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OVERVIEW OF HYBRID SILICA AEROGEL AS BIOMATERIAL

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ABSTRACT

Application of hydroxyapatite as a biomaterial in tissue engineering is challenging by its issue on stability. Hence, the capability of silica aerogel in improving the stability and biocompatibility of hydroxyapatite was proposed. Silica aerogel attracts much interest in various applications ranging from construction to medicine because of its excellent properties. This review summarizes the potential of hybrid silica aerogel in biomedical applications in regards to its different compositions. The review covers recent and previous studies on the hybrid silica aerogel, either organic or inorganic which are biocompatible to human cells. The future perspective focusing on the potential of hydroxyapatite incorporated silica aerogel as a biomaterial is also discussed here.

Keywords: Hydroxyapatite, silica aerogel, hybrid, biomaterial

1.0 INTRODUCTION

The development of bioceramic material for the application in medical science and engineering fields rises in the past few decades due to its biocompatibility and high stability in human body [1-2] . Bioceramic does not release toxic element to human body even after exposure for a long time [3-4]. Hydroxyapatite, $Ca_{10}(PO_4)_3(OH)_2$, (HA) which is a type of bioceramic is a common active material suitable for implant and widely used and studied as an alternative material for bone grafting [5-7]. Hydroxyapatite is a major mineral component in natural bone and because of this; it has excellent biocompatibility [6]. During bone remodeling, it can induce the generation of new bone and support bone growth which leads to the formation of a strong bond between hydroxyapatite and natural bone [7]. The bonding strength of the interface is so high that the bone fracture is usually generated within the hydroxyapatite structure. The porosity of the hydroxyapatite contributes to a mechanical interlock which could lead to a stable and strong fixation of the material. Because of this, the strength of the hydroxyapatite implant will be increased with the increasing growth of bone cells inside the pores of the hydroxyapatite [8]. Due to this bonding interface, the bonding strength of hydroxyapatite and bone is much higher than other metal implants [9]. Thereby, the relative micro-movement between the implant and

bone is dramatically reduced by this direct bonding. This is actually very crucial for the recovery of the patient after the implantation procedure taken place [10-11].

However, hydroxyapatite shows some drawbacks when compared with other bioactive materials. The drawbacks of the hydroxyapatite include naturally brittle and poor mechanical properties although it has high biocompatibility and bioactivity [12-13]. The maximum fracture toughness of hydroxyapatite is about 1.0 MPa $m^{1/2}$ while the fracture toughness of human cortical bone ranges from 2-12 MPa $m^{1/2}$ depending on the type and age of the bones [6,14]. The poor impact resistance and low fatigue strength limit the clinical application of this material. In addition, the high chemical stability of stoichiometric hydroxyapatite with body fluids could lead to restrict bioactivity and lowering the effects of osteoconductive [15-16]. This resulted in a longer rehabilitation time for the patients and thus increases the probability of failure due to deficient implant fixation. It is clear that hydroxyapatite cannot be used as a bulk material sustaining tension or impact. Therefore, in order to improve the fracture toughness and flexural strength of hydroxyapatite, there are various techniques could be applied, for instance, refining the microstructure of hydroxyapatite and incorporating reinforcing phases [17–19].

2.0 SILICA MODIFIED HYDROXYAPATITE

Silica, or silicon dioxide (SiO_2) is one of the abundant material on earth formed by silicon and oxygen. It can exists as its own which is not chemically bonded by other elements or it can combine with other elements forming silicates [20]. Silica exists in two major forms which are crystalline and amorphous where both of which may be derived naturally or synthetically produced [21]. Silica could affect human health in which the crystalline silica could give adverse health effects such as silicosis and possibly cancer whereas, there is still unclear effects of amorphous silica on human health [22–24]. It is perhaps surprising that silica is more often associated with humans and animals [25-26]. The normal blood level of silica in humans is reported less than 5 mg/L and the level of silica in organs such as brain and muscle varied between 2 and 10 mg/L [27-28]. The silica content of bone and other connective tissues was found to be much higher ranging between 12 and l00 mg/L [24,27]. In animals, silica is found in skin, muscle, tendon, hair and feathers [28].

