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Review Article

A Comprehensive Overview of the Pertinence and Possibilities of Bioactive Glass in the Modern Biological World

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Abstract: An unbelievable revolution happened in medical science during the late '60s. A casual conversation with a colonel led Larry Hench to the invention of a biomaterial that is more biocompatible, biodegradable, and bioactive, which was named as Bioglass. The material started its journey with its application in the replacement of ossicles in the middle ear, and today Bioglass is dominating in major medical fields like bone tissue engineering, drug delivery, dentistry, and so on. The wide range of applications and such bio-friendly properties of the material also convey a message that this material is a promising area to work in the field of research. Bioglass is synthesized by two methods i) melt quenching and ii) sol-gel. We aim to help new optimistic researchers in uplifting their interest to conduct researches with this auspicious biomaterial. This paper provides a bird's eye view of the history, preparation process, composition of different bioactive glasses and their biological feedback, biocompatibility mechanism, fundamental properties, noteworthy applications, possibilities along with the shortcomings of Bioglass. The shortcomings of Bioglass are elaborated so that the researchers can explore more about those limitations. We have also depicted the chronological advancements of bioglasses over the years. We believe that the prospects of more advanced researches with Bioglass can bring more success in the modern biomedical world.

Keywords: Bioglass, Properties, Diseases, Applications, Challenges

1. Introduction

Billions of people are alive today because of the lifesaving, life-altering and life-sustaining treatments that have emerged from curiosity-based research. Over the last hundred years, we have dramatically changed life expectancies with the introduction of advanced biomaterials. As a result, humans are living longer and longer. We have seen that the human life span has increased from an average of 40 to 80 plus years and it is expected that within 2050 more than 1 billion will breath ageing 60 or more [1]. As we grow older and older, the quality of our tissues decreases which means we need more and more replacements parts not just to stay alive but to lead a healthy lifestyle as well. The advancement of biomaterial is a revolutionary contribution to medical science. It takes extraordinary effort to design things that work directly with the human body. The most crucial challenge to create a biomaterial is that it should be compatible with the biological system. A biomaterial should also have bioinert behaviour, bioactivity, biostability, and biodegradability [2]. They can be

categorized into i) natural or synthetic polymers ii) metals iii) composites and iv) ceramics. The bond-forming ability with the living tissues in the physiological system gives them the tile 'bioactive' [3]. In the mid-'60s, biomaterials were made biocompatible and long-lasting by minimizing their contact with the host tissues [4]. But the problem was scar tissues were formed as metals used to corrode while remaining within the host for a long time. The invention of Bioglass provided an excellent substitute for the traditional metallic implants back then. Bioglass is biocompatible, bioactive, mechanically stable, biodegradable and favours osteointegration when implanted in a host body [5]. The present article provides a general idea of Bioglass.

Bioglass was invented by Larry Hench, a professor at the University of Florida in 1969. The foundation of this discovery was a casual conversation between Hench and US colonel who just returned from the Vietnam war. They were talking mainly about the rejection of chemically inert polymeric and metallic implants used in the replacement of living tissues during the war [6]. It is to be mentioned that the bioinert biomaterials used at that time did not form stable bonds with host tissues. They initiated fibrous encapsulation after implantation [7]. Hench was telling about some studies conducted by him and his co-workers about radiation tolerance of materials. At one point in this conversation, the colonel said: "If you can make a material that will survive exposure to high energy radiation, can you make a material that will survive exposure to the human body?" [6]. These words inspired Hench to invent a material that can alter the use of polymeric and metallic materials. Hench and his team based on a simple hypothesis "*The human body rejects metallic and synthetic polymeric materials by forming scar tissue because living tissues are not composed of such materials. Bone contains a hydrated calcium phosphate component, Hydroxyapatite (HA) and therefore, if the material can form a HA layer* in vivo, *it may not be rejected by the body"* [8]. The US army agreed to fund for one-year research based on this hypothesis. Hench and his team tried to make a degradable glass by using the Na_2O-CaO-SiO_2-P_2O_5 system, which will be rich in calcium content [7]. They used a composition which is close to a ternary eutectic in the Na_2O-CaO-SiO_2 phase diagram. This glass is known as 45S5 Bioglass, which consists of 45%wt of SiO_2, 24.5 wt% of CaO, 24.5 wt% of Na_2O, and 6.0 wt% of P_2O_5 [6]. At first, they tested their newly synthesized material on rats. The implants were made in the Department of Material Science and Engineering and inserted into rats at the Gainesville, Florida Veterans Administration Hospital [8]. After six weeks, they reported, *"These experimental ceramic implants will not come out of the bone. They are bonded in place. I can push on them, I can shove them, I can hit them with an osteotome, and they do not move. Control implants easily slip out of their fibrous capsule, but the special ceramic implants are firmly bonded to the bone"* [9]. The presence of a high amount of Na_2O and CaO, as well as a comparatively high CaO/P_2O_5 ratio, makes the 45S5 Bioglass very bioactive [6].

Today's success of Bioglass has not gained in one night, and it takes many years for achieving this position (as shown in Table 1). Over the last 40 years, different modifications were made in the bioglass composition to make it appropriate for several clinical applications. For instance, borate glasses are used for their excellent apatite forming ability, and phosphate glasses show high solubility in contact with the biological fluids [6]. Bioglass has plenty of applications in the clinical field. Bioglass is used to repair bone. For regenerating bones, bioglass scaffolds are used, which acts like a 3D template [10]. The high calcium to phosphorus ratio enhances the formation of apatite crystal. Besides, bioglasses have a vast application in toothpaste, repairing periodontal defects, repairing cranial and maxillofacial imperfections etc. Bioglasses can be categorized into, (i) Class A bioglasses: they are osteoproductive and can bind with both soft tissues and bone (the Hydroxy carbonate apatite layer forms within several hours) and (ii) Class B bioglasses: they are osteoconductive and cannot form a bond with soft tissues (the hydroxy carbonate apatite layer can take several days to create) [3]. The article has focused on the composition, essential properties, noteworthy applications and some shortcomings of Bioglass. We aim to provide a basic idea about Bioglass to the readers so that they can conduct research to innovate more.

