

# 45S5 Bioactive Glass: Comprehensive Swot Analysis and Future Prospects in Tissue Engineering

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**Abstract:** 45S5 bioactive glass (Bioglass®), introduced by Larry Hench in 1969, remains a foundational material in regenerative medicine due to its excellent ability to form a hydroxycarbonate apatite (HCA) layer and directly bond with bone and soft tissues [1–3]. This review presents a structured SWOT (Strengths, Weaknesses, Opportunities, and Threats) analysis to critically assess the material's current applications and upcoming prospects. The strengths of 45S5 lie in its remaining bioactivity, stimulatory ion release ( $Ca^{2+}$ ,  $Na^+$ ,  $PO_4^{3-}$ ), and wide-ranging clinical authentication in craniofacial, dental, and orthopedic fields [4–7]. Its chemical effortlessness, scalability, and role as a standard in biomaterials research further emphasize its significance [8–10]. However, prominent weaknesses include poor mechanical strength, brittleness, high sodium content, and a slight thermal processing window that complicates scaffold fabrication and sintering [11–13]. Emerging opportunities encompass the development of composites, ion-doped derivatives, mesoporous architectures, and additive manufacturing to enhance mechanical properties and functionality [14–17]. The combination of ions such as  $Ag^+$ ,  $Sr^{2+}$ , or  $Zn^{2+}$  offers further antibacterial and osteogenic capabilities [18]. Additive manufacturing techniques also cover the way for patient-specific scaffolds with tailored degradation and bioactivity profiles [19]. Conversely, 45S5 faces intimidation from next-generation glasses like borate-based and 13-93 compositions, which offer greater mechanical properties or bio functionality [20–22]. Regulatory hurdles, biological variability, and environmental concerns linked to high-temperature processing pose further challenges [23–25]. In conclusion, while 45S5 bioactive glass is not without limitations, its verified performance and adaptability ensure its continued relevance. Strategic innovations across composition, structure, and processing are key to maintaining its clinical utility and expanding its role in personalized regenerative therapies.

**Keywords:** 45S5 bioactive glass, bone bonding ability, ion release therapy, scaffold design challenges, regenerative medicine applications

## 1. Introduction

The field of biomaterials has seen remarkable progress over the past few decades, with bioactive glasses standing out due to their ability to bond chemically with bone and soft tissue. Among them, 45S5 bioactive glass, commonly referred to as Bioglass®, represents a milestone material introduced by Larry Hench in 1969 for biomedical applications such as bone regeneration and dental repair [1]. This particular glass has a unique composition of 45 wt%  $SiO_2$ , 24.5 wt%  $Na_2O$ , 24.5 wt%  $CaO$ , and 6 wt%  $P_2O_5$ , which imparts it with extraordinary bioactivity and biocompatibility [2]. The rapid formation of a hydroxycarbonate apatite (HCA) layer on its surface upon implantation facilitates a direct bond with host tissues, making it a benchmark for bioactive materials [3].

Despite its pioneering success and long-standing clinical usage, 45S5 bioactive glass also exhibits several limitations that restrict its broader application, especially in load-bearing orthopedic scenarios. Its inherently low mechanical strength and brittleness, combined with a narrow thermal processing window, make it challenging to fabricate robust and complex scaffolds using conventional sintering or melting techniques [4]. Consequently, newer compositions such as borate-based and 13-93 bioactive glasses have emerged, claiming to offer superior mechanical and processing properties without compromising bioactivity [5,6].

Given this context, it becomes crucial to assess the current and future potential of 45S5 bioactive glass systematically. A SWOT (Strengths, Weaknesses, Opportunities, and Threats) analysis offers a strategic framework for evaluating materials science research from both technical and translational standpoints [7]. It aids in identifying key material advantages,

uncovering intrinsic limitations, exploring untapped potential, and understanding external pressures that may shape future developments.

This paper aims to provide a comprehensive SWOT-based review of 45S5 bioactive glass, integrating insights from materials science, biomedical engineering, and clinical practice. The goal is to not only highlight the enduring relevance of this material but also to chart a roadmap for its evolution in response to emerging technologies and clinical needs. Recent advances such as polymer and ceramic composites [8], ion-substituted variants [9], additive manufacturing [10], and sol-gel synthesis routes [11] are discussed as mechanisms to harness opportunities and mitigate threats.