Silica is one of the most important element in cell growth, as it plays a role in initial calcification and the formation of collagen in cells and tissues [29]. The role of silica in the development of skeletal tissue and formation of bone has been proven by Carlisle [17] and its role in osseointegration has been extensively studied by other researchers [25,29-30]. In term of its usage for chicks' development, silica was shown to assist the growth of feather and skeleton as well as production of connective tissue [31-32]. The concentration of silica in young growing bones was in the same range with that of calcium, phosphorus and calcium [32-33]. Silica has a role in bone matrix formation prior to calcium deposition where the calcium is replaced with silica which could happen at the stage of bone maturity progressing [25,34].

The positive effect of silica in the cell growth could cause increasing interest of researchers to work on silica modified hydroxyapatite as an advanced biomaterial [35]. A series

of studies related to the incorporation of silica into hydroxyapatite structure have been reported [18,36, 37]. Previous studies have demonstrated that the incorporation of silica into hydroxyapatite significantly increase the rate of bone apposition to hydroxyapatite bioceramic implants [15]. Furthermore, a composite matrix of hydroxyapatite-silica core-nanorods enhanced vascularization in the chicken chorioallantoic membrane and enhanced new bone formation of critical-sized femoral segmental defect in rats [37]. The formation of new bones and tissues increased with the increasing silicate substitution for phosphate ions in hydroxyapatite [11,38]. Silica was reported to be important in enhancing the bioactivity of hydroxyapatite [39]. It is due to the existent of silanol groups and resorption of silica during treatment and cells are positively influenced by this released phenomenon [40–42]. Recent reports confirm that the *in vivo* dissolution of silica modified hydroxyapatite increased with the silica content and it was found to be strongly affected by the silica modified hydroxyapatite structure [31]. Rapid release of soluble silica from bioactive glasses leads to rapid proliferation of new bone within a bone defect site [18,31,43]. Other study found that the volume of unit cell and the parameter length of the hydroxyapatite decreased as the silica content increased [44]. Thus, the disorder and defect structure of silica modified hydroxyapatite offers more improved performances due to unusual chemical synergistic effects of the materials [38,45-46]. The structural disorder and the microstructure defects of silica modified hydroxyapatite decreased the stability of apatite structure and was found to be the starting point of dissolutions and contributed to the higher reactivity [46–48]. The reactivity is also enhanced when silica exists as a tetrahedral silicate, SiO_4, groups rather than in SiO_2 polymeric form [25,49]. The tetrahedral distortion provides excellent surface for integration of osteoblast cells [50]. However, the incorporation of tetrahedral silicate into hydroxyapatite lattice requires high temperature treatment under controlled stoichiometry conditions using several precursors [51-52]. Whereas, a high temperature treatment significantly decrease the concentrations of silanol groups and increase the crystallinity of hydroxyapatite [53-54]. Thus, apparently it limits the bioactivity of silica modified hydroxyapatite.

Therefore, the sol-gel technique, which is the established technique for the synthesis of tetrahedral silica modified hydroxyapatite, is capable to improve various conventional techniques [19,34,55, 56]. Sol-gel technique is used in various applications because of its capability in forming pure and homogenous yield at a lower temperature [57-58]. This technique can control the composition and microstructure at the molecular level. In addition, the sol-gel technique is able to shape the materials at room temperature such as by casting bulk gels in the moulds, dip coating thin film or spinning fibres. Because of these advantages, the sol-gel technique could be an alternative technique in the conventional process of ceramic where the powder is designed into an object and eventually, densified at a temperature close to its liquids condition [59]. Dong and his coworkers [56] successfully fabricated a novel hydroxyapatite-chitosan-silica hybrid by combining the sol-gel method and 3D plotting technique. The hybrid material showed increased mechanical strength under humid condition.

