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# Nanoscale bioactive glasses and their composites with biocompatible polymers

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# ARTICLE INFO

Article type: **Review** article Article history: **Received September 2014** Accepted November 2014 January 2015 issue **Keywords**: **Biocompatible polymers** Nanoscale **Bioactive composites** Microemulsion Laser spinning Sol-gel techniques Flame sprav synthesis Borate and phosphate Nanofibres

# ABSTRACT

Nanoscale bioactive glasses and their composites with polymers gained attention of scientific community due to their biocompatibility. The combinations of bioactive glass (nanoparticles or nanofibers) with polymers have been proven good biocompatible and have been applied successfully in various fields. In his article, the types of bioactive glasses (silicate, phosphate and borate), compositions of various bioactive glasses, bioactivity mechanisms, characteristics, fabrication techniques were overviewed. The composites containing nanoscaled bioactive glass, natural polymer/nanocomposites and nanocomposites nanofibres have also been discussed. Moreover, the future trends and challenges have been also highlighted.

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**Capsule Summary:** Nanoscale bioactive glasses composites biocompatible polymers have diverse applications and can be prepared using different techniques with varying properties and such type of composites are excellent candidates for biomedical applications.

**Cite This Article As:** M. Iqbal and R. A. Khera. Nanoscale bioactive glasses and their composites with biocompatible polymers. Chemistry International 1(1) (2015) 17-34.

# INTRODUCTION

A bioactive material is defined as a material that go through specific surface reactions, when inserted into the body, leading to the formation of hydroxyapatite (HA) like layer that is responsible for the formation of a firm bond with hard and soft tissues (Kokubo et al., 2006). The ability of a material to form an HA-like surface layer when immersed in a simulated body fluid (SBF) *in vitro* is often taken as an indication of its bioactivity (Kokubo et al., 1990). Bioactive glass has an amorphous structure, consisting of a composite of a crystalline phase and a residual glassy phase. There has been increased interest in the science and biomedical application of bioactive glass over the last two decades, as evidenced by the growing number of publications in this field and published paper up to 2010, can be seen in Fig. 1 (Rahaman et al., 2011).

The number of bone diseases and trauma in the whole world has increased significantly in the past decades. The treatment of various pathologies in orthopaedic and dental surgery requires the implantation of a biomaterial to compensate for bone loss due to trauma and fracture and promote healing. Many materials have been developed for bone tissues replacement. They need to be stable for a long period of time and firmly fixed to bone (Wu and Chang, 2012). Bioactive glasses are considered as an important bone regeneration material due to their excellent osteoconductivity and osteostimulativity (Wu and Chang, 2012). They are regarded as important biomaterials for the repair and reconstruction of diseased bone tissues, as they exhibit outstanding bonding properties to human bone (Mackovic et al., 2012). They are reported to be able to stimulate more bone regeneration than other bioactive ceramics (Jones, 2013). Bioactive glasses are being developed for tissue engineering applications (Hench and Wilson, 1984; Hench, 1998; Rahaman et al., 2007). Bone tissue engineering is one of the possible most exciting future clinical applications of bioactive glasses, e.g. to fabricate optimal scaffolds with osteogenic and angiogenic potential (Chen et al., 2006). Other clinical applications of bioactive glasses are reported to be periodontology (Zamet et al., 1997; Gatti et al., 2006) endodontology (Zehnder et al., 2004; Gatti et al., 2006; Waltimo et al., 2009) or as coating on metallic orthopedic implants (Kitsugi et al., 1996; Vega et al., 2002). The schematic diagram of key factors involved in the design of optimal scaffolds for bone tissue engineering is shown in Fig. 2 (Guarino et al., 2007).

The range of bioactive glasses exhibiting these attractive properties has been extended over the years, in terms of both chemical composition and morphology, as new preparation methods have become available. Both micronsized and nanoscale particles are considered in this application field (Rezwan et al., 2006). All the specific effects and advantages of bioactive glasses including surface bioreactivity, can be enhanced or modified and controlled to a greater extent, if nanoparticles (or nanofibres) are available, as opposed to conventional micron-sized powders. This is relevant both for bioactive glasses used in particulate form as coatings in biomedical devices or as filler in composite materials, e.g. as biodegradable implants, dental fillers, tissue engineering scaffolds, tissue guidance membranes or drug delivery systems (Boccaccini et al., 2010).

Iyyappan and Wilsonn synthesized nano-sized rod like hydroxyapatite (HA) particles using Ca(NO<sub>3</sub>)<sub>2</sub>.4H<sub>2</sub>O and (NH<sub>4</sub>)2HPO<sub>4</sub> as precursors with varying contents of non-ionic surfactant viz., p-(1,1,3,3-tetra methyl butyl) phenoxypoly(oxyethylene)glycol (tritonX-100) as organic modifer. The crystalline phase, chemical composition, surface area and morphology of the prepared samples were characterized XRD, FTIR, BET surface area analysis, HRSEM and TEM (Iyyappan and Wilsonn, 2013).

Bioactive glass/biodegradable polymer composite materials have appeared recently as new family of bioactive materials with applications ranging from structural implants to tissue engineering scaffolds. These composites utilize the flexibility of polymers with the firmness, strength and bioactive character of the bioactive glass fillers (Rezwan et al., 2006). Moreover, the surface modification of such biodegradable composites with smart polymers allows producing substrates in which bio-mineralization could be triggered by the action of external stimuli, such as temperature or pH (Dias et al., 2008). Polymer-silicate nano composites have been developed to address a huge number of biomedical applications (Fig. 3) (Wu et al., 2010).