Moreover, this review includes a comparative evaluation with next-generation bioactive glasses to position 45S5 within the competitive biomaterials landscape. By incorporating insights from over 30 high-impact studies published in Q1 journals, this work endeavours to serve as a guiding reference for researchers and clinicians aiming to develop advanced bioactive glass-based solutions for regenerative medicine.

## 2. Material Composition and Historical Context

The development of 45S5 bioactive glass marked a transformative moment in the field of biomedical materials. Invented by Larry Hench and colleagues in the late 1960s at the University of Florida, 45S5 was developed in response to a U.S. Army challenge to develop materials that could bond to living bone [1,2]. Unlike bioinert materials such as titanium or alumina, 45S5 demonstrated an unprecedented ability to form a biologically active hydroxycarbonate apatite (HCA)

layer on its surface in physiological environments, thereby initiating strong chemical bonds with bone [3].

The composition of 45S5 is precisely balanced:

- **45 wt% SiO<sub>2</sub>** provides the backbone for the silicate network,
- **24.5 wt% CaO** and **24.5 wt% Na<sub>2</sub>O** act as network modifiers to facilitate ion release,
- **6 wt% P<sub>2</sub>O<sub>5</sub>** contributes to the nucleation of apatite crystallites [4].

This relatively high sodium and calcium content makes the glass less chemically durable, but enhances its reactivity with physiological fluids, which is the foundation of its bioactivity [5]. The glass undergoes a five-step reaction mechanism upon immersion in body fluid: leaching of Na<sup>+</sup> and Ca<sup>2+</sup>, dissolution of SiO<sub>2</sub>, formation of a silica-rich layer, deposition of Ca<sup>2+</sup> and PO<sub>4</sub><sup>3-</sup>, and ultimately formation of a crystalline HCA layer [6]. This process is responsible for triggering cellular responses such as osteoblast adhesion, proliferation, and differentiation [7].

Over the past five decades, 45S5 bioactive glass has been commercialized in various medical applications. It is incorporated in bone graft substitutes (e.g., NovaBone®), middle ear implants, and dental care products like PerioGlas® [8]. It is also the basis for S53P4, a slightly modified version with higher silica content and lower Na<sub>2</sub>O concentration used for antimicrobial bone void fillers [9]. Its success led to widespread interest in other silicate, borate, and phosphate glass systems for bioactive applications [10].

Nevertheless, the original melt-derived 45S5 glass has inherent limitations due to its processing characteristics. Its narrow sintering window between the glass transition temperature (~550 °C) and crystallization onset (~610 °C) makes it prone to devitrification, limiting its application in scaffold fabrication [11]. Moreover, the high Na<sub>2</sub>O content can lead to localized pH elevations upon implantation, raising concerns about cytocompatibility in some settings [12].

Efforts to circumvent these limitations have led to innovations such as sol-gel synthesis, which allows for lower-temperature processing and greater textural control [13]. Additionally, researchers have explored compositional modifications, such as incorporating therapeutic ions (e.g., Ag<sup>+</sup>, Sr<sup>2+</sup>, Zn<sup>2+</sup>), to enhance properties like antibacterial activity, osteogenesis, and angiogenesis without compromising biocompatibility [14–16].

Today, 45S5 bioactive glass remains a benchmark material in the field of regenerative medicine, with hundreds of publications attesting to its efficacy and versatility. However, its clinical dominance is now challenged by next-generation glasses and composite systems designed to address its shortcomings. Understanding the original composition and its historical context provides a vital foundation for interpreting the strategic analysis that follows.

### 3. SWOT Analysis of 45S5 Bioactive Glass

#### 3.1 Strengths

##### 1) Outstanding Bioactivity and Osteoconductivity

One of the primary strengths of 45S5 bioactive glass is its unparalleled bioactivity. Upon exposure to physiological fluids, the material undergoes a well-characterized reaction sequence that leads to the formation of a hydroxycarbonate apatite (HCA) layer.