Table 1. *Chronological advancement of Bioactive glasses in the medical sector [1, 6, 11].*

Year	Accomplishments	References
1969	Discovering of 45S5 Bioglass®	[US Army Medical RD Command report]
1971	Publication of first review paper of bioactive glasses and glass-ceramics considering the interactions ceramic prosthetic materials with human bones.	[12, 13]
1972	Establishment of Bioglass bone segments and coated femoral stems in monkeys	[14]
1975	Establishment of Bioglass coated alumina bones in the hip joints of sheep	[15]
1977	Treatment of the ear diseases of guinea pig through the substitution of middle ear small bones with Ceravital® glass-ceramics	[16]
1977	The innovation of potential sources for the application of Bioglass metals and alumina ceramics.	[16]
1981	The invention of connectivity between soft tissue and 45S5 Bioglass®	[17]
1981	Establishment of safety for Bioglass products by Toxicology and biocompatibility studies (20 *in vitro* and *in vivo*)	[17]
1985	The first approval of Bioglass Ossicular Reconstruction Prosthesis (MEP) by the Food and Drug Administration (FDA) through the 510 (k) process.	[18]
1987	The invention of osteostimulation by using Bioglass particulates for the treatment of periodontal diseases	[16]
1988	Approval of Endosseous Ridge Maintenance Implant by FDA.	[16]

Year	Accomplishments	References
1988	Clinical use of Endosseous Ridge Maintenance Implant in the human body	
1991	Development of a sol-gel method to prepare Bioglass of high bioactivity	[19]
1993	Acceptance of Perioglas by FDA to use in bone grafting to restore bone loss from periodontal disease in infrabony defects	[16]
1995		
1996	Acceptance of Perioglas by FDA to use it for tooth extraction sites, alveolar ridge augmentation	[16]
1998	Used of Bioglass in repairing peripheral nerve	[20]
1999	Acceptance of radioactive glass by FDA for cancer treatment and use of 45S5 glass for orthopaedic bone grafting in Europe	[16]
2000	Acceptance of Novabone by FDA to use it in general orthopaedic bone grafting in non-load bearing sites and analysis of the use of 45S5 Bioglass to control osteoblasts cell cycles	[16]
2001	Gene expression profiling of Bioglass 45S5	[21]
2002	FDA acceptance of a bioglass composite Medpor-plus	[6]
2003	Use of dental cement	[22]
2004	FDA acceptance of 45S5 Bioglass for the treatment of dentine hypersensitivity and use of Bioglass in lung tissue engineering	[23]
2005	Use of Bioglass for the repair of skeletal muscle and ligament.	[24]
2005	Use of Bioglass for the treatment of gastrointestinal ulcers	[25]
2010	Use of Bioglass in cardiac tissue engineering	[26]
2011	Commercialization of bioactive borate glass as veterinarian medicine and launching of bioglass toothpaste for the treatment of dentine hypersensitivity.	[27]
2012	Use of Bioglass for embolizing fibroids and repairing spinal cord	[28]
2018	Use of radioactive glass for the treatment of metastatic colorectal carcinoma of the liver	[29]
2019	Use of Bioglass in spinal fusion	[30]
2020	Regeneration of bones by cellulose reinforced gelatin or bioactive glass nanocomposite scaffolds	[31]

2. Generalized Compositions of Bioglass

Typically, Bioglass is a multi-component system, and its composition is featured from the ternary phase diagram of the SiO_2-Na_2O-CaO system [Book2]. Several compositional variations can be obtained by assimilating various compounds like MgO, P_2O_5, K_2O, B_2O_3, CaF_2, etc. Amongst the features, Na_2O and P_2O_5 contribute mostly to form bonds with the living bones. So, the presence of either Na_2O or P_2O_5 or both need to be satisfied. Similarly, B_2O_3 performs in the formation of bonds with the bones to provide effective biocompatibility, even if the ratio of Ca/P is lower [32]. Besides, CaF_2 controls the dissolution mechanism and the corresponding rate of dissolution of the glass. Generally, Bioglass can be categorized into four different classes based on the silica content, as shown in Table 2.

Table 2. *Categorized Bioglass with compositions and their biological responses [33].*

Classes of Bioglass	Composition	Biological feedback
Class 1	35-60 mol% SiO_2 10-50 mol% CaO 5-40 mol% Na_2O	Bioactive Bonding to bone Bonding with soft tissues
Class 2	< 35 mol% SiO_2	Non-reactive Encapsulated by a fibrous capsule
Class 3	> 50 mol% SiO_2 < 10 mol% CaO < 35 mol% Na_2O	Bioactive Resorbed within 10-30 days
Class 4	> 65 mol% SiO_2	Impractical Yet not practically implanted

Bioglass differs from traditional soda-lime silicate glass in several factors such as SiO_2 quantity, Na_2O and CaO quantity and Ca/P ratio (Several bioglass compositions are displayed in Table 3). Bioglass possesses a higher amount of SiO_2 content (< 60 mol%), a more considerable amount of Na_2O and CaO contents and a larger Ca/P ratio compared to soda-lime silicate glass. These factors significantly influence the bio-compatible characteristics of Bioglass.

Table 3. *Constitutional percentage of different bioactive glasses [3, 8, 11, 34, 35].*

Glass type	Composition							Others
	SiO_2	Na_2O	K_2O	MgO	CaO	P_2O_5	B_2O_3	
45S5	45.0	24.5	0	0	24.5	6.0	0	-
19-93	53.0	6.0	12.0	5.0	20.0	4.0	0	-

Glass type	Composition							Others
	SiO_2	Na_2O	K_2O	MgO	CaO	P_2O_5	B_2O_3	
6P53B	52.7	10.3	2.8	10.2	18.0	6.0	0	-
58S	58.2	0	0	0	32.6	9.2	0	
70S30C	71.4	0	0	0	28.6	0	0	-
13-93B1	34.4	5.8	11.7	4.9	19.5	3.8	19.9	-
13-93B3	0	5.5	11.1	4.6	18.5	3.7	56.6	-
$P_{50}C_{35}N_{15}$	0	9.3	0	0	19.7	71.0	0	-
S53P4	53.0	23.0	0	0	20.0	4.0	0	-
42S5	42.1	26.3	0	0	29.0	2.6	0	-
55S4	52.1	21.5	0	0	23.8	2.6	0	-
45S5F	45	24.5	0	0	12.25	6.0	0	12.5 CaF_2
40S5B5	40	24.5	0	0	24.5	6.0	5.0	-
42S5.6	42.1	26.3	0	0	29.0	2.6	0	-
46S5.2	46.1	24.4	0	0	26.9	2.6	0	-
49S4.9	49.1	23.8	0	0	25.3	2.6	0	-
52S4.6	52.1	21.5	0	0	23.8	2.6	0	-
55S4.3	55.1	20.1	0	0	22.2	2.6	0	-
60S3.8	60.1	17.7	0	0	19.6	2.6	0	-
45S5.4F	45	24.5	0	0	14.7	6	0	9.8 CaF_2
52S4.6	52	19.5	0	0	21	6	0	-

3. Preparation Processes

Two procedures are followed for the formulation of 45S5 Bioglass, i.e., High-temperature quenching method and Sol-gel method.