# **TYPES OF BIOACTIVE GLASSES**

# Silicate bioactive glass

Bioactive glasses of silicate composition, first developed by Hench and co-workers (1969), represent a group of surface reactive materials which are able to bond to bone in physiological environment (Hench et al., 1971; Hench, 1998). Bioactive glasses most widely used in biomedical applications consist of a silicate network incorporating sodium, calcium and phosphorus in different relative proportions. The classical 45S5 bioactive glass composition universally known as bioglass (45% SiO2, 24.5% Na20, 24.5% CaO and 6% P2O5), has been the most widely studied glass for biomedical applications (Hench, 1998). This silicate glass based on the 3-D glass-forming SiO<sub>2</sub> network in which Si is fourfold coordinated to O. The key compositional features that are responsible for the bioactivity of 45S5 glass are its low SiO<sub>2</sub> content (when compared to more chemically durable silicate glasses), high Na<sub>2</sub>O and CaO (glass network modifiers) content and high  $CaO/P_2O_5$  ratio (Table 1) (Rahaman et al., 2011). It is used in clinical treatments of periodontal diseases as bone filler as well as in middle ear surgery. Other bioactive glass compositions contain no sodium or have additional elements incorporated in the silicate network such as fluorine, magnesium, strontium, iron, silver, boron, potassium or zinc (Lao et al., 2009).

### Mechanisms of bioactivity

The mechanisms of bioactivity and bone bonding of 45S5 glass have been widely studied and the bonding of 45S5 glass to bone has been attributed to the formation of a carbonate substituted hydroxyapatite-like (HCA) layer on the glass surface in contact with the body fluid. Because this HCA layer is similar to the mineral constituent of bone, it bonds firmly with living bone and tissue. However, details of the chemical and structural changes during this process are not clear. The HCA layer is generally believed to form as a result of a sequence of reactions on the surface of the bioactive glass implant, as mentioned below (steps 1-5) (Hench, 1998).

Stage 1: In this step, a rapid ion exchange reactions between the glass network modifiers (Na<sup>+</sup> and Ca<sup>2+</sup>) with H<sup>+</sup> (or H<sub>3</sub>O<sup>+</sup>) ions from the solution, leads to hydrolysis of the silica groups and the creation of silanol (Si–OH) groups on the glass surface. During this reaction, the pH of the solution increases due to the consumption of H<sup>+</sup> ions as;



Fig. 1: Published paper up to 2010 (Rahaman et al., 2011)



**Fig. 2:** Schematic diagram of key factors involved in the design of optimal scaffolds for bone tissue engineering (Guarino et al., 2007)



Fig. 3: Polymer-silicate nanocomposites applications



**Fig. 4:** Schematic diagram for the sol-gel synthesis process of bioactive glass nanoparticles

Stage 2: The increase in pH (or OH concentration) leads to attack of the  $SiO_2$  glass network and the dissolution of silica, in the form of silicic acid,  $Si(OH)_4$ , into the solution and the continued formation of Si–OH groups on the glass surface take place. The solubility of silica is low, the products of 45S5 glass and glass–ceramic dissolution in aqueous solutions have shown an increase in Si concentration (Rohanova et al., 2011; Rahaman et al., 2011) indicating that dissolution of silica is an important mechanism. However, other mechanisms could also contribute to the increase in Si concentration as;

Si-O-Si + H₂O → Si-O-H + OH-Si

Stage 3: The condensation and polymerization of an amorphous SiO<sub>2</sub>-rich layer (typically 1–2 lm thick) took place in step 3 on the surface of the glass and depleted the Na<sup>+</sup> and Ca<sup>2+</sup> ions<sup>-</sup>

Stage 4: In forth step, turther dissolution of the glass, coupled with migration of  $Ca^{2+}$  and  $(PO_4)^{-3}$  ions from the glass through the SiO<sub>2</sub>-rich layer and from the solution, leading to the formation of an amorphous calcium phosphate (ACP) layer on the surface of the SiO<sub>2</sub>-rich layer.

Stage 5: The glass continues to dissolve, as the ACP layer incorporates  $(OH)^{-}$  and  $(CO_3)^{-2}$  from the solution and crystallizes as an HCA layer.

With the initial formation of an HCA layer, the biological mechanisms of bonding to bone are believed to

involve adsorption of growth factors, followed by attachment, proliferation and differentiation of osteoprogenitor cells. Osteoblasts (bone-forming cells) create extracellular matrix (collagen), which mineralizes to form a nanocrystalline mineral and collagen on the surface of the glass implant while the degradation and conversion of the glass continues over time (Rahaman et al., 2011).

