Periodontal Bone Substitutes Application Techniques and Cost Evaluation: A Review

Jamaluddin Syed, Najmus Sahar, Raffaella Aversa, Relly Victoria V. Petrescu, Davide Apicella, Erum Khan, Michele Simeone, Florian Ion T. Petrescu and Antonio Apicella

Introduction

The earliest bioactive materials which were used within the body were identified as called Prostheses (Hench and Thompson, 2010). These Prostheses had to be standardized according to the physical properties of living tissues. Professor Bill Bonfield et al. (1981) was the pioneer of researching mechanical properties of living tissues, its skills were especially centered on bone to make Prosthesis. The basic objective of making the Prosthesis was to achieve a combination of physical properties of living tissue with minimal toxic response to the surrounding structures (Hench and Thompson, 2010). These prostheses had the limitation of stress shielding and bone resorption. Professor Bill Bonfield explore the concept of Bioactive materials and design bio composite that matches more to the mechanical properties of living tissues and removed the limitation i.e., resorption of the underlying bone structure (Hench and Thompson, 2010). The Bio active mechanism is the procedure through which living tissues are attached and integrated to an artificial implant with a chemical bond (Tilocca, 2009).

There are many applications of bioactive materials in tissue engineering (Tilocca, 2009). Tissue engineering is the art and science of biological substitution through which tissue function is restored. This is achieved with the formation of biological scaffold provide structural support to the tissue which later filled with number of cells and implantations (Chen et al., 2012). The requirements of scaffold materials to fulfill the demand of tissue engineering, are biocompatibility, the material doses not respond on unresolved inflammatory reaction, mechanical properties must be sufficient to prevent surface failure, controllable interconnected porosity which can help to grow cells and support vascularization (Chen et al., 2012). About 90% porosity with 100micrometer is essential for cell growth and proper vascularization (Chen et al., 2012). Bone has natural combination of inorganic calcium phosphatase appetite and a biological polymer called Collagen in which associates are deposited (Chen et al., 2012; Buzea et al., 2015).

In tissue engineering 3-dimensional scaffold is formed which is fabricated with natural or artificial materials exhibit high porosity and pore interconnectivity (Hoppe et al., 2011; Maeno et al., 2005; Sachot et al., 2013). The function of scaffold is not only to provide structural support to the bony structure but also to enhance cell proliferation and differentiation of Osteoblastic cell (Hoppe et al., 2011; Aversa et al., 2016). Several Inorganic Bioactive materials could form a desired porous scaffold with suitable mechanical properties. According to the
researched literature the ionic dissolution is the key procedure through which inorganic material behavior in forming scaffold and interact with living tissue can be understood in vitro and Vivo. Some inorganic elements such as Sr, Cu, Co, Zn was already present in the human body and play anabolic effect on bone metabolism (Hoppe et al., 2011). The introduction of therapeutic ions in the scaffold material to increase its bioactivity (Sachot et al., 2013). The release of ions after exposure of physiological environments is effected on the bioactivity of scaffold related to osteogenesis and angiogenesis (Hench and Wilson, 1993; Hoppe et al., 2011; Huttmacher, 2000; Okuda et al., 2007).

Role of Inorganic Ions in Bone Metabolism

Human bone has natural process of healing through the process of remodeling. Remodeling is the process of deposition and resorption of bone tissue by Osteoblastic and Osteoclastic cell activities. As remodeling occurs, Osteoblastic cells produced new bone cells and Osteoclastic bone cells destroyed or resorbed existing bone. This formation and resorption process called Remodeling. Failure in maintaining the balance of remodeling results in multiple problems like Osteoporosis (Habib et al., 2007).

The remodeling procedure is regulated by few growth factors, hormones and inorganic ions such as Calcium (Ca) (Heinemann et al., 2013; Julien et al., 2007; Liu, 2003; Saltman and Strause, 1993), Phosphorous (P) (Heinemann et al., 2013; Julien et al., 2007), Silicon (Si) (Liu, 2003), Strontium(Sr) (Liu, 2003), Zinc(Zn) (Liu, 2003; Saltman and Strause, 1993), Boron(B), Vanadium(V), Cobalt (Co), Magnesium(Mg) (Cepelak et al., 2013), Magneese (Mn, Copper(Cu) (Liu, 2003; Saltman and Strause, 1993). Inorganic ions dissolution plays a very important role in the process of bone healing (Mouriño et al., 2012).