3.1. Melt Quenching Method

Melt quenching is a widespread technique used to prepare glasses. Traditionally glasses were developed using this technique, including bioglass 45S5 [36]. It is a preparation process where glasses are prepared by melting a mixture of required stoichiometric amounts of high purity different constituent oxides of carbonates at high temperature [37]. Ingredients in the form of powder are melted at high temperature, notably exceeding 1300°C and quickly quenched to freeze the atomic structure [38]. But this technique creates some problems such as reduction of bioactivity at higher sintering temperature and impotence to fabricate porous scaffolds [39]. Mechanical properties of silica-based bioactive glasses can be affected due to heat treatment as it leads to the formation of the crystalline phase along with the glassy phase with the release of stress [40]. Ionic diffusivity and bioactivity are gradually decreased by the crystallization of glass [38].

3.2. Sol-gel Method

Sol-gel technique is an excellent way of glass preparation. It is an elegant chemical way to synthesis single or multiple components in the form of thin solid film, ultrafine powders, high surface area porous materials, dense abrasive materials, and continuous glass and ceramic fibres [41]. Oxide materials require high temperatures for fabrication, which creates a significant hindrance. The sol-gel method is a wet chemical process to fabricate oxide materials at low temperatures. Here inorganic alkoxides and metal chlorides are used as precursors and are made to undergo hydrolysis and polycondensation reaction in an acidic or basic environment [37]. The sol then evolves with more condensation reactions to form a network with the liquid phase as a gel, then finally, it is sintered to create glass [42]. Porous scaffold with Bioglass is challenging to prepare by the melt quenching method as it gets crystallized during high-temperature sintering. The gel glasses have a greater surface area, which makes them more bioactive than the glasses produced by melt quenching [37]. The sol-gel method provides an efficient way in this regard. It is possible to create a wide variety of glass compositions and shapes using the sol-gel process. Porosity, apatite forming ability, and greater surface area compared to melt quenched glasses can be obtained by using the sol-gel process, which ultimately brings excellent mechanical properties [43].

4. Properties of Bioglass

4.1. Bioactivity and Biocompatibility

It seems that bioactivity and biocompatibility refer to the same meaning, but they don't. In general, bioactivity means the effects of a given agent on living matters or tissues, where biocompatibility of a material is defined as the state of being compatible or suitable with living tissues and causing no toxic/immunological response when it exposes in the body. Bioglass develops a strong bond with surrounding tissues in bone tissue engineering [16]. Compared to other bioactive materials, Bioglass shows super bioactivity and allows both osteoconduction and supplying scaffolds for growing new bone. Osteoinduction, on the other hand, inducts the osteogenesis seen in any bone healing process, which makes Bioglass a class A bioactive material. It is to be mentioned that, class B bioactive material such as Hydroxy Apatite only allows osteoconduction [44].

Bones are capable of self-regeneration, i.e., if any bone is damaged anyhow, that bone will be reproduced and healed by itself. But when massive damage happens, bone tissues itself can't regenerate to fill the damage. In this circumstance's other materials are used to fill the damage and help to grow new tissues with the same strength of natural one. Bioglass is applied to the wound and works so effectively as it is very compatible with the human body and particularly bone tissues. It is very efficient in healing the defected area as it has a great ability to perform with an appropriate host response in situations.

Bioglass implants, when implanted into the human body, form a layer of hydroxyl carbonate apatite on its surface, which is similar to the constituent of bone. At the interface of the osteoblast, the hydroxy carbonate apatite crystals form a bond with the collagen fibrils creating a strong chemical interface. The hydroxy carbonate apatite is formed due to some sequence of reactions that occur when the implant gets in touch with the body fluids. The sequence of reactions is stated bellow (as shown in Figure 1) [45]:

Stage 1: Formations of silanols: Silanols are created due to the hydrolysis of silica groups, which occurs due to the rapid exchange of sodium and calcium ions with hydrogen and hydronium ions.

