Manjunathan, J., Revathi, M., & Ramasamy, P. (2024). Removal of hexavalent chromium from electroplating wastewater by ion-exchange in presence of Ni(II) and Zn(II) ions. Journal of Water Process Engineering, 58(104815), 104815. https://doi.org/](http://paperpile.com/b/a6ZUVZ/JGnG)[10.1016/j.jwpe.2024.104815](http://dx.doi.org/10.1016/j.jwpe.2024.104815)
47. [Tiwari, A., & Jain, R. K. (2021). The effect of motivational and reminder therapy on the compliance of patients wearing fixed appliances. Int J Dent Oral Sci, 8(7), 3303–3305.](http://paperpile.com/b/a6ZUVZ/GwhRT) <https://www.academia.edu/download/73131909/IJDOS_2377_8075_08_7079.pdf>
48. [Varghese, R., Maliael, M., & Subramanian, A. (2023). Antibacterial activity of nanoparticle-coated orthodontic archwires: A systematic review. Journal of International Oral Health: JIOH, 15(1), 1. https://doi.org/](http://paperpile.com/b/a6ZUVZ/Rxmeb)[10.4103/jioh.jioh\_152\_22](http://dx.doi.org/10.4103/jioh.jioh_152_22)
49. [Venugopalan, S. (2021). Retrospective Analysis of Immediate Implants: A Prism with a Different Dimension. Journal of Long-Term Effects of Medical Implants, 31(2), 51–54. https://doi.org/](http://paperpile.com/b/a6ZUVZ/j63m)[10.1615/JLongTermEffMedImplants.2021038020](http://dx.doi.org/10.1615/JLongTermEffMedImplants.2021038020)