Experimental studies have confirmed that 45S5 bioactive glass initiates hydroxycarbonate apatite (HCA) formation within 24 to 48 hours when immersed in simulated body fluid (SBF). Characterization by Fourier-transform infrared spectroscopy (FTIR) reveals the appearance of bands at 560 and 600 cm<sup>-1</sup>, indicative of apatite, while X-ray diffraction (XRD) patterns show increasing crystallinity over time. This rapid bioactive response contributes directly to its exceptional osteoconductive performance (Wang et al., 2020).

Chemically and structurally similar to natural bone mineral [1,2]. This HCA layer enables direct bonding between the implant and host bone, distinguishing 45S5 from bioinert alternatives like titanium and alumina [3]. Studies using in vivo models have shown that bone can integrate with 45S5 within a matter of weeks, accelerating healing and minimizing fibrous encapsulation [4].

##### 2) Proven Clinical Efficacy

45S5 bioactive glass has a long-standing clinical track record dating back over four decades. It has been successfully applied in numerous commercial products for craniofacial repair, middle ear ossicles, dental regeneration, and bone void fillers [5]. Products such as NovaBone®, PerioGlas®, and BioGran® have received FDA approval, further validating their safety and effectiveness [6]. In clinical practice, these materials have shown high success rates with minimal immune response or postoperative complications [7].

##### 3) Stimulatory Ion Release

The controlled release of biologically active ions—including Ca<sup>2+</sup>, Na<sup>+</sup>, and PO<sub>4</sub><sup>3-</sup>—plays a significant role in modulating cellular behaviour at the material-tissue interface [8]. These ions activate signalling pathways. In vitro ion release assays demonstrate a marked increase in calcium and sodium concentrations within the first 12–24 hours of immersion in DMEM, accompanied by a pH rise from 7.4 to ~9.2. This ion exchange triggers elevated alkaline phosphatase (ALP) activity and Runx2 gene expression in osteoblast-like MC3T3-E1 cells, supporting enhanced osteogenic differentiation (Xynos et al., 2000). That promote osteoblast proliferation, angiogenesis, and gene expression related to bone remodelling [9]. For example, calcium ions upregulate osteogenic markers such as ALP and Runx2, while phosphate ions contribute to mineral deposition [10]. The dissolution process also causes a localized increase in pH, which can inhibit bacterial colonization, contributing to the material's mild antimicrobial effect [11].

##### 4) Benchmark in Materials Science

From a research perspective, 45S5 serves as a benchmark for evaluating the bioactivity of novel biomaterials. It has been

widely studied across various experimental platforms, including in vitro cell cultures, animal models, and clinical trials [12]. The extensive literature base allows for consistent comparisons and provides a rich framework for understanding bio-glass interactions with biological systems [13]. Furthermore, its relatively simple composition makes it an ideal candidate for fundamental mechanistic studies in materials science and regenerative medicine.

### 5) Chemical Simplicity and Tunability

Although 45S5 itself has a fixed stoichiometry, its four-component oxide system ( $\text{SiO}_2\text{-Na}_2\text{O-CaO-P}_2\text{O}_5$ ) offers a solid foundation for compositional tuning. Researchers can easily develop derivative glasses by substituting additional oxides (e.g.,  $\text{K}_2\text{O}$ ,  $\text{MgO}$ ,  $\text{ZnO}$ ) without significantly altering the base glass structure [14]. This flexibility supports innovations aimed at improving properties like radiopacity, mechanical strength, or antibacterial function [15].

### 6) Cost-Effective and Scalable Synthesis

The production of 45S5 bioactive glass via conventional melt-quenching methods is relatively straightforward and cost-effective. Raw materials such as silica, sodium carbonate, and calcium phosphate are inexpensive and readily available, making the material attractive for commercial scale-up [16]. Moreover, the sol-gel method, which produces glass at lower temperatures, has enabled the synthesis of nano- and mesoporous forms that further expand its applications [17].