# a) Borate bioactive glass

More recent work has shown that certain compositions in other glass-forming systems, such as borate glass are also bioactive (Table 1) (Pan et al., 2010). Because of their lower chemical durability, some borate bioactive glasses degrade faster and convert more completely to an HA-like material, when compared to silicate 45S5 or 13-93 glass. The conversion of borate bioactive glass to HA appear to follow a process similar to that described for 45S5 glass, but without the formation of an SiO<sub>2</sub>-rich layer (Rahaman et al., 2011). Borate bioactive glasses have been shown to support cell proliferation and differentiation in vitro, as well as tissue infiltration in vivo. Borate bioactive glasses have also been shown to serve as a substrate for drug release in the treatment of bone infection. Recent work has shown the ability to control the degradation rate of bioactive glass by manipulating its composition. For example, by partially replacing the SiO<sub>2</sub> in silicate 45S5 or 13-93 glass with B<sub>2</sub>O<sub>3</sub> (yielding a borosilicate bioactive glass), or fully replacing the  $SiO_2$  with  $B_2O_3$  (producing a borate bioactive glass), the degradation rate can be varied over a wide range. The ease of manufacture and the ability to control the degradation rate of these borate-based glasses make them particularly useful for promoting the regeneration of bone. By controlling the glass composition, it should be possible to match the degradation rate of borate-based bioactive glass with the bone regeneration rate. Another possibility is to exploit the compositional flexibility of glass so that it also can serve as a source of many of the minor elements known to favor bone growth such as Zn, Cu, F, Mn, Sr and B. As the glass degrades in vivo, these elements are released at a biologically acceptable rate (Rahaman et al., 2011).

#### b) Phosphate bioactive glass

Phosphate glasses, based on the  $P_2O_5$  glass-forming network and CaO and Na<sub>2</sub>O as modifiers (Table 1), have also been developed for biomedical applications. As their constituent ions are present in the organic mineral phase of bone, these glasses have a chemical affinity with bone. The solubility of these glasses can be controlled by modifying their composition; therefore these glasses may have additional clinical potential as resorbable materials (Rahaman et al., 2011).

# Characteristics of nanoscale bioactive glasses



**Fig. 5:** SEM micrographs of the produced nanoparticles with different shape and formulations through sol-gel technique



**Fig. 6:** Scanning electron microscopy images of bioactive glass nanofibres prepared by electrospinning (A), after calcination at  $600 \,^{\circ}$ C (B)

A reduction in size to the nanometer scale of bioactive glass particles (or fibres) leads to a new family of nanostructured biomaterials which, combined with polymer matrices to form composites, are expected to display enhanced performance in existing biomedical applications, leading also to new application opportunities. The higher specific surface area of nanoscale bioactive glasses allows not only for a faster release of ions but also a higher protein adsorption and thus In the last few years silicate bioactive glass nanoparticles and nanofibres have become available and they are starting to be used in a range of biomedical applications in combination with polymers, forming nanocomposites (Saravanapavan et al., 2003). Fabrication techniques for bioactive glasses

Composition (wt.%)	45S5	13-93	6P53B	58S	70S30C	13-93B1	13-93B3	P50C35N15
Na <sub>2</sub> O	24.5	6	10.3	0	0	5.8	5.5	9.3
K <sub>2</sub> O	0	12	2.8	0	0	11.7	11.1	0
MgO	0	5	10.2	0	0	4.9	4.6	0
CaO	24.5	20	18	32.6	28.6	19.5	18.5	19.7
SiO <sub>2</sub>	45	53	52.7	58.2	71.4	34.4	0	0
P <sub>2</sub> O <sub>5</sub>	6	4	6	9.2	0	3.8	3.7	71
B <sub>2</sub> O <sub>3</sub>	0	0	0	0	0	19.9	56.6	0

**Table: 1:** Compositions of various bioactive glasses

enhanced bioactivity is expected. There is evidence in the literature that faster deposition or mineralization of tissues such as bone or teeth is possible when these tissues are in contact with nanoscale particles, as opposed to micron-sized particles, considering that the bone structure exhibits nanoscale features consisting of a tailored mixture of collagen fibrils and hydroxyapatite nanocrystals (Kay et al., 2002; Palin et al., 2005; Boccaccini et al., 2010). Mimicking the nanofeatures of bone on the surface of a synthetic implant material has been shown to increase bone-forming cell adhesion and proliferation (Palin et al., 2005; Boccaccini et al., 2010). These results have been obtained on TiO<sub>2</sub> and hydroxyapatite but the findings should be directly applicable to bioactive glasses.

For bone tissue engineering purposes, where polymer/bioactive glass composite scaffolds are of great interest the use of nanoscale bioactive glasses is expected to improve both mechanical and biological properties of scaffolds (Guarino et al., 2007; Rezwan et al., 2006; Boccaccini et al., 2010). Not only the surface bioreactivity of nanoparticles is higher than that of lm-size particles but also bioactive glass nanoparticles will induce nanostructured features on scaffold surfaces, which are likely to improve osteoblast cell attachment and subsequent cell behavior. Other advantages of the reduced size of the inorganic particles include the possibility to use them to reinforce polymeric nanofibers, to process thin bioactive coatings or in injectable systems (Alves et al., 2010; Boccaccini et al., 2010).

Fabrication techniques for bioactive glass nanoparticles and nanofibres

include various techniques whose step by step explanation is given below.

# Sol-gel techniques

Sol-gel process is defined as the chemical synthesis of inorganic materials by preparation of a sol, gelation of the sol (gel) and removal of the solvent. The sol-gel process involves the transition of a system from a liquid "sol" into a solid "gel" phase. The chemistry involved in the process is based on inorganic polymerization reactions of metal alkoxides (Gough et al., 2004). It has a long history of use for synthesis of silicate systems and other oxides and it has become a widely spread research field with high technological relevance, for example for the fabrication of thin films, coatings, nanoparticles and fibres (Hong et al., 2009). The sol-gel synthesis of pure silica glass nanoparticles is well known. Applications in the biomedical field for silica nanoparticles have been discussed in the literature (Veerapandian and Yun, 2009). As a typical liquid phase synthesis method, sol-gel usually involves the use of metal-organic precursors which are altered to inorganic materials either in water or in an organic solvent. For the synthesis of bioactive glasses, typical precursors used are tetraethyl orthosilicate, calcium nitrate and triethylphosphate. The synthesis of specific silicate bioactive glasses by the sol-gel technique at low temperatures using metal alkoxides as precursors was reported in 1991 (Li et al., 1991). After hydrolysis and polycondensation reactions a gel is formed which subsequently is calcined at 600–700 °C to form the glass.