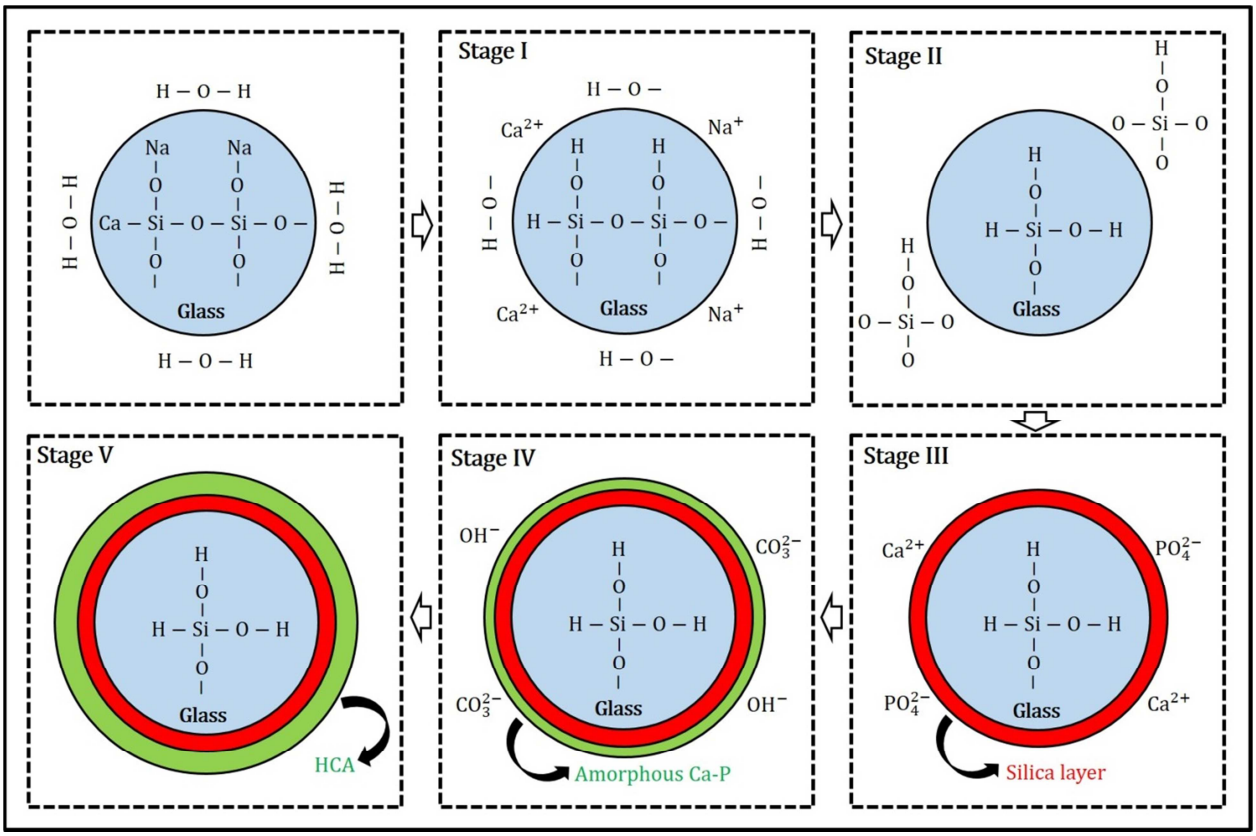

Figure 1. *The formation mechanism of the hydroxyl carbonate apatite (modified image) [5, 135].*

$$Si - O - Na^+ + H^+ + OH^- \rightarrow Si - OH^+ + Na^+(aq) + OH^- \quad (1)$$

Stage 2: Continuity of silanol formation at glass interface: Rapid increase in hydroxyl concentration results in the attack of silica glass network. Silica is lost in the form of $Si(OH)_4$. In this way, Si-O-Si bonds are broken down, and silanol is formed continuously at the interface.

$$Si - O - Si + H_2O \rightarrow Si - OH + OH - Si \quad (2)$$

Stage 3: Formation of silica gel layer: Silinaol groups condense to form silica gel layer by repolymerization reaction.

$$Si - OH + OH - Si \rightarrow Si - O - Si \quad (3)$$

Stage 4: Formation of the first layer: Amorphous calcium and phosphate ion from the surrounding bodily fluid gather at the silica-rich layer and bulk up the Bioglass. A first layer is formed at the top of the silica layer.

$$CaO + P_2O_5 \rightarrow CaO - P_2O_5 \quad (4)$$

Stage 5: Formation of mixed carbonate hydroxylapatite layer: The primary layer formed from stage 4 now incorporates with the hydroxyl and carbonate ions from the bodily fluid to form a layer of mixed carbonate apatite causing it to crystallize.

$$CaO - P_2O_5 + OH^- + CO_3^{2-} \rightarrow Ca_5(PO_4, CO_3)_3(OH) \quad (5)$$

The growth factors then adsorb to the surface of the glass because of having similarities with bone tissue. The adsorbed growth factors activate the M2 macrophages, which promote wound healing. With the activation of M2 macrophage, mesenchymal stem cells and osteoprogenitor cells move to the site and attach to the hydroxy carbonate apatite layer. Stem cells and osteoprogenitor cells at the Hydroxy carbonate apatite surface to produce osteoblast cells. The osteoblasts then generate extracellular matrix which mineralizes as occurs typically in bones (as shown in Figure 2). In this way, bone growth continues [45].

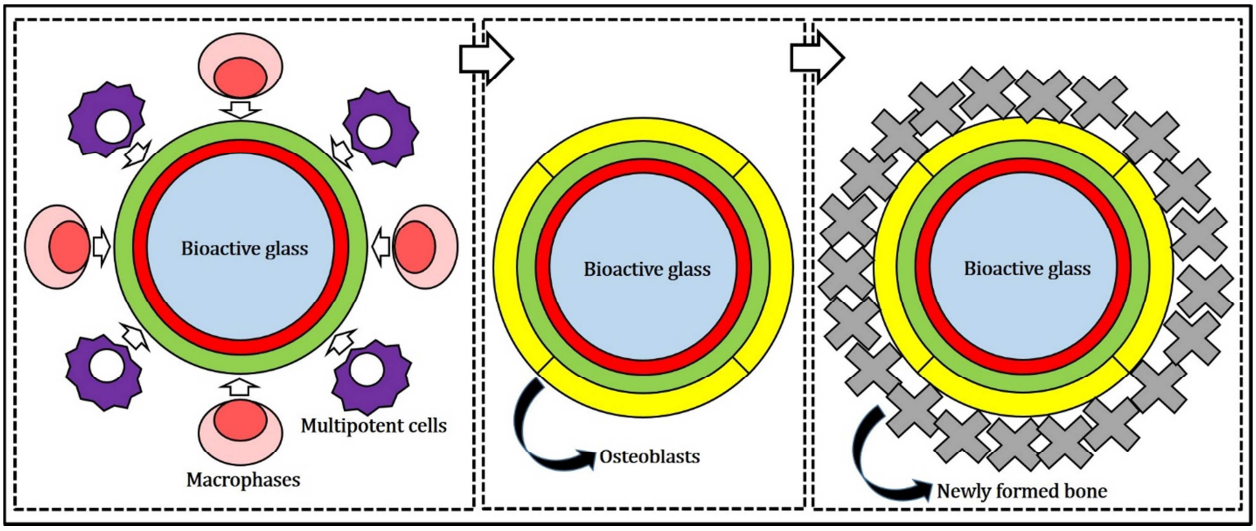

Figure 2. *Formation of bone and growth mechanism (modified image) [135].*

4.2. Mechanical Property

The physical properties that material possesses due to the application of forces are referred to as mechanical properties. These are the properties that affect the mechanical strength of a material and ability to be moulded in a definite shape. Mechanical features include strength, toughness, hardness, brittleness, malleability, ductility, Crip and slip, resilience and fragility. It is essential that the mechanical strength of the synthetic material matches to the nearby tissues. Dense 45S5 Bioglass has a compressive strength of 500 MPa, a tensile strength of 42 Mpa, Young's modulus of 35 Gpa and fracture toughness of 0.7-1.1 Mpa\m^2 [46]. Bioglass has high mechanical strength, so it is used to create composite material to serve as reinforcement. It is used to improve the properties of the polymer, particularly chitosan. It is a great challenge to use the Bioglass to tolerate physiological loads in load-bearing sites. The first-ever bioactive glass foam produced from the 45S5 Bioglass had a lower compressive strength which was not sufficient to meet the strength of trabecular bone. The fracture toughness and wear resistance of 45S5 are also areas to work with to make it more efficient in orthopaedic [47]. A comparison of mechanical properties between bioglass and human bones is stereotyped in Table 4.