Metal ions act as an enzyme co-factored effect on signaling pathways to stimulate the metabolic effect on tissues engineering (Hoppe et al., 2011). Metal ions play important role as therapeutic agent in hard and soft tissue engineering. Ca and P ions are the part of the main component of inorganic apatite of human bone (Ca\textsubscript{10}(PO\textsubscript{4},CO\textsubscript{3})\textsubscript{6}OH\textsubscript{2}) (Bielby et al., 2005; Habib et al., 2007; Hoppe et al., 2011; Mouriño et al., 2012).

Bioactive Material has ability to release inorganic ions and contributes in natural bone metabolism (Bielby et al., 2005; Habib et al., 2007; Karageorgiou and Kaplan, 2005; Maeno et al., 2005).

Bioactive Materials

First Generation Biomaterials

Early biomaterials were used to replace damage or missing living structure that’s why biomaterial assumed to have compatible physical properties similar to the natural structure with minimal tissue reaction or toxic effect on tissue. Most of the materials were bioinerts (Sundar et al., 2012; Petrescu et al., 2015).

Second Generation Biomaterials

During early 70s bioactive material such as bioactive glass, ceramic glass and composites were introduced in the field of tissue engineering. These materials make a chemical bond with natural tissue and elicit tissue generation by enhancing production of tissue forming cells, through the ion dissolution process from the surface of materials (Sundar et al., 2012).

Second Generation bio materials also includes resorbable biomaterial such as calcium phosphates. It has ability to breaks down chemically and reabsorb to equivalent ratio of that regrowth tissue (Shirtliff and Hench, 2003; Gramanzini et al., 2016).

The material tissue bonding involves 11 steps of reacting. First 5 steps involves surface material reaction of ion exchange which followed by poly condensation reaction. This surface reaction provides a layer of hydroxyapatite layer that equivalent to the inorganic layer of natural bone tissue.

Third Generation Biomaterials

The concept of resorbable materials and bioactive material is merged to form third generation bioactive resorbable glass and ceramic material that can activate gens in tissue engineering (Shirtliff and Hench, 2003). Bioactive materials are used in powder, solution or micro particles form to stimulate tissue repair (Sorrentino et al., 2007; 2009). The release of chemicals in the form of ions dissolution from the bioactive materials and growth factors such as bone morphogenic protein that enhance the cell proliferation (Hench and Polak, 2002; Sundar et al., 2012) due to osteo conduction and osteoproduction process. The surface reaction of material that gives ions dissolution responsible in intracellular and extracellular response (Hench and Polak, 2002; Sundar et al., 2012).

Cell Cycle and Gene Activation

Osteoblastic cell differentiation and proliferation is controlled by the activation of a synchronized sequence of genes which undergo mitosis of cells after that the synthesis of extracellular matrix by bone cells occur (Polak and Hench, 2005). There is genetic control of cellular response to the bioactive material also present. When human Osteoblastic cells expose to ionic dissolution of bioactive material seven families of genes are activated. These activated genes express protein that effect on differentiation and proliferation of osteoblast (Sundar et al., 2012). The ion dissolution of bioactive materials that enhance cell repair at molecular level by creating scaffold on the damage bone tissue (Polak and Hench, 2005; Sundar et al., 2012). After construction of scaffold it is necessary to build blood vessels in it.
Polymers are in amorphous or semi-crystalline form. Its crystalline state can be increased by short side group and chain regularity. Its crystallization increase its mechanical property which determines the thermal behavior and also increases its fatigue strength (Ratner et al., 2004). The deformation behavior is the key factor for tensile strength. Amorphous, rubbery polymers are soft and extensible. Semi crystalline polymers are less extensive.

The most important property of polymers to use as biomaterial is the stress at the point of breakage or failure. Failure means catastrophic (complete breakage). The fatigue behavior is also making polymer to use as biomaterials. In liquid or melted state polymer has high thermal energy. Viscoelastic property also represented by its thermal behavior (Perillo et al., 2010). Linear amorphous Polymer with increase temperature 5-10°C, converted from stiff glass to leathery material (Boccaccini and Ma, 2014; Ratner et al., 2004).