3.0 SILICA AEROGEL

A new generation of bioactive glasses has emerged in biomedical applications after silica-based bioactive glasses have been found and researched by Hench in 1971 [60-61]. It leads to the development of a wide area of research on the new silica-based bioactive materials and recently, the potential applications of silica-based materials have been expanded for bone tissue regeneration and drug delivery purposes [17]. The use of silica in medical devices is mainly based on the development of silica based glasses which have been found to form bonding with living tissues [30,33]. The immersion of silica based glasses in body fluids generates reactive layers on its surfaces [25,62]. These reactive layers facilitate the formation of chemical bonding between the glasses and the bone [63-64].

According to preliminary finding by Hench [60], only composite ceramics contained SiO_2, Na_2O and CaO in a specific composition have the ability to build bonds with bone due to their ability in creating super-saturation Ca/P condition at surface glass and body fluid boundary. However, recent studies confirmed that pure silica glass which was prepared by hydrolysis and condensation of silicone alkoxide precursors after heat treated at 400ºC could also induce the formation of apatite on its surfaces upon immersion in simulated body fluid (SBF) [39,65]. However, the rate of apatite formation on silica glass decreased with the increment of heat treatment up to 900ºC [66]. Studies also showed that conventional silica glass which was heat treated at 900°C and dense silica glass or quartz did not exhibit any bioactivity after immersion in SBF [42,67]. Since the formation of apatite layer depends on silanol groups on silica surface, heat treated silica glass at 900°C that can reduce silanol groups on its surfaces, prevents the formation of apatite layers [68]. Hence, the sintering process involved in the synthesis of conventional silica glass can cause the reduction of silanol groups, thus lowering its bioactivity [58]. Therefore, it is crucial to develop a new class of pure silica gel which its synthesis route and its properties are compatible to human body. This is due to the finding that the calcination of the silica aerogel did not affect its bioactivity [69].

Silica aerogel is one type of silica-based material having unique properties. It is a strong material and very light (Figure 1). Since its appearance is in hazy blue form and made up by the transparent polymer, it is often called “frozen smoke” [70]. This happen based on the synthesis procedure of the silica aerogel where the entrapped solvents inside the prepared wet gels are removed without damaging its porosity thus, making it lighter than other materials [71]. The synthesis procedure of silica aerogels is typically known as a sol-gel technique which involves hydrolysis and condensation reactions of typical source of silica which is silicon alkoxide in a solvent and finally, the removal of this solvent at supercritical drying stage [58,72]. Examples of the source of silicon alkoxide are tetramethylorthosilicate (TMOS) and tetraethylorthosilicate (TEOS) [72]. This synthesis procedure produced silica aerogels with microstructure particles that link together creating nano-sized pore and nano-particles [73].

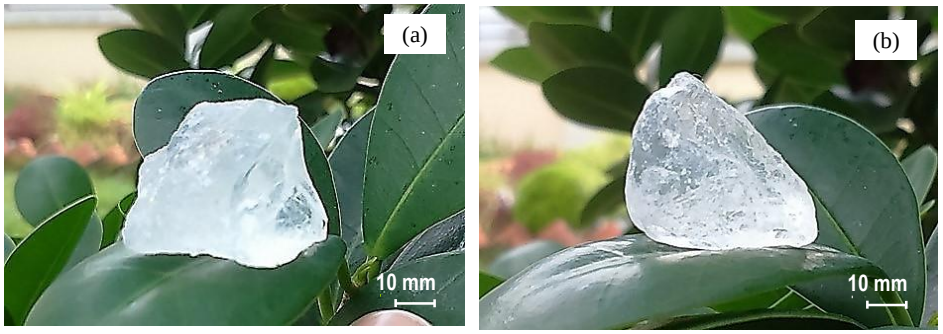

Figure 1 Photographs of (a) before and (b) after calcination at 900°C, silica aerogel that synthesized from rice husk ash, on a leaf of Ficus Bonsai Tree

Like other silica based material, one of the applications of the silica aerogels is an insulator where electric charges do not flow inside this material. It is an excellent insulator having low bulk density, high melting point and a low thermal conductivity [56]. Besides that, its pore size and volume could be tuned at the synthesis or post-synthesis stage [73]. These are some applications of silica aerogels: major component in ceramics, cement [35] and glass [74], as an adhesive agent in pharmaceuticals [75], as a catalyst [76], drug delivery system [77–79], as a magnetic fluorescent nanoprobe in biomedical imaging [80] and as an adsorbent for the removal of oil from water stream [71,81]. The overview of the types and applications of silica aerogels is summarized in Table 1.