Table 4. *Mechanical characterization of 45S5 AND 52S4.6 bioglass and analogy with original human bones [48].*

Implants	Compressive strength (MPa)	Compressive modulus (GPa)	Fracture toughness (MPa $m^{1/2}$)	Bending strength (MPa)	Vickers Hardness (MPa)
45S5		60	0.6	40	-
52S4.6		60		40	-
Trabecular bone	1.5-7.5	0.05-0.6	0.1-0.8	10-20	40-60
Cortical bone	100-135	7-30	2-12	50-150	60-75s

4.3. Thermal Behavior

The suitable sintering condition of Bioglass is 1050°C for about 140 minutes [49]. But To make composite materials, Bioglass can have to experience high-temperature sintering treatment which is about 1300°C. 45S5 Bioglass gets crystallized during heat treatments [50]. The suitable sintering condition of Bioglass is 1050°C for approximately 140 minutes [49]. But, the optimal temperature range for sintering is very close to its crystallization temperature. Therefore, it causes a wide devitrification of the system. Bioglass tends to crystallize during heat treatments because of the low silica content and more network modifiers [50]. The ongoing transformation influences the sintering behaviour of glass in the glass structure during heat treatment. It is thought that the double oxygen bond in P_2O_5 enhances the formation of the phosphate phase and thus causes crystallization [51]. The crystallization causes a slight decrease in hydroxy carbonate apatite formation at the early stages of implantation [52]. The amorphization of the crystalline bioglass implant takes place due to the exchange of the ions [53]. The resulting amorphous Bioglass then shows strong bioactivity [54]. Therefore, it can

be said that though heat treatment causes some sort of decrease in the hydroxy carbonate apatite formation ability, the bioactivity is not decreased at all.

4.4. The Antibacterial Properties of Bioglass 45S5

The antibacterial property is highly associated with the environmental pH. There are various conflicting reports about the antibacterial activity of Bioglass. Bioglass has a better efficiency against the skin and oral pathogens [55]. But its antibacterial mechanism is still unclear. Different mechanisms regarding its mode of action like environment pH change increased osmotic pressure and needle-like sharp glass debris which could destroy bacteria [56]. The antibacterial activity is enhanced with the increase in pH value caused by the release of ions from the Bioglass when immersed in an aqueous environment [57]. Different locations around an implant site have a different level of exposure to bioactive glass. It is thought that the released ions deregulate the extracellular and intracellular enzymatic activities of the bacterial cells.

Moreover, the basic environment resulted from the release of ions, alters the integrity of the cytoplasmic membrane provoking protein denture [58]. A study was published to test the antibacterial activity of bioglass 45S5 under a variety of clinically relevant conditions like direct and indirect contact, the effect of the dissolution products, static and immobile incubation conditions and elevation or neutralized pH. That study illustrated that the antibacterial effect of 45S5 Bioglass particles is primarily driven by pH and that contact between 'needle-like' particles and bacterial cells or changes in osmotic pressure have minimal antibacterial efficacy [59]. However, the antibacterial ability of Bioglass can be enhanced by inorganic modifications. For example, the addition of Ag+, Zn^{2+}, Cu^{2+}, Ce^{4+} and Sr^{2+} all increased the antimicrobial activity of the glasses (as shown in Table 5) [58]. It is to be mentioned this ion also causes the glass to disrupt from its glassy phase to some extent. However, the hypothesized mechanism on how the metallic ions enhance the antibacterial activity is shown in Figure 3.

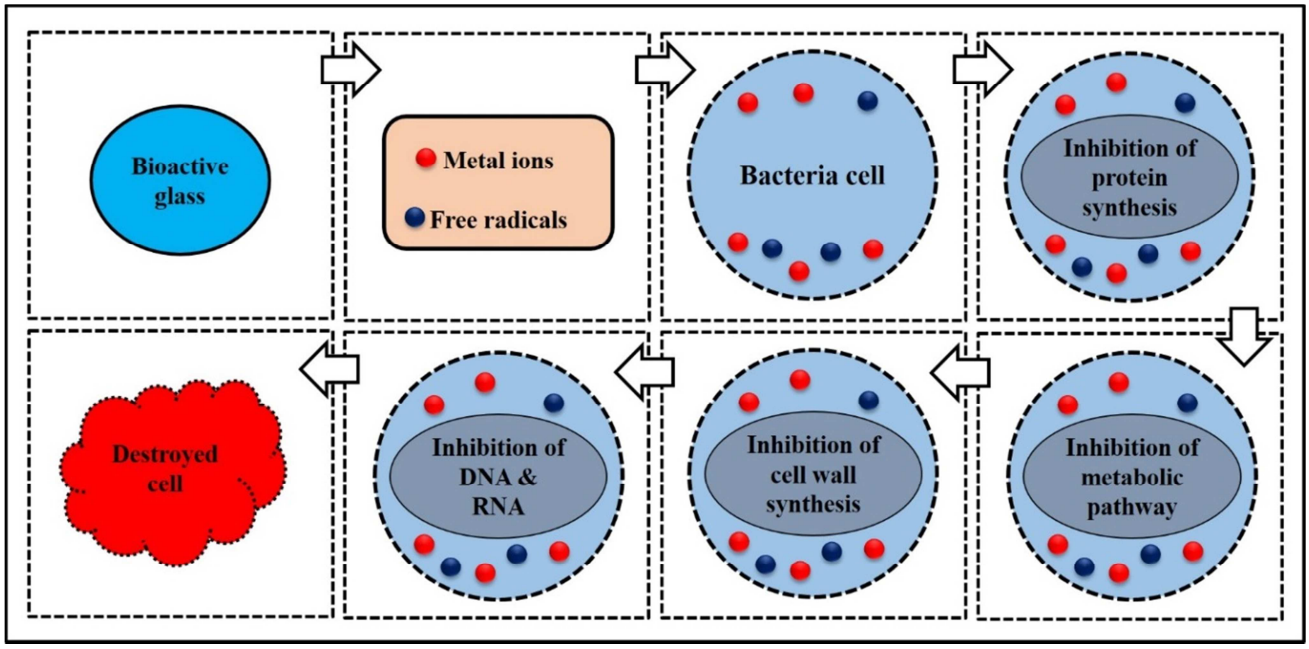

Figure 3. *A hypothesized mechanism for the antibacterial activity of Bioactive glasses (modified image) [58].*