## 3.2 Weaknesses

### 1) Poor Mechanical Strength and Brittleness

One of the most significant limitations of 45S5 bioactive glass is its poor mechanical performance. The material exhibits low tensile strength, low fracture toughness ( $\sim 0.5\text{-}1 \text{ MPa}\cdot\text{m}^{1/2}$ ), and brittle failure behaviour, making it unsuitable for load-bearing applications such as long bone replacements or spinal implants. While it performs adequately in non-load-bearing defects, its mechanical properties limit its structural utility in orthopaedics compared to ceramics like alumina or zirconia, or metals such as titanium alloys. Experimental measurements show that sintered 45S5 scaffolds have a compressive strength between 2–10 MPa, significantly lower than the 100–150 MPa of cortical bone (Rahaman et al., 2011).

### 2) Narrow Thermal Processing Window

Another critical drawback is the narrow processing window of 45S5. Its sintering temperature ( $\sim 550 \text{ }^\circ\text{C}$ ) is very close to its crystallization onset ( $\sim 610 \text{ }^\circ\text{C}$ ), making it prone to devitrification during thermal treatment. This crystallization reduces bioactivity by disrupting the glass's amorphous network, which is essential for ion exchange and HCA layer formation. These constraints complicate scaffold fabrication and limit advanced processing methods like 3D printing or sintering of porous structures.

### 3) High Sodium Content and Cytotoxicity Concerns

The high  $\text{Na}_2\text{O}$  content ( $\sim 24.5 \text{ wt}\%$ ) in 45S5 causes rapid ion exchange, leading to a significant pH rise in physiological environments. In vitro experiments show that immersion in DMEM results in a pH increase to  $\sim 9.2$  within 24 hours. Mesenchymal stem cells (MSCs) exposed to this elevated pH

exhibit reduced viability—dropping to approximately 65–70%—indicating early cytotoxic effects (Xynos et al., 2000). This can impair cell adhesion, particularly in sensitive or small-volume implantation sites. Furthermore, elevated  $\text{Na}^+$  levels may disrupt ionic homeostasis and interfere with cell signalling pathways.

### 4) Limited Ductility and Toughness

In addition to being brittle, 45S5 glass lacks the viscoelastic behaviour seen in polymers or composite systems. This severely limits its impact resistance and capacity to absorb mechanical shock, characteristics essential for dynamic load environments [10]. Even with porosity optimization, its mechanical resilience remains far below that of cortical bone ( $\sim 100\text{-}150 \text{ MPa}$  compressive strength), restricting its role to filler materials or coatings rather than load-bearing implants [11].

### 5) Lack Of Intrinsic Antibacterial Activity

While 45S5 does show some bacterial inhibition due to elevated pH and ion release, its antimicrobial activity is modest compared to glasses doped with bactericidal ions such as  $\text{Ag}^+$ ,  $\text{Cu}^{2+}$ , or  $\text{Zn}^{2+}$  [12]. This limits its effectiveness in infected wound settings, osteomyelitis, or maxillofacial infections without additional modifications or coatings [13]. In contrast, glasses like S53P4 or Ag-doped derivatives have shown superior antibacterial profiles [14].

### 6) Poor Integration with Polymers Without Surface Treatment

When incorporated into composite systems, 45S5 often demonstrates weak interfacial bonding with polymers unless surface modification is applied [15]. The chemical incompatibility between the inorganic glass surface and organic polymer matrix can lead to delamination or failure under stress. Surface treatments like salinization or plasma activation are often necessary to improve adhesion, adding complexity to the fabrication process [16].

### 7) Limited Control Over Porosity in Melt-Derived Glasses

Although porosity plays a vital role in cell infiltration and nutrient transport, melt-derived 45S5 glasses generally have limited tunability in pore architecture without compromising structural integrity [17]. The production of well-controlled macro- and micro-porous scaffolds remains challenging using traditional methods. Techniques such as sol-gel or foam replication can improve porosity control but are often limited by scalability and reproducibility [18].

## 3.4 Threats

### 1) Competition from Advanced Bioactive Glasses

While 45S5 remains a benchmark material, its position is increasingly challenged by newer glass formulations that offer enhanced mechanical properties, improved bioactivity, or multifunctionality. Notable examples include borate-based glasses, which dissolve faster and release therapeutic ions more efficiently, and the 13-93 glass series, which displays higher mechanical strength and better sinter ability than 45S5 [1,2]. Furthermore, melt-derived and sol-gel hybrid glasses have been optimized for superior thermal processing windows and customized degradation profiles [3]. These

alternatives present viable options for both orthopaedic and soft tissue applications, gradually eroding the dominance of 45S5 in clinical and research domains.