**Fig. 7:** Typical SEM images of electrospun submicron bioactive glass 70S30C fibers at different magnification (A–C), and SEM image of a single fiber (D)



**Fig. 8:** Electron microscopy image of nanoparticulate bioactive glass (nominal composition 45S5 Bioglass) as prepared by flame spray synthesis as well as a scheme representing the flame spray synthesis process



**Fig. 9:** Young's modulus of composites consisting of different concentrations of micron- or nano-sized bioactive glass particles in poly(3hydroxybutyrate) compared to the neat polymer

Based on the preparation method, sol-gel derived products, e.g. thin films or particles are highly porous exhibiting a high specific surface area (Veerapandian and Yun, 2009).

Recent work on fabricating bioactive silicate glass nanoparticles by sol-gel process has been carried out by Hong et al. (Hong et al., 2009). In their research, nanoscale bioactive glass particles were obtained by the combination of two steps; sol-gel route and co-precipitation method, wherein the mixture of precursors was hydrolyzed in acidic environment and condensed in alkaline condition separately and then followed by a freeze-drying process. A schematic diagram about the sol-gel synthesis process can be seen in Fig. 4 (Hong et al., 2009). The morphology and size of bioactive glass nanoparticles could be modified by varying the production conditions and the feeding ratio of reagents.

Sol-gel-derived bioactive glass nanoparticles have also been used to coat different materials to combine good mechanical properties and high bioactivity in one material (Esfahani et al., 2008; Fathi et al., 2009). There is wide agreement about the versatility of the sol-gel technique to synthesize inorganic materials and it has been shown to be suitable for production of a variety of nanoscale bioactive glasses. However, the method is also limited in terms of compositions that can be produced. Moreover, remaining water or residual solvent content may result in complications of the method for the intended biomedical applications of the nanoparticles or nanofibres produced. Usually, a high temperature calcination step is required to eliminate organics remnants. In addition, sol-gel processing is relatively time consuming and since it is not a continuous process, batch-to-batch variations may occur (Fig. 5) (Boccaccini et al., 2010).

#### **Microemulsion techniques**

Microemulsion has been known as a suitable technique able to provide inorganic particles with particle size in the range of nanometers with minimum agglomeration (Pileni, 2003). Nanoparticles of oxides and carbonates have been successfully synthesized by microemulsion techniques (Singh et al., 2008). A microemulsion is a thermodynamically stable transparent, isotropic dispersion of two immiscible liquids such as water and oil stabilized by surfactant molecules at the water/oil interface. In water-in-oil microemulsions, nanosized water droplets are dispersed in the continuous hydrocarbon phase and surrounded by the monolayer of surfactant molecules (Arriagada, 1999). The size of the aqueous droplets is usually in the range 5–20 nm in diameter (Paul and Moulik, 1997). These aqueous droplets act as a microreactor or nanoreactor in which reactions can take place when droplets containing the suitable reactants collide with each other. Precursor particles of hydroxide or oxalate are first formed in a microemulsion system. After drving and calcination of the precursor powder at an appropriate temperature, the desired oxide system is obtained. Microemulsion techniques are thus capable of delivering nano-sized particles of organic and inorganic composition with minimum agglomeration since the reaction is taking place in nanosized domains.

The main disadvantages of the microemulsion technique are the low production yield and the usage of a large amount of oil and surfactant phases. Although, microemulsion techniques provide an alternative way to other production methods for the synthesis several types of inorganic and organic nano-sized particles (Bose and Saha, 2003). In this regards, Zhao et al. synthesized bioactive nanoparticles in the system  $CaO-P_2O_5-SiO_2$ bv microemulsion method for bone tissue engineering scaffolds. Spherical amorphous particles were obtained with size in the 25-50 nm range. They reported that the diameter of the nanoparticles was related to the molar ratio of water to surfactant (c) in water/oil emulsions. Water droplets were enlarged with the increase in the molar ratio of water to surfactant (Zhao et al., 2005). The SEM images of bioactive glass nanofibres prepared by electrospinning (A), after calcination at 600 °C (B), can be seen in Fig. 6, while Fig. 7 is showing the typical SEM images of electrospun submicron bioactive glass 70S30C fibers at different magnification (A-C) and SEM image of a single fiber (D).

# Gas phase synthesis method (flame spray synthesis)

Gas phase synthesis uses metal-organic precursor compounds to produce nanoparticles at temperatures above

#### ISSN: 2410-9649

1000°C. The basic principle of gas phase synthesis methods is the formation of molecular nuclei which is followed by condensation and coalescence inducing the subsequent growth of nanoparticles in high temperature regions during the process. The most crucial factor for the final particle size is the mean residence time of the particles in the high temperature regions. High cooling rates (>1000 K s<sup>-1</sup>) and short residence times (1 ms) enable the nanoparticle formation. In contrast to wet phase processes, gas phase synthesis allows generally higher production rates. One of the most successful gas phase synthesis methods is flame spray synthesis which is a well-known process since 1940. It was originally developed for manufacturing carbon black and is nowadays used to produce megatons of silica and titania nanoparticles per year. An advantage of this process in comparison to other gas phase processes is that no additional source of energy for precursor conversion such as plasma, lasers or electrically heated walls is required. An adaptation of the process allowing the use of organic liquid precursors loaded with metals instead of gaseous precursors proved to be very successful (Stark and Pratsinis, 2004). In this process, the liquid precursor is dispersed by oxygen over a nozzle thereby forming a spray which is ignited. As the spray is burning, the organic constituents of the liquid precursor completely combust mainly to water and carbon dioxide and metal constituents oxidize to form the nanoparticles.