Table 5. *Antibacterial activity of different bioactive glasses showing the most active species during this bacterial deactivation process [58].*

Reactive species	Bioactive glass	Microorganisms	References
pH	45S5	*S. aureus, S. epidermidis, S. aureus*	[56, 59]
	Ti-45S5-Ag	*S. mutans, S. aureus*	[60]
	58S, 63S and 72S	*E. coli, P. aeruginosa,* S. aureus	[61]
	S53P4	*S. aureus, P. aeruginosa, S. epidermidis, E. coli, K. pneumonia, E. faecalis, C. albicans*	[62–64]
Ag+	SiO_2-CaO-P_2O_5-Ag_2O	*E. coli*	[65]
	P_2O_5-CaO-Na_2O-Ag_2O	*S. aureus, P. aeruginosa, E.coli*	[66]
	B_2O_3-Na_2O-P_2O_5-Ag_2O	*L. monocytogenes*	[67]
	Ag_2O-B_2O_3-SiO_2-CaO	*S. aureus, E. coli*	[68]
Zn^{2+}	CaO-MgO-P_2O_5-ZnO	*S. mutans*	[69]
	SiO_2-Na_2O-CaO-P_2O_5-ZnO	*P. gingivalis, P. intermedia, A. actonomycetemcomitans*	[70]
Cu^{2+}	SiO_2-Na_2O-CaO-P_2O_5-B_2O_3-Al_2O_3-Cu	*S. epidermidis*	[71]
	Na_2O-CaO-P_2O_5-Cu	*S. sanguis*	[72]
Ce^{4+}	SiO_2-CaO-P_2O_5-CeO_2	*E. coli*	[73]
Sr^{2+}	SiO_2-CaO-CaF_2-MgO-SrO	*S. aureus, S. faecalis*	[74]
	SiO_2-CaO-SrO-Ag_2O	*E. coli, S. aureus*	[75]

5. Applications of Bioglass

5.1. Bone Tissue Engineering

Bone tissue transplantation is the second most widely used tissue transplantation. Every year over 2 million operations take place in the world [76, 77]. Human bones are rigid organs which can facilitate the mobility of the body and can protect various organs of the body. The bones are formed through two different processes; one is modelling, and the other is remodelling [78]. When a bone is created either by osteoblasts or resorption of bone by osteoclasts, then the bone formation process is called the modelling process.

Whereas, the remodelling process occurs when bone formation follows resorption [79]. In the remodelling process, osteoblast and osteoclast activity occurs sequentially in a coupled manner on a bone surface. Bones are self-regenerative, which means bones can repair and heal itself. Primary or direct bone healing and secondary or indirect bone healing are two bone healing process [80].

Primary bone healing occurs when the fracture gap is less than 0.1 mm, and the defect area is rigidly stabilized. The wound is supposed to fill with continuous osteogenesis and subsequent Harversian remodelling, with the absence of connective tissue [81]. The most common form of bone healing is secondary/indirect bone healing. It happens when the fracture edges are less than twice the diameter of damaged bone [82]. Generally, blood clotting, inflammatory response, fibrocartilage, callus formation, endochondral ossification and bone remodelling help to repair the fracture [83]. Small damages can be repaired or regenerated. In case of significant defects due to degenerative pathologies, injuries, trauma, tumours, infection (osteomyelitis), etc., unique treatments are required. To heal the damages, bone grafts are supplied to the affected area. Bone grafts (Autografts and allografts) are the options for this operation but have some limitations [84, 44].

Some drawbacks of bone grafts are limited availability of tissues, donor site morbidity, pain, disease transmission and immune response to allografts [85]. Scaffolds of different biomaterials are another option of bone regeneration. Bioglass can be used as scaffold and bone graft materials. Before bioactive material, Hydroxyapatite was an excellent choice for scaffold material in significant bone defects, but Bioglass overcomes the limitations of synthetic Hydroxyapatite [86]. The advantages of Bioglass over Hydroxyapatite are fixation with the tissues and the ability to form bonds with both hard and soft bone tissues, whereas Hydroxyapatite only bonds with hard tissues and also requires an exogenous covering for holding the implant in the affected area [87].

Bioglass has excellent bone-bonding ability; to utilize this property, composites containing stainless steel (SS) 316-L fibres and magnesium alloys have been developed for dental and orthopaedic applications [88–93].

Bioglass based composites containing carbon nanomaterials (carbon nanotubes, graphene, and graphene oxide) as reinforcements are used to promote biocompatibility and bone-bonding capability for hard tissues. Also, bioglass reinforcement in ceramic and polymeric matrices can rise the mechanical performance. For soft tissue engineering, Bioglass based composite has been developed by reinforcing Bioglass in biodegradable polymers. Some significant characteristics like mechanical stability, bioactivity and degradation behaviour can be controlled by this reinforcement [94].

Though the mechanical properties of porous polymer-bioglass based composites don't match with natural bones, polymer-bioglass composites are more suitable for soft tissue engineering [95].

To ensure long term successful application of bioglass scaffolds in contact with soft tissues, Pacheo *et al*. suggest three important requirements:

1) Formation of interfacial bond with collagen during the initial stages of implantation.
2) Creation of a stable long-term interfacial bond to prevent the micromotion that has the chance to lead inflammatory responses and
3) Presence of a stress transfer gradient at the interface for discouraging the signals for resorption of either the implant or tissues [96].

Bioglass composites, when coming in contact with tissues, don't show any immune response to the fluid. Another characteristic of bioglass composites is they are entirely biodegradable into the body tissue fluid. After implantation, the composites totally can be reabsorbed by the body tissues and become a part of hard tissues [97, 98]. The controlled degradation property helps patients a lot [99, 100].

5.2. Drug Delivery

For the selection of any drug delivery system, there are some basic criteria such as it is to be inert, biologically compatible, has to possess suitable mechanical strength, needs to be good from the aspect of patient comfort; ability to carry high doses of the drug with no risk of accidental release and must be in easy administering, removal, fabrication, and sterilization. There are three underlying mechanisms of delivering active agents, and these are Diffusion, activation of solvent or swelling, and degradation [4].