Table 1 Overview of various types of aerogels and their applications.

Type of Aerogel	**Application**	**Ref.**
Silica aerogels (thin films). Thicknesses from 1 µm to 100 µm	Electrodes, batteries capacitors, high voltage insulators	[82]
Aluminosilicate aerogels. Specific surface area 680 ± 10 m^2/g	Piezoelectric devices	[83]
Carbon aerogels. Specific surface area 600-800 m^2/g	Supercapacitors	[84]
Silica aerogels. Thermal expansion coefficient 4 × 10^{-6} K^{-1}	Cherenkov detectors	[85]
Organic aerogels. Thermal conductivity 0.003-0.011 W/mK	Thermal superinsulators	[86]
Carbon aerogels. Density 0.07 g/cm^3	Solar-energy collectors	[87]
Silica aerogels. Extreme fragility	Aerospace applications	[88]

Table 1 (*Cont.*) Overview of various types of aerogels and their applications.

Type of Aerogel	Application	Ref.
Nanocellulose fibers-collagen composite aerogels. Density 0.02-0.03 g/cm3, porosity 90-95 %	Tissue engineering, wound dressing	[89]
Polysaccharide aerogels. Surface area 570 m^2/g (calcium-cross-linked sodium alginate aerogels), density 0.27 g/cm^3 (starch monolith aerogel), mesopore volume 2.6 cm^3/g (Ba-alginate beads)	Food-related technologies	[90]
Hydrophobic bimodal mesoporous silica aerogels. Surface area 1329 m^2/g, pore volume 5.3 cm^3/g and pore size 19.82 nm using cetyltrimethyl ammonium bromide as a structure directing agent	Green application	[91]
Copper silica aerogel catalyst. Surface area 836 m^2/g	Hydrogen fuel cells	[76]

4.0 HYBRID SILICA AEROGEL IN BIOMEDICAL APPLICATION

Like other silica based materials, silica aerogels could also be applied in biomedical area because of its microstructure which is in amorphous state and pores in nano-sized created by the interconnection of their particles [92-93]. Currently, intense research works have been done on the applications of silica aerogels as a controlled release of drugs, peptides, enzymes and hormones [94–96]. The important feature of silica aerogel is its ability to host molecular size of particles within its network. Several works also showed that the silica aerogel is a biocompatible material, which can interact safely with human cells. Because of its biocompatible, it can be used as a scaffold to immobilize biological compounds for various applications as well as a matrix in the biosensor design [97-98]. One of its unique characteristics related to its application as a bone implant is its ability to be tuned and engineered so that it can stimulate the bone bioactive characteristics similar to that of conventional bioactive glass [57]. Silica aerogel can act as a carrier for biological active agents, bone substitute and drug delivery system because it can be synthesized at low temperature and this condition could preserve the activities of the biological and drugs compounds [99]. Besides that, its tetrahedral networks with silanol-rich groups make it a potential biomaterial with enhanced biocompatibility properties [69,100].

Salinas and her colleagues [49] have successfully synthesized hybrid organic-inorganic silica aerogel having bone bioactive characteristics similar to the bioactive glass via sol-gel technique. However, the synthesized material has higher mechanical properties and also the elastic modulus of 72.4 MPa which is suitable for bone implant. In other works, the composite of silica aerogel with crosslinked dialdehyde nano-cellulose fibres and collagen could be used

for wound dressing [89]. This was due to the properties of the composite which has 93% porosity, biocompatibility against fibroblast cells and also 3000% water absorption ratio. Thus, the hybrid organic-inorganic silica aerogel is also an alternative material for biomedical application. Silica aerogels were also reported to have interaction with physiological fluids. This resulted in the apatite layer formation similar to that of natural bone because of the presence of silanol group (Si-O-H) on their surfaces [50,101] and thus could lead to their application for bone tissue regeneration [62,102]. As a bone tissue regeneration, the unique properties of silica aerogels such as highly interconnectivity and porosity enhance cells penetration and eventually, aid the cell attachment [57]. The synthesis conditions of silica aerogels which is low pressure and low temperature will produce silica aerogels that are rich in silanol groups and it could enhance the bioactivity of the material, promote cell attachment; proliferation and differentiation and also exhibit controlled biodegradation or resorption rate simultaneous with the new tissue formation [69,95].