## 2) Regulatory Complexity and Clinical Translation Barriers

Although 45S5-based products have received regulatory approval in several countries, the pathway to clinical adoption for modified or doped versions is complex and time-consuming. The inclusion of therapeutic ions such as  $\text{Ag}^+$  or  $\text{Sr}^{2+}$  may raise toxicological concerns, necessitating extensive preclinical testing and validation under evolving regulatory frameworks like those of the FDA, EMA, and ISO standards [4]. Moreover, translating laboratory innovations into scalable, GMP-compliant products remains a significant hurdle due to batch variability, sterilization issues, and stability concerns [5].

## 3) Cost-Effectiveness Compared to Established Materials

In many clinical settings, 45S5 bioactive glass must compete with established biomaterials like hydroxyapatite (HA), titanium alloys, and biodegradable polymers. These materials benefit from mature supply chains, lower production costs, and well-characterized clinical performance. The relatively higher cost of bioactive glass production—particularly when using advanced synthesis methods like sol-gel or additive manufacturing—may limit its use in resource-constrained healthcare systems [6].

## 4) Limited Mechanical Load-Bearing Applications

Despite efforts to enhance its mechanical properties through composite development, 45S5 still cannot match the performance of materials specifically engineered for high-stress environments. This limits its use to non-load-bearing scenarios such as craniofacial reconstruction, dental void filling, and ear prostheses [7]. For spinal implants, joint replacements, or long bone scaffolds, clinicians often favor metal or dense ceramic alternatives that offer superior compressive strength, fatigue resistance, and fracture toughness [8].

## 5) Risk of In Vivo Crystallization and Degradation Variability

The risk of uncontrolled crystallization during processing may compromise the consistency and performance of 45S5-based implants. Crystallized phases typically reduce ion release and bioactivity, altering the biological response post-implantation [9]. Additionally, variability in degradation rates—affected by manufacturing method, particle size, and implantation site—can lead to unpredictable performance, particularly in long-term or load-bearing applications [10].

## 6) Biological and Immunological Uncertainties

While 45S5 has generally demonstrated favourable biocompatibility, the biological response can vary depending on the host environment and formulation. In some studies, rapid ion release has been associated with inflammation or cytotoxicity, particularly in soft tissues or small-volume environments [11]. The risk of foreign body reaction or fibrous encapsulation increases when degradation is too rapid or the pH change is excessive [12]. These uncertainties make clinicians cautious about adopting new or modified versions without robust clinical data.

## 7) Environmental and Sustainability Concerns

Manufacturing of traditional melt-derived glasses requires high-temperature furnaces ( $\sim 1300\text{--}1500\text{ }^\circ\text{C}$ ), which are energy-intensive and carbon-emitting processes. As sustainability becomes a major concern in materials science and healthcare, bioactive glasses may face scrutiny regarding their environmental footprint compared to low-energy alternatives like natural polymers or bioresorbable ceramics [13].

## 4. Comparative Analysis with Emerging Bioactive Glasses

In recent years, the rapid evolution of bioactive glass formulations has introduced several alternatives to 45S5, each tailored to address specific clinical limitations or expand functional capabilities. These next-generation bioactive glasses aim to retain the advantageous ion release and bioactivity of 45S5 while improving mechanical properties, degradation profiles, and multifunctionality. This section critically evaluates 45S5 in comparison with emerging compositions, focusing on borate-based glasses, 13-93 glass, and ion-doped derivatives.

### 1) Borate-Based Bioactive Glasses

Borate glasses, which substitute  $\text{B}_2\text{O}_3$  for  $\text{SiO}_2$ , have attracted attention due to their superior degradation rates and high bioactivity. Unlike silicate-based 45S5, borate glasses dissolve more rapidly, facilitating faster ion release and tissue regeneration [1]. They have been particularly effective in promoting angiogenesis and wound healing, as demonstrated in wound dressings and skin graft applications [2]. Moreover, borate glasses can accommodate a wider variety of dopants—such as  $\text{Sr}^{2+}$ ,  $\text{Cu}^{2+}$ , and  $\text{Co}^{2+}$ —that enhance vascularization and antimicrobial activity [3].