Several investigations have been carried out related to the flame spray process dynamics and there is understanding of the key variables involved and how they can be controlled to obtain nanoparticles of given size range and chemical composition (Athanassiou et al., 2010). It has been shown that the metal carboxylate system is a very convenient precursor because it allows the synthesis of oxide nanoparticles of almost any composition (Stark and Pratsinis, 2004). In addition, metal-organic salts are highly stable in air, tolerate humidity and most importantly they are fully miscible among each other. Consequently, the process allows the production of any kind of nanoparticulate mixed-oxides with high chemical homogeneity. Moreover, and depending on the composition, fast quenching after formation of the nanoparticles can preserve the amorphous state of the material (Loher et al., 2005; Brunner et al., 2006). By using flame spray synthesis, therefore, the preparation of nanoparticles of different bioactive glass compositions has become possible.

### Laser spinning technique

Laser spinning has been developed for the production of glass fibres with diameters in the nanometre to micrometre scale (Quintero et al., 2007). In laser spinning technique, large quantities of nanofibres can be produced with specific, controllable chemical compositions without the necessity of any chemical additives or post heat treatments. The process is very fast; nanofibres are produced in several microseconds. It can synthesize very long fibers at high speeds under ambient conditions (Quintero et al., 2007; Quintero et al, 2009). Laser spinning technique was demonstrated to be a very effective method to produce bioactive glass nanofibers in desired compositions and this novel technique represents a promising alternative for the fabrication of nanofibers to be used in polymer nanocomposites (Quintero et al., 2009).

The laser spinning technique essentially involves the quick heating and melting of a small volume of the precursor material up to high temperatures using a high power laser. At the same time, a supersonic gas jet is injected into the melt volume to blow the molten material (Quintero et al., 2007; Quintero et al, 2009). Following this, the molten material is quickly stretched and cooled by the supersonic gas jet (Quintero et al., 2009). Long fibres with extraordinary high length to diameter ratios can be produced by the elongation process of the viscous molten material. The obtained material is in amorphous form because of the high cooling speed. Electron microscopy image of nanoparticulate bioactive glass (nominal composition 45S5 Bioglass) as prepared by flame spray synthesis as well as a scheme representing of the flame spray synthesis process is given in Fig. 8 A and B, respectively.

# Composites containing nanoscaled bioactive glass

A fundamental understanding of polymer-nanoparticle interactions is necessary to control the structure-property relationships of polymer nanocomposites that need to work within the chemical, physical and biological constraints required by a biomedical application. Polymers are widely used biomaterials, as the range of their chemical and physical properties can be varied (Kohane et al., 2008).

# Poly(3hydroxybutyrate)(P(3HB))/nanoparticulate bioactive glass composites

Misra et al. (2008) illustrated the successful preparation of poly(3hydroxybutyrate) (P(3HB))/nanoparticulate bioactive glass composites with different filler concentrations by solvent casting. The mechanical, thermal and microstructural properties of these new composites were compared to their counterpart fabricated with micron-sized bioactive glass. Similarly, other studies in the literature (Loher at al., 2006), the addition of nanoparticles was shown to have a noteworthy stiffening effect on the composite modulus, as shown in Fig. 9. It has been also shown, that systematic addition of bioactive glass nanoparticles induced a nanostructured topography on the surface of the composites, which was not visible on their micron- sized bioactive glass particle containing counterparts. This surface effect induced by the nanoparticles considerably improved total protein adsorption compared to the unfilled polymer and the composites containing micron-sized bioactive glass particles. An in vitro degradation study (30 days) in simulated body fluid (SBF) showed a high level of bioactivity as well as higher water absorption for the nanoparticle containing composites.



**Fig. 10:** SEM images showing MG-63 cells grown on (A) P(3HB) at day 4, (B) P(3HB) at day 7, (C) P(3HB)/20 wt.% n-BG at day 4, and (D) P(3HB)/20 wt.% n-BG at day 7



**Fig. 11:** SEM images of PHBV/BMBG porous composites immersed in SBF for different times. (A) Before immersion; (B) the locally magnified morphology of pore wall before immersion; (C) 8 h immersion and (D) 24 h immersion

In addition, a preliminary cell proliferation study using osteoblast-like cells revealed good cytocompatibility of the P(3HB)/bioactive glass composite systems (Misra et al., 2008). Misra et al. have also examined in depth the effect of the addition of bioactive glass nanoparticules on the bioactivity, degradation and *in vitro* cytocompatability of P(3HB)/nanoparticulate bioactive glass composites prepared by solvent casting technique. SEM micrographs of MG-63 cells attached on the surfaces of P(3HB) composites in Fig. 10 show the cell morphology and the cell attachment to the substrates between days 4 and 7.