Study by Mallepally et al. [98] on the application of silk fibroin silica aerogel scaffolds as biomaterial showed the presence of human foreskin fibroblast cells in the scaffolds, as shown in their *in vitro* cytocompatibility test. Silica aerogel could increase the proliferation of the cells because of its unique properties where its network allows unhibitied transfer of nutrients and metabolic wastes. The chitin silica aerogel prepared by Ding [103] could improve the fibroblast cells attachment and its morphologies were maintained as compared to the control sample. This was due to the high surface area and porosity of the prepared material that resulted in the ability to adsorb liquids similar to that of extracelullar matrices. There are other types of hybrid aerogels that could be applied in biomedical area and they are tabulated in Table 2.

Table 2 Overview of the application of hybrid aerogel in biomedical area.

Type of Aerogel	**Application**	**Ref.**
Polyurea-nanoencapsulated macroporous silica aerogels, chitosan-silica hybrid aerogels	Tissue engineering, wound dressing	[104]
Alginate-starch aerogels. BET surface 183-544 m^2/g, pore volume 2.0-6.8 cm^3/g	Tissue engineering, wound dressing	[102]
Surface-functionalized aerogels, composite aerogels	Drug delivery applications	[105]
Poly-e-caprolactone (PCL) hybrid aerogels	Bone tissue engineering	[106]
Pectin-sodium montmorillonite clay-aerogel composite. Modulus of 114 ± 9 MPa and a specific modulus of 609 ± 53 Mpa cm^3g^{-1}	Biodegradable and bio-based polymers	[107]
Macroporous silica aerogels. Density: 400 kg/m^3, diameter 47 mm (disks), thickness 1 mm	Biosensors and diagnostics	[97]

Table 2 (*Cont.*) Overview of the application of hybrid aerogel in biomedical area.

Type of Aerogel	Application	Ref.
Polysaccharide aerogels. Surface area 570 m^2/g (calcium-cross-linked sodium alginate aerogels), density 0.27 g/cm^3 (starch monolith aerogel), mesopore volume 2.6 cm^3/g (Ba-alginate beads)	Food-related technologies	[90]
Calcined silica aerogel from rice husk ash	Resorbable biomaterial	[69]
Polysaccharide-based aerogels. Surface area 70-680 m^2/g, porosity 90-99 %, density 0.07-0.46 g/cm^3	Drug delivery applications	[108]
Silica-pseudowollastonite aerogels	Bone tissue regeneration	[50]
Silk fibroin aerogels. Surface area 308 m^2g^{-1}, compressive modulus 174 kPa.	Tissue engineering, wound dressing	[98]
Hydroxyapatite incorporated silica aerogel	Biomaterial for soft tissue applictaion	[109]

5.0 Hydroxyapatite Incorporated Silica Aerogel

Although vast studies have been reported on the synthesis techniques and roles of silica-substitute hydroxyapatite in bone repairing, the immobilization of hydroxyapatite in silica aerogel sphere matrices has so far not been reported. Owing to its nanostructure, high porosity, high specific surface area and extremely low thermal conductivity, silica aerogel is considered as an efficient system for implant application [69,102,108]. The high porous silica aerogel could enhanced the bioactivity of cell, bone ingrowth, mineral opposition rate and bone organization, as the porous structure stabilizes the interface between the material and the surrounding bone tissue [94-95]. Hydroxyapatite could be incorporated into silica aerogel tetrahedral networks (hydroxyapatite- silica aerogel) via ambient colloidal sol-gel technique [109]. It can be synthesized by the immersion of commercial hydroxyapatite in silica sol prior to the synthesis of silica aerogel [110]. Through this method, hydroxyapatite is expected to be incorporated in the silica aerogel network since the hydroxyapatite could be added into the silica sol before the gelation stage [109]. Theoretically, hydroxyapatite-sol interaction that established from the addition of hydroxyapatite into the sol before the aging process promotes the incorporation of hydroxyapatite into growing silica aerogel networks. The large number of non-bridging electrons available on the surface of hydroxyapatite promote an extensive weakly hydrogen bonding with the silicate polymer containing Si-O(H)-Si and Si-OH fragments, during the initial stages of the network formation [111]. This stimulates the formation of gel networks around the hydroxyapatite, as it acts as a template, and eventually forms a porous inorganic polymer cage surrounding the hydroxyapatite.