**Saturated Polymer**

The most often used for 3D scaffold biodegradable synthetic polymers, saturated polymers includes Poly-x-hydroxy esters, poly (lactic acid) PLA and poly (glycolic acid) (PGA) as well as poly (lactic-Co glycolide) (PLGA) Co polymer (Rezwan et al., 2006).

Due to the chemical properties of these polymers which allows hydrolytic degradation through de-esterification. As degradation occurs, the monomer component of these polymers eliminates from the natural pathways of the body. The body has the mechanism of tri-carboxylic acid cycle, which remove monomer of PLA. The Monomer of PGA also eliminated by the highly regulated mechanism of body.

The process of degradation is accelerated by the auto catalysis due to its carboxylic end groups. This heterogeneous degradation contributes in neutralization of the carboxylic end group at the surface and diffusion of soluble oligomers from the surface towards inside (Rezwan et al., 2006), this helps to reduce acidity on the surface layer. The degradation rate is increased due to the auto catalyzing of the carboxyl end group. Hydrolysis of amorphous polymer such as PDLLA is more frequent because of it less crystalline property.

The molecular weight and degree of polymerization within the polymer determine the amount of water to be diffuse, temperature, buffering capacity, pH and ionic strength. The degree of crystallinity also effect on the rate of degradation. The crystals are chemically more stable as compared to amorphous material so it resist penetration of water into the matrix.

The acidic by product of PLA, PDLLA use in tissue engineering. Some other products are used to counter acidic environment and control degradation. PDLLA has biocompatibility and good osteoconductive potential. PDLLA application used for scaffold formation in tissue engineering.

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**Table 1. First, second and third generations of bioactive materials with their applications**

<table>
<thead>
<tr>
<th>Generation</th>
<th>Material</th>
<th>Difference in function</th>
</tr>
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<tbody>
<tr>
<td>First generation</td>
<td>Bio inert</td>
<td>Replace tissues without reaction with tissues</td>
</tr>
<tr>
<td>Second generation</td>
<td>Bioactive</td>
<td>Making chemical bond with tissues</td>
</tr>
<tr>
<td>Third generation</td>
<td>Bioactive plus resorbable</td>
<td>Gene activation</td>
</tr>
</tbody>
</table>

Third Generation bioactive materials are also useful in making vascularization in scaffold.

Third Generation Bioactive materials work by the activation of genes for rapid differentiate and proliferation of cells for healing at molecular level.

This is revolution in molecular biology it makes connection between inorganic materials with living tissue (Sundar et al., 2012).

The materials used in scaffold are synthetic polymers such as Polysaccharides, Poly (x-hydroxy ester), hydrogels or thermoplastic elastomers (Boccaccini and Ma, 2014; Rezwan et al., 2006) and other important materials are bioactive ceramic such as calcium phosphate and bioactive glasses or glass ceramic (Boccaccini and Ma, 2014; Rezwan et al., 2006) composites of polymers and ceramics are being produced to enhance mechanical scaffold stability and to improve tissue interaction (Bielby et al., 2005; Kim et al., 2004).

**Synthetic Polymers**

Polymers are the chain of molecules which has repeated unit in it. Repeated unit make polymers differ from other small molecules. Monomer, the elimination of small molecules such as water and HCL during polymerization (Ratner et al., 2004).

Linear polymers with variety of molecular weight are used for biomedical application. But molecular weight may depend on the polymers chain integration with other hydrogen bond which give it more strength. Higher molecular weight corresponds to more physical properties melting viscosity also increases with respect to the molecular weight.

The syntheses of polymers are of two methods, additional polymerization chain reaction and condensation polymerization (Ratner et al., 2004).
Polyhydroxyalkanoates (PHA) are produced by microorganism and aliphatic poly esters. Due to its biodergrable and thermoprocesseble properties it is used for scaffold in tissue engineering (Hedberg et al., 2005; Mano et al., 2004; Rezwan et al., 2006).

Unsaturated Polymer

Polypropylene fumarate is an unsaturated polyester. Its degraded products, propylene glycol and fumaric acid, are biocompatible and also removed from the body. The double bond at the back-bone of polymer that become cross linkage causes hardening in it. Its mechanical properties depend on its molecular weight. Polypropylene fumarate is used for scaffold in tissue engineering (Hedberg et al., 2005; Mano et al., 2004; Rezwan et al., 2006).