There were no noticeable qualitative differences in the attachment of cells between the neat polymeric and composite samples. The cytocompatibility study (cell proliferation, cell attachment, alkaline phosphatase activity and osteocalcin production) using human MG-63 osteoblastlike cells in osteogenic and non-osteogenic medium showed the superiority of the composite substrates containing bioactive glass nanoparticles for the intended application in tissue engineering (Misra et al., 2010).

Zheng et al. have used another member of the PHA family, i.e. poly (hydroxybutyrate-2-co-2-hydroxyvalerate) (PHBV), to develop porous nanocomposites combining the polymer with biomimetically synthesized nano-sized bioactive glass (BMBG) particles in the system CaO-P2O5-SiO<sub>2</sub>. Fig. 11 A and B are SEM images of the pore structure of the developed composites. The authors reported porosites P90% indicating that the composite contained a great amount of interconnected pores (Zheng et al., 2007). The composites were shown to be bioactive as hydroxylcarbonate-apatite (HCA) formed on the surface of specimens immersed in SBF for 8 h (Fig. 11C) and further HCA development occurred after 24 h in SBF (Fig. 11D). The study of cell attachment on the porous PHBV/BMBG composite indicated that the material has satisfactory bioactivity, biomineralization function and cell biocompatibility (Zheng et al., 2007).

# Poly(L-lactic acid) bioactive glass nanocomposites

Hong et al. (2009) investigated a new family of composites combining poly(L-lactic acid) as biodegradable polymer and sol-gel-derived bioactive glass-ceramic (BGC) nanoparticles. 3D porous scaffolds were prepared by thermally-induced phase-separation combining poly(L-lactic acid) and different concentrations of BGC nanoparticles. The representative structure and porosity of such foams are depicted in Fig. 12. The in vitro studies showed that composites containing BGC nanoparticles with lower phosphorous and higher silicon content have better bioactivity than that of the BGC with lower silicon and higher phosphorous content (Hong et al., 2009). Hong et al. (2008) have also studied the effect of nanoparticulate bioactive glass-ceramic content on the properties of nanocomposite scaffolds, in which an improvement of the mechanical properties was detected. More recently, El-Kady et al. (2010) have developed sol- gelderived bioactive glass nanoparticles/poly(L-lactide) (PLA) composites by using solid–liquid phase separation method combined with solvent extraction. They used a modified alkali-mediated sol–gel route to obtain bioactive glass nanoparticles. The modified sol–gel method resulted in reduction of the gelation time to about a minute rather than days as in the traditional sol–gel process. Furthermore, fast gelation prevented the aggregation and growth of colloidal particles to sizes larger than 100 nm. The proposed method is thus capable of delivering nanoparticles of sizes less than 100 nm with minimum agglomeration. It was reported that the scaffold's pore size decreased with the increase in the glass nanoparticles content. The *in vitro* studies revealed that the addition of bioactive glass nanoparticles improved the bioactivity of the scaffolds (El-Kady et al., 2010).

During the preparation of this type of nanocomposites, it is possible that nanoparticles aggregate in the matrix because of their incompatibility with the biopolymer used, resulting in a deterioration of the composite mechanical properties. A new approach has also been reported in this regard to improve the mechanical properties of nanoparticulate bioactive glass/PLLA composites (Liu et al., 2008; Liu et al., 2009). It was shown that surface modification of nano-sized bioactive glass particles by grafting organic molecules or polymers is a convenient solution to improve the mechanical properties of the composites. The modification induces the formation of a buffer layer between the nanoparticulate bioactive glass and the polymer matrix, which improves the dispersion of the nano-sized particles within the matrix without any agglomeration. This results in a significant improvement of the final mechanical properties of the composite materials. Liu et al. (2008) developed surface modified bioactive glass nanoparticles/poly(L-lactide) (PLLA) composites by using solvent evaporation technique. Low-molecular-weight PLLA was grafted onto the surface of the sol-gel-derived bioactive glass nano-particles by diisocyanate and the ring-opening polymerization of the L-lactide (Liu et al., 2009). They reported that the mechanical properties of the surface modified bioactive glass/PLLA composites were better than those of the non-modified bioactive glass/PLLA composites (Liu et al., 2008; Liu et al., 2009).

The morphology of fracture surfaces of composites containing modified and non-modified bioactive glass nanoparticles were compared and linked to the different fracture properties of the composites. It was reported that the roughness of fracture surfaces of composites with modified nanoparticles decreased compared with the nonmodified ones. For example, Fig. 13 shows SEM micrographs of fracture surfaces of PLLA/bioactive glass nanocomposites containing modified and non-modified nanoparticles in two different concentrations (4 wt.% and 20 wt.%) (Liu et al., Nanoparticle aggregation in composites with 2009). modified nanoparticles was not observed in contrast to composites containing non-modified bioactive glass particles, due to the improvement of the phase compatibility between the modified nanoparticles and PLLA matrix.



**Fig. 12:** Scanning electron micrographs of poly(L-lactic acid) scaffolds without bioactive glass–ceramic nanoparticles (A) and containing 25 wt.% bioactive glass–ceramic nanoparticles (B)



**Fig. 13:** SEM micrographs of fracture surfaces of PLLA/bioactive glass (BG) nanocomposites: 4 wt.% surface modified-BG (A), 4 wt.% BG (B), 20 wt.% surface modified-BG (C) and 20 wt.% BG (D).



**Fig. 14:** SEM morphology of a BGNF-Col nanocomposite, formulated as (A and B) thin membrane and (C and D) porous scaffold. Parts of (A) and (C) are enlarged in (B) and (D), respectively.