However, the rapid degradation of borate glasses may lead to structural instability if not carefully controlled. In addition, the toxicity of boron ions at high concentrations remains a concern, especially in closed biological systems [4]. Compared to 45S5, borate-based glasses offer enhanced biofunctionality but require more precise compositional tuning and degradation control for safe in vivo use.

### 2) 13-93 Bioactive Glass

The 13-93 glass composition, developed by the Kokubo group, consists of  $\text{SiO}_2\text{--Na}_2\text{O--K}_2\text{O--MgO--CaO--P}_2\text{O}_5$  and provides better mechanical properties and sinterability than 45S5 [5]. Its broader thermal processing window reduces the risk of devitrification, enabling the fabrication of porous scaffolds via conventional sintering or foam replication techniques. It also demonstrates good cytocompatibility and forms an HCA layer upon immersion in simulated body fluid (SBF), confirming its bioactivity [6].

Compared to 45S5, 13-93 offers improved compressive strength ( $\sim 50\text{--}100\text{ MPa}$ ) and more robust scaffolds suitable for load-bearing applications [7]. However, its ion release rate and apatite formation are generally slower, which may affect early-stage healing kinetics [8]. Thus, 13-93 may be preferred in scenarios where mechanical stability is prioritized over rapid biointegration.

### 3) Ion-Doped and Mesoporous Bioactive Glasses

A prominent trend in the design of advanced bioactive glasses involves doping the base glass with bioactive or antimicrobial ions. Zinc-, strontium-, and silver-doped variants of 45S5 have shown enhanced osteogenic and antibacterial activities [9]. These glasses can be tailored to achieve specific clinical outcomes, such as bone regeneration in osteoporotic patients or infection control in trauma cases [10].

Mesoporous bioactive glasses (MBGs), synthesized via sol-gel routes and surfactant templating, exhibit high surface area and pore volume, significantly enhancing ion exchange and drug loading capabilities [11]. Mesoporous bioactive glasses (MBGs), prepared via sol-gel techniques, exhibit surface areas exceeding 300 m<sup>2</sup>/g. These materials not only enhance ion exchange kinetics but also improve cell compatibility, with MC3T3-E1 osteoblast viability consistently above 90% over 7 days. By comparison, melt-derived 45S5 samples often show 60–80% viability under identical conditions (Chen et al., 2021). These materials are especially promising for dual-functional applications, such as bone regeneration and localized drug delivery [12].

Compared to melt-derived 45S5, MBGs offer superior interaction with soft tissues and controlled degradation, but they are often less mechanically robust and harder to scale industrially [13].

### 4) Hybrid and Polymer-Inorganic Composites

To bridge the gap between mechanical strength and bioactivity, recent studies have explored organic-inorganic hybrids and composite scaffolds. For example, incorporating 45S5 particles into PCL, PLA, or gelatin matrices allows for flexible, biocompatible, and mechanically reinforced materials [14]. These hybrid systems can be fabricated via electrospinning, freeze-drying, or 3D printing to create biomimetic scaffolds with tenable architecture [15].

Although composite systems extend the application scope of 45S5, the interfacial bonding between phases remains a challenge, often requiring surface modification or coupling agents [16]. Additionally, degradation mismatch between phases can compromise structural integrity over time.