Polyhydroxyalkanoates (PHB, PHBV, P4HB, PHBHHx, PHO)

Polyhydroxyalkanoates (PHA) are produced by microorganism and aliphatic poly esters. Due to its biodergrable and thermoprocesseble properties it is used as biomaterials. PHA, particularly poly-3-hydroxybutyrate (PHB), copolymers of 3-hydroxybutyrate and 3-hydroxyvalerate (PHBV), poly-4-hydroxybutyrate (P4HB), copolymers of 3-hydroxybutyrate and 3-hydroxyhexanoate (PHBHHx) and poly-3-hydroxyoctanoate were used in tissue engineering. For obtaining desirable application PHA may use by blending with other polymers, enzymes.

The challenge is to have a cost effective industrial production for some PHA polymers due to their lengthy and expensive exploration process (Rezwan et al., 2006).

Surface Bioeroding Polymers

These polymers undergo heterogeneous hydrolysis interaction with water. This process referred as surface eroding. Surface eroding behavior is opposed to bulk degradation behavior. With these properties, polymers are known as poly (anhydrides), poly (ortho-esters) and polyphosphazene. Having surface eroding property these polymers have minimal toxic effect, having mechanical integrity and increase bone growth in porous scaffold (Apicella and Hopfenberg, 1982; Rezwan et al., 2006).

Ceramic Materials

Ceramic materials were used in daily routine. Ceramics are solid which inorganic and non-metallic in nature. They present in both crystalline and monocrystalline form. Glasses and glass-ceramic are subclasses of ceramic (Rezwan et al., 2006; Morales-Hernandez et al., 2012).

Bioactive Glass

Although, the first Bioactive glass 45S5 was discovered by L. Hench in 1969, Bioactive glasses with the composition of SiO2, P2O5, Na2O, CaO started to be clinically use only from 1985 (Brauer, 2015).

The clinical success depends on its properties of degradation in solution forming surface layer of hydroxycarbonate appetite, making bond with bone and ultimately replaced by natural tissues (Döhler et al., 2016). It is biocompatible in vivo. It has tendency to crystallize, which makes processing into sintered porous scaffolds (Döhler et al., 2016; Gorustovich et al., 2010). It tends to show a lower solubility, degradation and bioactivity.

Bioactive mats used for healing application and soft tissue repair, making pours scaffold and reinforcing degradation of polymers. Bioactive glass also help in preparation of glass fiber-reinforced polymers to get composites with anisotropic properties, which can be used in degradable fixation devices for bone fractures (Döhler et al., 2016; Gorustovich et al., 2010).

The ability of bioactive glass to release ions in physiological solution provide therapeutic benefits. It also provides help in bone regeneration bactericidal action orvascularization (Saiz et al., 2002; Rezwan et al., 2006).

Hybrid ceramo-polymeric materials have been also developed (Schiraldi et al., 2004; Aversa et al., 2009) with improve biocompatibility and mechanical properties.

Structure of Bioactive Glass

The degradation of Bioactive glass in physiological solution that form hydroxyl appetite layer which allow bonding between glass and the bone which enhance bone regeneration instead of just bone replacement (Rezwan et al., 2006). All this procedure is strongly supported by the specific structure of bioactive glass with both the polymerization of phosphate and silicate (Cormack and Tiloca, 2012).

Glasses have two things amorphous structure and temperature behavior makes it versatile. There are long intervals between temperature variables from super cold liquid to solid glass that is a crystalline solid. At high temperature decrease its viscosity. Oxides glass is manufactured by melting of precursors (Jones and Clare, 2012).

Bioactive glass particle size also affect on the resorption and formation of bone. Smaller the size may affect more rapid resorption and involve in substitution of new bone than the larger particles (Cormack and Tiloca, 2012).

Effect of PH and heat on Bioactive Glass

Bioactive glass has an ability to make bond with bone tissues by releasing ions, to form appetite layer. Ions release process increases in low pH and the formation apatite layer become faster through which cells adhere and proliferate (Shah et al., 2014).

Bioactive glass has tendency to crystallize on heating that reduce its capability of making appetite. If Potassium is substituted with sodium and fluoride is added to it thus increasing calcium alkalication ration, the crystallization
process at sintering scaffold and degradation process forming appaite in few hours (Shah et al., 2014).