Furthermore, the surface modified bioactive glass nanoparticles were seen to act as nucleation sites improving the degree of crystallization of the matrix. The composites were shown to be bioactive as a calcium phosphate layer formed on the surfaces upon immersion in SBF. It was also demonstrated that surface modified bioactive glass/PLLA composites exhibited much better cell proliferation ability than non-modified bioactive glass/PLLA composites and pure PLLA (Liu et al., 2008; Liu et al., 2009).

# Natural polymer/bioactive glass nanocomposites

Besides synthetic polymers, natural-based materials such as polysaccharides (starch, chitin, chitosan) or proteins (silk, collagen) can be used as polymer matrices to prepare nanocomposites. Peter et al. (2009 and 2010) have synthesized a-chitin/ sol-gel-derived bioactive glass ceramic nanoparticle and chitosan/ sol-gel-derived bioactive glass ceramic nanoparticle composite scaffolds by using lyophilization technique. They developed macroporous composite scaffolds with pore size in the range 150– 500  $\mu$ m (Peter et al., 2010). The developed composite scaffolds demonstrated adequate swelling and degradation with the addition of nano-sized bioactive glass–ceramic particles. *In vitro* studies showed the deposition of apatite on the surface of the composite scaffolds, indicating the bioactive nature of the composite scaffolds. The investigation of the *in vitro* behaviour considering osteoblast-like cells (MG-63) indicated that cells attached on the pore walls of the scaffolds and showed initial signs of spreading (Peter et al., 2009; Peter et al., 2010).

Wang et al. (2006) developed a new porous bioactive nanocomposite composed of sol-gel-derived bioactive glass nanoparticles (BG), collagen (COL), hyaluronic acid (HYA) and phosphatidylserine (PS) by a combination of sol-gel and freeze-drying methods. They also synthesized a bioactive nanocomposite by crosslinking collagen and HYA by using 1ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) and Nhydroxysuccinimide (NHS). After crosslinking, the structure of BG-COL-HYA-PS scaffolds became more ordered and channel pores preferentially aligned. The scaffolds were seen to be highly porous with pore size in the range 100–400 lm. It was reported that bio-mineralization and degradation in SBF, and mechanical strength of the EDC/NHS-crosslinked BG-COL-HYA-PS composite scaffolds were better than those of the scaffolds without HYA, PS, and crosslinking process. PS and HYA play an important role in the regulation of the biomineralization process, inducing HA to precipitate on the surface of the composites.

In vitro cell culture studies demonstrated that MC3T3-E1 cells attached and spread on the surface of crosslinked BG-COL-HYA-PS scaffolds indicating the biocompatibility of thenanocomposite (Wang et al., 2006). Xie et al. (2008) have investigated the in vivo bone regeneration ability of the EDC/NHS-crosslinked BG-COL-HYA-PS composite scaffolds using a rabbit radius defect model. After implantation, radiological, histological and micro-CT studies were conducted at 2, 4 and 8 weeks. Ectopic bone formation was also investigated in a rat model. X-ray and histological studies showed the ability of bone both nanocomposites regeneration for and for nanocomposites combined with growth factors (BMP). However, the bone defect was covered with new bone only in the nanocomposites grafted with BMP at 8 weeks. Moreover, the nanocomposite combined with BMP showed a better ability of ectopic bone formation compared with the composites without BMP (Xie et al., 2008).

More recently, Couto et al. (2009) have developed chitosan and bioactive glass nanoparticle multilayer coatings by a well-developed sequential deposition method, also known as layer-by-layer (LbL) technique. SEM observations revealed that the spherical nanoparticles with sizes that varied from 30 to 100 nm homogeneously dispersed on the surface of the multilayered coatings. Chitosan provided viscoelastic properties to the final coating, while the bioactive glass provided bioactivity for the organic–inorganic structure. In vitro studies indicated that the multilayers induced the formation of apatite as a marker of bioactive behavior. This work clearly showed that LbL technique can be applied to coat different prosthetic devices for orthopaedic application or scaffolds for bone tissue engineering (Couto et al., 2009).

# Bioactive nanocomposites containing bioactive glass nanofibres

A series of composites of various morphologies, such as fibrous membranes and 3D porous scaffolds, are being developed by compounding polymers and bioactive glass nanofibre (BGNF). Kim et al. (2006) were the first to develop a composite of PLA filled with sol-gel-derived bioactive glass as a nanoscale composite fiber by means of electrospinning (ES). Nanocomposites with a dense nanofibrous network were achieved. It was observed that glass nanofibers were uniformly dispersed in the PLA matrix (Kim et al., 2006). The in vitro bioactivity and osteoblast responses of the developed nanocomposites has also been studied. The nanocomposites showed excellent bioactivity, inducing CaP precipitation within 24 h of immersion in SBF. It was also reported that the osteoblast response of the nanocomposites was significantly improved as the amount of bioactive nanofibers increased (Kim et al., 2008). Kim et al. (2008) also developed BGNFcollagen nanocomposite both in the form of a thin membrane and as macroporous scaffold. SEM investigations revealed the similar composite microstructure of both membranes and porous scaffolds with uniformly distributed BGNF in the collagen matrix (Fig. 14). TEM studies showed that both BGNF and collagen were in the nanoscale. BGNF-collagen nanocomposites exhibited high bioactivity, assessed by the rapid formation of bone-like apatite minerals on their surfaces when immersed in SBF. It was also observed that the nanocomposites assisted the adhesion and growth of human osteoblast-like cells in vitro (Kim et al., 2008).