#### Experimental Data on 45s5 Bioactive Glass

Property	Measured Range / Value	Conditions	Cell Type / Model	Reference
Compressive Strength	2–10 MPa	Sintered 45S5 scaffolds	In vitro	Rahaman et al., 2011
HCA Formation Time	24–48 hours	SBF immersion	—	Wang et al., 2020
pH Increase in Medium	~9.2	24 h in DMEM	MSC cultures	Xynos et al., 2000
Bone Regeneration	~85% new bone	6 weeks implantation	Rabbit femoral defect model	Zhang et al., 2019
Cell Viability	60–80%	Direct contact, 7 days	MC3T3-E1 osteoblasts	Chen et al., 2021
Surface Area (MBGs)	>300 m <sup>2</sup> /g	Sol-gel derived	—	Chen et al., 2021

#### Summary Comparison Table

Property	45S5	Borate Glasses	13-93	MBGs
Bioactivity (HCA formation)	Very High	Very High	High	Very High
Mechanical Strength	Low	Low–Moderate	Moderate–High	Low
Thermal Processability	Poor	Good	Good	Moderate
Ion Release Control	Moderate	High	Moderate	High
Antibacterial Potential	Moderate	High (if doped)	Low–Moderate	High (if doped)
Drug Delivery Capability	Limited	Moderate	Limited	Excellent
Clinical Use	FDA-approved	Emerging	Limited Use	Research Stage

In conclusion, while 45S5 bioactive glass remains a cornerstone in the biomaterials field, newer compositions offer attractive alternatives with improved mechanical, functional, and therapeutic characteristics. However, none has yet fully replaced 45S5 across all dimensions, indicating that it still holds a central role in both research and clinical practice

### 5. Future Prospects and Research Directions

Although 45S5 bioactive glass has long served as a benchmark material in bone regeneration and other biomedical fields, its future relevance hinges on addressing its intrinsic limitations while capitalizing on emerging opportunities. As the field of biomaterials evolves toward multifunctionality, patient-specific customization, and environmentally sustainable processing, several strategic directions for research and development of 45S5 can be identified.

#### 1) Development of Multifunctional Composites

Future work should focus on engineering multifunctional composites that combine 45S5 with mechanically robust and

biologically active components. These may include biodegradable polymers (e.g., PCL, PLA), hydrogels (e.g., alginate, gelatin), or nanoceramics (e.g., HA, TCP). Beyond simple reinforcement, next-generation composites should incorporate smart properties such as shape memory, self-healing, or stimuli-responsive degradation [1,2]. A deeper understanding of the interfacial bonding between phases and degradation synchronization will be essential to ensure long-term performance and biointegration.

#### 2) Precision Ion Substitution and Functional Doping

Recent work on ion-doped 45S5 has demonstrated functional enhancements without compromising biocompatibility. Silver-doped 45S5 glass achieved a 2-log reduction in *Staphylococcus aureus* colonies within 24 hours and retained >85% osteoblast viability, balancing antibacterial and regenerative properties. Similarly, co-doping with Sr<sup>2+</sup> and Zn<sup>2+</sup> increased ALP activity by 1.8-fold and collagen expression by 2.2-fold in MC3T3-E1 cells, highlighting the therapeutic potential of precision ion substitution (Liu et al., 2021).

Controlled ion doping represents a potent strategy to endow 45S5 glass with additional functionalities. For example, Ag<sup>+</sup> and Cu<sup>2+</sup> ions can impart antibacterial effects; Sr<sup>2+</sup> and Zn<sup>2+</sup> enhance osteogenesis; and B<sup>3+</sup> or Co<sup>2+</sup> can stimulate angiogenesis [3–5]. Future studies should focus on fine-tuning ion concentrations to balance efficacy with cytocompatibility. Co-doping strategies—where multiple ions are incorporated in synergistic ratios—could yield materials that simultaneously promote bone regeneration and infection control, particularly valuable in complex trauma or diabetic wound environments [6].

### 3) Nanostructured and Mesoporous Architectures

Nanotechnology opens new avenues for enhancing the functionality of 45S5. Mesoporous bioactive glasses (MBGs), with their high surface area and tunable pore sizes, can significantly improve drug loading capacity and ion release control [7]. The ability to engineer nanoscale features can also influence protein adsorption, cellular adhesion, and immune response [8]. Combining MBG technology with hierarchical scaffold design—integrating macro-, micro-, and nanopores—may enable the development of materials that mimic the architecture of trabecular bone more effectively.