A study used Fick's diffusion law to treat osteomyelitis with teicoplanin [101]. The results concluded that Bioglass formed Hydroxyapatite when the drug was released. Bioglass application cured the osteomyelitis in the tibial bone of rabbits in vivo and also helped in the formation of the tibial bone. Vancomycin on bioglass carrier has been tested for treating osteomyelitis with success [102].

Treating significant bone defects, osteoporotic fractures, bone infections and bone tumours, bioceramics act as local drug delivery systems [103].

Some problems were found in traditional drug delivery systems. One of the issues was premature degradation which is the phenomenon of losing the drug activity before reaching the target tissue. Bioglass is used as an alternative since it is excellent in drug delivery as it offers some new possibilities and can overcome the problems. No additional operation is needed as it's for polymeric beads. The synergy of the bioactive behaviour of

bioceramics and the ability for local drug delivery is a great point of view for bone therapy purposes [104].

5.3. Bioglass as Scaffold and Grafting Material

Scaffolds are referred to as supporting materials that are applied to repair or to regenerate the damaged tissues. After the invention of bioglass 45S5 by Professor Hench, it is widely known as a scaffolds material as it possesses such capability and properties [105, 106]. A bone tissue engineering scaffold must be able to act as a transitory skeleton for the attachment, proliferation and differentiation of parent cells. Additionally, the scaffolds need to resorb at the same rate as the tissue regrows [107]. Scaffolds provide mechanical support to the bones as they are porous and degradable as well as allow cells to proliferate and differentiate [108, 109]. The important properties of scaffold materials are biocompatibility, bioactivity, porosity, biodegradability, etc. Bioglass possesses most of these properties such as biocompatibility, bioactivity, degradability over time, and interconnected porosity suitable for bone ingrowth and also provides similar strength to damaged bone [110, 111, 112]. Another important two factor are porosity and degradation interplay. Soon after growing new tissues, the scaffolds are supposed to degrade after a particular time. And pores are vital to interconnect the cells for supply food and oxygen as well as removing the waste products [76]. If the degradation rate of the material increases, then the initial porosity must decrease. Otherwise, the scaffold again absorbs too fast and disables the mechanical support and also the growth will be damaged.

On the other hand, if the materials degrade at a low rate, then high porosity is a must to ensure optimal degradation rate [113]. In this case, the higher specific area increases the degradation rate. The presence of these qualities makes Bioglass very favourable in this sector. Ceramic scaffolds are strong and brittle, whereas polymer scaffolds are weak and malleable. Bioglass scaffolds are very suitable because they interconnect with bones and also provide mechanical strength like actual bone.

Polymers and Bioglass together make great scaffolds having superior properties. Some polymer/bioglass scaffolds designs became successful like foam/sponge-like structure, fibre composite, microsphere scaffolds, Bilayer or multilayer scaffolds and Cell-seeded scaffold [46].

In general idea, bone grafting is a surgical process that fixes several problems related to bones or joints. A bone can be damaged by trauma, infection, or congenital malformations. But bone grafting is a miracle since it replaces the missing bone parts from the bone of the patient's own body or a donor or by the synthetic, artificial or natural substance. The graft is used as a medical procedure to repair damages. It also helps to grow the bone tissues around the implanted device. As bone is capable of regenerating, it fills the area where the bone is missing with the same strength [114].

There are three types of grafts; Xenograft, autograft and allograft.

1) Xenograft: Tissue transplantation from one donor to a completely different species. It is mostly forbidden in most of the country. It is risky and occurs in disease transmission.
2) Autograft: The Source of tissue is the patient's body. The tissue is transplanted from one part of the body to another in the same body. It is not risky at all; no chance of any disease's transmission.
3) Allografts: Tissue transplantation happens from one body to another body of the same species. Allografts are not a great choice of bone grafting. They can always be rejected if the patient's immunity is not that good. Allograft will lose strength over time. Also, there is a risk of disease transmission and the unavailability of donors. Most of the time, tissues of host and donor don't match.

Autografts as regarded as gold standard bone grafts; in possession with osteoconductive, osteoinductive and osteogenic properties, an autologous bone graft can merge into the host bone more quickly [79]. So, an autograft is considered to be the best grafting. But it is to be mentioned that insignificant and critical damage, autograft can't help all the time. There are a lot of differences between the tissues of the same body. Also, limited supply, pain, more blood loss and operative time are the drawbacks of this type of grafting [115, 84, 116, 117].

To overcome these limitations and risks, bioglass bone grafts are too useful in bone tissue engineering. A bone grafting material must be biocompatible, bioresorbable, and osteogenic. Earlier autogenous bone grafts were used, but it doesn't provide enough tissue for filling the wound. Bioglass is way better than the alloplastic materials that transmit diseases [4]. Bioglass makes a strong bond with bone tissues, and it's also biocompatible, osteogenic. Bioglass regenerates the tissues with high compressive strength.

5.4. Dentistry

Due to having compositional similarities, superior bioactive properties and antimicrobial properties, researchers got inspired to work with bioglasses to make them applicable in dentistry. Bioglass was first used as a dental substitute in dentoalveolar and maxillofacial reconstruction, periodontal regeneration and implants [118–120]. Today bioglass possesses a wide range of clinical applications in the dental field. Nowadays Bioglass and its composites are used in implant dentistry, maxillofacial dentistry, dental adhesives, periodontics, enamel remineralization, bone regeneration, dental hypersensitivity, pulp capping and root cannel therapy, restorative materials, air abrasion etc. [38].

Around 35% of patients suffer from dental hypersensitivity. The management of hypersensitivity remains as a challenge among different clinical situations. The specific osteogenic activity of bioactive glass made it very suitable for the management of hypersensitivity by occluding dentinal tubules. Remineralization is a natural repair process for non-cavitated lesions that occurs on the tooth surface. NovaMin®, a branded ingredient that is doing an excellent job in this case. To get relief from immediate and long-lasting tooth sensitivity,

NovaMin® is outstanding.

With the application of Bioglass, white spot lesions can be remineralized. 45S5 is used vastly for this purpose. Novamin and bioglass 45S5 are identical in compositions, but Novamin has an average particle size of 18μm [121]. It is mainly used in commercial toothpaste. Novamin toothpaste releases calcium and phosphate ions when it comes in contact with saliva, which increases the pH level and forms a calcium phosphate layer over the teeth. In this way, Novamin toothpaste helps to reduce hypersensitivity. Fluoride doped bioactive glass has recently proved more efficient in remineralization than Novamin. Bioerodible gel films are also very useful in the delivery of remineralizing agents [122, 123].