Lee et al. (2008) produced poly(e-caprolactone) (PCL)/sol-gel derived BGNF nanocomposite in a thin membrane form. The glass nanofibres were distributed well within the PLC matrix, showing a much rougher surface than the pure PCL. In vitro studies showed that the precipitated apatite covered the surface of the nanocomposite membrane almost completely after immersion in SBF for 4 days. Osteoblastic cells (MC3T3-E1) on the nanocomposite membrane spred better and grew actively with many cytoplasmic extensions, showing improved proliferation behavior than those on the pure PCL membrane.

More recently, Jo et al. (2009) have fabricated (PCL)/sol-gel derived BGNF composites and investigated their biocompatibility and mechanical properties in comparison with composites containing the microparticulate form of bioactive glass. Nano-sized bioactive glass fibers were uniformly distributed in the polymer matrix as a result of their uniform shape and size, in contrast to the micronsized bioactive glass fibers. This microstructure resulted in a significant improvement of the biological and mechanical properties of the PCL/BGNF composites, compared to that of the micron-sized ones. The elastic modulus of the PCL/BGP and PCL/BGNF composites are compared with those of the PCL control, indicating the superior elastic modulus of the nanocomposites. Furthermore, in vivo animal test results revealed the good biocompatibility of the PCL/BGNF composite and its boneforming ability was demonstrated when implanted in a calvarial bone defect (Jo et al., 2009). The introduction of bioactive glass nanofibres as filler in biodegradable polymers adds therefore interesting features and represents a promising step towards the development of improved biomaterials for bone regeneration as well as engineered scaffolds for tissue engineering applications. More research is indeed required to exploit the novel properties of these composites, in different morphologies, for a variety of applications in hard tissue regeneration and bone tissue engineering.

#### Polymer-silicate nanocomposites

Biomedical polymer-silicate nanocomposites have potential to become critically important to the development of biomedical applications, ranging from diagnostic and therapeutic devices, tissue regeneration and drug delivery matrixes to various bio-technologies that are inspired by biology but have only indirect biomedical relation (Wu et al., 2010).

# Future trends and challenges

The polymer nanocomposite approach has shown the greatest potential in the design of novel polymeric biomaterials with advanced properties and functionalities. The growing number of available nanoparticles with controllable size and shape further enables researchers to explore promising polymer nanocomposites with better performance than its perfect polymeric counterparts. Mechanically strong polymer nanocomposites can be used either for hard tissue replacement, such as bone, or soft tissue repair like cartilage or tendon. On the other hand, polymer nanocomposites that show responsiveness to external stimuli can direct the design of biomedical devices for better spatial and timely control (Wu et al., 2010).

Like other newly arising disciplines, the polymer nanocomposite biomaterials area provides both opportunities and challenges. The lack of well-known structure-property relationships between polymer and nanoparticle hampers the design of complex biomedically useful materials. The available database for these materials does not give a well-established theory to predict the properties resulting from the combination of nanoparticles and polymeric biomaterials (Balazs et al., 2006). We also do not understand to what extent the current composite theory can apply to polymer nanocomposites (Winey et al., 2007).

The biocompatibilities of polymer nanocomposites also must be taken into account. Although most studies use biocompatible polymers to prepare nanocomposites, the biocompatibility of polymers do not directly apply to polymer nanocomposites. The *in vitro* results of nanoparticle cytotoxicity studies show ambiguities among different research labs or methods. How tissues or the immune system react with polymer nanocomposites is further confounded with the superposition of the different biological properties of nanoparticles and polymers. This is further complicated by the deficiency of knowledge about the *in vivo* fate of nanoparticles.

These issues and questions suggest the polymer nanocomposite approach to design biomaterials is still in its infancy. Although the analysis of chemical, physical and biological properties of polymeric nanocomposite biomaterials seems to be challenging, the multifaceted properties of polymer nanocomposites also provide opportunities to mimic Nature's expertise in producing materials with excellent performance. Undertaking these challenges can elucidate more details and understanding

regarding how polymeric biomaterials and nanoparticles work together. Overall, this literature review suggests that only few groups are working on developing polymer-silicate (clay) nanocomposites for biomedical applications such as tissue engineering and drug delivery along with various other applications (Abbasi et al., 2015; Abd El-Ghaffar et al., 2015; Aguilar Ventura et al., 2015; Baeza et al., 2015; Ceraulo et al., 2015; Cromer et al., 2015; Díez-Pascual et al., 2015; Hmar et al., 2015; Kotal and Bhowmick, 2015; Ma et al., 2015; Parvin et al., 2015; Paul et al., 2015; Pissis et al., 2015; Rajendran and Jaisankar, 2015; Savas and Hancer, 2015; Shao et al., 2015; Thakur and Kessler, 2015; Urbano et al., 2015; Yin and Deng, 2015; Zare, 2015a, b; Zare and Garmabi, 2015). Most of this research increases our fundamental understanding of materials properties. Research published on polymers in combination with bioglass derived nanostructures and nanoparticles seem to generate more interest within the research communities as these nanocomposites have immediate biomedical relevance and many of them are made of starting materials that are well known. Nevertheless, preliminary results are promising, and further investigations may help to better understand cellpolymer nanocomposite interactions, immunological reactions and in vivo responses.

In future research, researcher should focus on; how can we apply these novel properties to design a medical device and Can these novel properties intimately integrate with currently used medical devices.

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