Hydroxyapatite is expected to be easily bound to silica aerogel networks via sol-gel technique due to the silica-rich gel layers of silica aerogel which consists of hydroxyl groups

[111]. A mechanically strong bonding between silica aerogel and hydroxyapatite can be achieved and hence, the leaching of hydroxyapatite can be avoided. It is expected that the diffusion resistance of cell in silica aerogel network will occur [112]. However, this effect can be reduced due to the open pore structure of silica aerogel and its network is in nano-sized [94]. The gel undergoes solvent extraction process before submitted to drying process. Thus, solvent extraction will avoid drastic changes of a gel texture due to the capillary stressed during the drying process [113-114]. In this way, its structure does not collapse and the silica aerogel retains its original nano-structured [115]. Thus, the silica aerogel network will be preserved and the interconnected pores of silica aerogel will facilitate cellular colonization and vascularization as well as to provide channels for tissue-fluid circulation and the removal of metabolic waste products. It allows cells to quickly move into the interior regions of the particles and subsequently interacts with hydroxyapatite [116-117]. The incorporated hydroxyapatite will act as guidance for bone migration and thus promoting the cells penetrating and growing in the materials. Hence, new bone will form a bonding at the interface and inside the materials, eventually it will cause a strong cell adhesion [118-119]. The reactivity of hydroxyapatite-silica aerogel will be improved due to the high surface area and silanol-rich properties of silica aerogel [58]. A mechanically strong bond between hydroxyapatite- silica aerogel and natural bond can be achieved as silica-rich gel layers are formed on the surface of natural bone at implantation site [31,108]. By using the sol-gel technique, the particle size of hydroxyapatite-silica aerogel can be controlled either in micro or nano-size and thus the resorption rate of silicon can be tailored [109]. Besides that, silica aerogel can exist in the form of hydrophilic or hydrophobic depending on the presence of hydroxyl groups on its surface [111]. Because of this, the solubility problem of hydroxyapatite can be resolved by the bonding of this ceramic with silica aerogel frameworks [120]. Sol-gel technique is capable to overcome the difficulty of synthesized hydroxyapatite in aqueous solution as it is normally tends to incorporate impurities in the crystal lattice and grows into larger particles than those found in bone [121-122].

Revealing the interactions between hydroxyapatite-silica aerogel and cells will contribute to better understanding of various chemical and biochemical processes that occur when different synthesis conditions are applied. The fundamental understanding of the hydroxyapatite-silica aerogel interactions can help in improving the fabrication of hydroxyapatite-silica aerogel as a potential biomaterial with enhanced mechanical properties and biocompatibility performance. Hence, this enables new biomaterials with better activities for implant technology to be developed.

4.0 CONCLUSION

This paper presents an inclusive review on the potential of hybrid silica aerogel in biomedical application. The vast number of available references shows that silica aerogel has a great application prospect in the development of modern biomaterial. In addition, the silica aerogels can be arranged and engineered to exhibit bioactive property similar to that of bioactive glasses. It can be synthesized at low temperature which could be beneficial for incorporating or encapsulating other bio-active agents and also suitable for bone substitution and drug delivery system. Thus, it drew the future perspectives on the ability of hydroxyapatite incorporated silica

aerogel as a potential biomaterial. The incorporation of hydroxyapatite into silica aerogel tetrahedral networks via ambient colloidal sol-gel technique could improve the mechanical properties and biocompatibility performance.

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