Air abrasion is a technique that is used to remove decay from a tooth without using dental drills. Bioglass, particularly Novamin, is widely used in this purpose. Novamin has a hardness of 7GP, which is harder than enamel [124]. Abrasiveness increases with the increase in particle size. Novain is used for teeth whitening because of its abrasion properties. Nowadays, to reduce dentine hypersensitivity and to whiten teeth, Novamin is preferred over sodium bicarbonate because of its air flowability [123].

Restorative dental materials are used to repair or replace a patient's teeth. They are used to create bridges, fillings, crowns and inlays to restore a tooth's appearance, structure and function. Teeth get demineralized by the bacterial attack. Bioactive glasses, particularly 45S5 Bioglass, helps to remineralize the dentine.

Bioglass is also used to maxillofacial surgeries. Bioglass prompts bone formation at higher quality and quantity at a fast rate [122]. Bioglass is very efficient in bone repairing and reducing donor site morbidity in both short-and long-term research [125]. Alkali free bioglass is a superior substitute to 45S5 Bioglass [38].

Bioglass also used in endosseous implantation. Endosseous implants are the most common type of implant. Implants are placed directly into the mandible or maxilla. Bioglass can be the endosseous ridge maintenance implant and is used in the periodontic surgery. This implant can be inserted into fresh extraction sockets. A study showed that cone retention of 85.7% can be achieved and is safe to be used in dental structures and dentures [126]. Stanley et al. found that Bioglass as the most promising implant material in his in vivo study on Baboons. In another implant study, Bioglass is seen as a highly biocompatible innovation because of inflectionless tissue healing with new bone formation [118, 120]. Endosseous implants are not recommended for patients below the age of 16 because of the potential for further growth of jaws.

6. Overview of the Shortcomings of the Bioglass

The glass transition temperature of Bioglass is very close to its crystallization temperature. It is for this reason this glass shows high crystallization tendency during heat treatment. The devitrification results in a decrease in the rate of hydroxy carbonate apatite formation. The crystallization is also responsible for the reduction of mechanical strength of the glass-ceramic scaffolds with low strength. A bioglass needs to have a reasonable degradation rate. It is because degradation avoids the harmful effects of the foreign entity and its gradual replacement with the bone. But the degradation rate of some bioglasses, particularly 45S5, is very slow; therefore, a more significant part of the glass remains unconverted to hydroxy carbonate apatite [2]. The degradation rate of this glass is slower than the formation of new tissue. The unconverted bone remains inside the scaffold creating some sort of in vivo stability issues.

It is mentioned earlier that different modifications (addition of ions like Sr, Cu, Zn) are done in the bioglass structure to show better performance in various clinical applications. But the concentration of these released ions from Bioglass must remain in control. The higher concentration of some ions such as Co^{2+}, Nb^{5+} enhances cytotoxicity. Different factors such as the size of released ion, sintering temperature and pore network of bioglass scaffold play a great role in the ionic release. The porous scaffold of silicate-based Bioglass undergoes denitrification as a result of sintering temperature [6]. A large amount of crystallization can cause an uncontrolled release of ions [127]. On the other hand, pore structures with larger modal diameter provide a faster release of therapeutic ions [127].

Bioglass has a considerable application in drug delivery. But the degradation of Bioglass loaded with biomolecules during sintering is regarded as one of the most significant challenges. Besides, the organic solvents used to prepare Bioglass can affect the biomolecules. The drug release from the bioglass composite is strongly related to its composition [128].

Improving the mechanical strength of Bioglass, particularly 45S5, is another challenge for the future. The macroporous bioglass scaffold is brittle and cannot be used as self-implantation. The poor sintering ability of the glass is mainly responsible for such drawback. It can be solved by applying polymeric coating on the surface of the struts or by tailoring the composition of the glass properly or by optimizing the thermal process [6].

In orthopaedics and dentistry, metallic implants with bioglass coating have been the oldest challenge. Bioglass coatings are biodegradable by nature, and it became a major limitation according to different types of dissolution depends on the glass composition and pH of the environment. Another drawback of Bioglass, used as surface coatings, is the mismatch between thermal expansion coefficient (TEC) and the substrate on which they are applied. So, it is clear that in future, the improvement of TEC and degradation rate of Bioglass will be a challenge [129–131].

Bioglass compositions are very suitable for repairing and regeneration of soft tissues and at present, this quality is assigned to improved angiogenesis because of the release of ionic dissolution products of Bioglass [132]. Understanding the biomolecular mechanism of Bioglass induced

angiogenesis will be a challenge for scientists. In some early applications, investigators reported positively that Bioglass highly contains calcium and that's why Bioglass is a key factor for healing damaged soft tissues.

Usually, if mammalian cells respond to the component positively, it is also effective for the human body. But as the cells are not the same as the Human body, some problems can arise. Again, to confirm cytocompatibility tumour-derived cell lines are used but do not represent specific cells or tissues that come in contact with Bioglass. Primary cells of the patient's body would be the best option, but these are often very delicate [133]. Another limitation is the incubation time. This incubation time (7 days) is short to appear the effects of bioglass composition. It has always been a challenge to use the animal for experiments, and it will always be. For analytical experiments and data, a good number of animals are needed; the experimental process can be crucial. But scientists are allowed to use a minimal number of animals [134].

7. Conclusion

Bioglass offers us a versatile area of research, and day by day, it is becoming an interesting field for researchers. Mainly bone tissue engineering and dentistry are the two sectors where bioglass and bioglass composites are highly used. Bioglass composites are using as an alternative to natural bone grafts. Biocompatibility and bioactivity; these two characteristics made Bioglass based composites suitable for bone transplantation. Despite being brittle, bioactive glasses possess a distinctive set of properties, for example, the ability to degrade at a controllable rate and convert to a Hydroxy Apatite-like material, the ability to bond firmly to hard and soft tissues and to release ions during the degradation process which can promote bone cell growth. Bioglass bone grafts and scaffolds cause no harm to the patient's body as well as being nontoxic plus they are similar to the bones. In this review paper, we highlighted an overall review of Bioglass. Bioglass scaffolds are undoubtedly used excellently because of optimum degradation rate and porosity.

Some limitations are low mechanical strength and low fracture resistance. These limitations can easily be overcome by modifying the composition. Skin regeneration is a new field of Bioglass. In this review paper, we highlighted an overall review of Bioglass. Undoubtedly, Bioglass is a revolutionary invention in medical science and engineering.

Declaration of Conflicting Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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