### 4) Additive Manufacturing and Patient-Specific Implants

The integration of 45S5 into additive manufacturing platforms—such as 3D printing, direct ink writing, and selective laser sintering—promises a new paradigm in patient-specific regenerative therapies. By enabling complex, biomimetic geometries with controlled porosity, additive manufacturing allows for implants that match the mechanical and biological needs of individual patients [9]. Challenges remain, such as achieving suitable rheological properties for printable pastes and preventing devitrification during thermal post-processing. However, these barriers are being actively addressed through binder selection, composite printing, and hybrid manufacturing strategies [10].

### 5) Controlled Degradation and Temporal Bioactivity

A key area of interest is tailoring the degradation kinetics of 45S5 to match tissue healing timelines. Rapid dissolution may cause cytotoxicity or mechanical failure, while overly slow degradation may hinder new tissue formation. Future research should aim to develop temporal control over bioactivity—i.e., tuning when and where specific ions are released or when the material transitions from a structural to a resorbable role [11]. This may involve multilayered structures, responsive coatings, or sequential degradation strategies.

### 6) Bioinspired and Hybrid Materials

Taking cues from natural materials, such as bone, nacre, or dentin, future generations of 45S5-based materials could incorporate hierarchical organization, mineral–organic interfaces, or gradient compositions. Biomimetic strategies aim to replicate the mechanical toughness and biological signalling of natural tissues [12]. Organic-inorganic hybrid glasses, which merge the covalent networks of silicates with organic polymers at the molecular level, offer a promising direction. These hybrids combine the flexibility and toughness of polymers with the bioactivity of glasses, potentially overcoming the brittleness and processing issues of conventional 45S5 [13].

### 7) Clinical Translation and Regulatory Optimization

Bridging the gap between laboratory research and clinical implementation remains a major hurdle. Long-term animal studies, multi-centre clinical trials, and robust biocompatibility assessments are needed to validate the efficacy and safety of modified 45S5-based systems [14]. Standardization of synthesis protocols, sterilization methods, and quality control parameters will help reduce batch-to-batch variability and streamline regulatory approval processes. Partnerships between academia, industry, and regulatory bodies will be crucial in accelerating clinical translation.

### 8) Sustainability and Green Manufacturing

Environmental sustainability is becoming an increasingly important consideration in biomaterials development. Traditional melt-derived glass production is energy-intensive and carbon-emitting. Future directions should include the development of low-temperature synthesis techniques, such as sol-gel, bioinspired synthesis, or microwave-assisted fabrication [15]. Additionally, the use of renewable precursors, recyclable materials, and life-cycle assessments can reduce the ecological footprint of 45S5-based products.

In summary, the path forward for 45S5 bioactive glass lies in interdisciplinary innovation—combining materials science, nanotechnology, bioengineering, and clinical insight. Through strategic enhancements in composition, architecture, processing, and functionality, 45S5 can continue to play a transformative role in next-generation regenerative medicine.

## 6. Conclusion

45S5 bioactive glass, since its invention over five decades ago, has served as a foundational material in the field of regenerative medicine. Its extraordinary bioactivity, clinical versatility, and simple composition have made it a gold standard in the design and evaluation of new biomaterials. Through this comprehensive SWOT analysis, we have outlined the key strengths that underpin its clinical success—namely, its rapid hydroxycarbonate apatite (HCA) formation, stimulatory ion release, and proven track record in dental and orthopedic applications.

Nevertheless, inherent weaknesses such as poor mechanical strength, narrow thermal processing range, and high sodium content continue to limit its broader utility, particularly in load-bearing applications. At the same time, emerging opportunities—including composite development, additive manufacturing, ion doping, and integration into tissue engineering platforms—offer promising pathways to expand the material's functionality and address its limitations.

However, these advances are not without threats. Competition from next-generation bioactive glasses, regulatory complexities, and environmental concerns underscore the need for ongoing innovation, translational research, and sustainable manufacturing practices.

In conclusion, while 45S5 bioactive glass may not be the ultimate solution for all regenerative applications, it remains a vital and evolving material platform. Its continued relevance will depend on strategic adaptations that enhance its

mechanical, biological, and functional performance to meet the changing demands of modern medicine. Through collaborative efforts between researchers, clinicians, and industry, the full potential of 45S5 and its derivatives can be realized in the next era of personalized and precision biomaterials.

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