**Gene Expression**

Bioactive glass has ability to effect on gene expression profiling of human osteoblasts. Ionic products of Bioglass® 45S5 dissolution increases the level of 60 transcript of twofold or more and regulates RCLgene. A c-myc responsive growth related gene and also control cell cycle regulators such as G1/S specific cyclin D1 and apoptosis regulators including calpain and defender against cell death (DAD1). It also contributes in gene regulation of cell surface receptors CD44 and integrin β1, various extracellular matrix regulators including metalloproteinases-2 and 4 and their inhibitors TIMP-1 and TIMP-2. It shows Bioactive glass has property to enhance the osteo productive process (Xynos et al., 2001; Yamamuro et al., 1991).

**Bioactive Silicate Glass**

The biological activity Hench Glass depends on the partial dissolution of silicate network and reactivity of the glass surface. Silicate glass is amorphous solid in nature. It is structurally covalent bond of SiO2 linked with (BO) oxygen atom (Lee et al., 2016).

**Bioactive Phosphate Glass**

The phosphate Bioactive glass has the structural formula of P2O5 having a network with CaO and Na2O as modifier. Their constituent’s ions are also natural ingredients of bone that’s why it has affinity with bone to make chemical bond with it. Its solubility can be regulated by modifying its composition therefore it is clinically potential and resorbable material (Lee et al., 2016).

**Bioactive Calcium Phosphosilicate Glass**

During the short healing period the putty of calcium phosphosilicate is the material of choice, which is also reliable material for osseous regeneration and to preserve. Crest bone and surgeries related to implants (Kumar et al., 2011). A very frequent changes of Ca and Na modifier occurs at high temperature, the fast migration of Ca and Na can be seen and at high temp phosphate and silicate network also affected (Kim et al., 2004).

**Composite Bioactive Material**

The composite of polymer and bioglass is achieve to get benefits of both types of materials for the reinforcement of porous scaffold. By taking advantage of formability of polymers and bioactive behavior of bio glass (Schipraldi et al., 2004; Rezwan et al., 2006).

**Metal Bioactive Material**

**Titanium**

Titanium is biocompatible to human body tissue. It has its physical properties which makes it more desirable material than other alloys. As compared to the gold alloy its four specific gravity is four time less. Titanium is a light metal and has resistant to corrosion. It is strong and ductile metal. Titanium has high strength and weight ratio that makes it popular among all. It has low thermal conductivity and low weight due to which patient can use it comfortably without experience of hot and cold sensation. It is biocompatible and hypo allergenic. It helps and encourage surrounding bone to grow that enhance rapid healing (Cortizo et al., 2006; Smith, 1981). New glassy metals alloy and hybrid metals-polymeric systems (trabecular sintered Titanium scaffolds) may be designed for optimum mechanical properties for osseeintegration (Apicella and Aversa, 2016; Aversa et al., 2016).

**Bioactive Materials Coating Techniques**

To improve surface properties some bioactive materials are coated on the surface of the implant. There is essential to understand the specific technique through which materials are deposited. Calcium phosphates are the largest group of materials most widely used for this purpose (Neifar et al., 2016).

**Dry Deposition Techniques**

Dry deposition techniques are physical coating techniques deal with the deposition of calcium phosphates (Kokubo et al., 2016; Annunziata et al., 2008). Among different types of techniques plasma spraying technique is most widely used commercially (Annunziata et al., 2008).

**Plasma-Spraying (PS) technique**

In this technique, the precursor material is deposited on the target metal (implant) through plasma hot jet. If this procedure is performed in atmospheric pressure (Atmospheric Plasma Spraying, APS) or it is performed under vacuum (Vacuum Plasma Spraying, VPS) or under reduced pressure (Low Pressure Plasma Spraying, LPS).

**Radio Frequency (RF) Magnetron Sputtering**

Sputtering is the technique through atoms or molecules are ejected and bombarded from vacuum chamber on to the target forming layer of precursor material with high energy ions (Perrotta et al., 2015).

**Pulsed Laser Deposition (PLD)**

PLD is the vapor deposition method through which focused pulse laser is subjected to the target and a thin layer of film CaP is deposited on the target and create these product Ca₃P₂O₇, Ca₃(PO₄)₂, CaO, P₂O₅ and H₂O (Rezwan et al., 2012). Forming high-energy plasma cloud is composed of Electron, atoms, ions, molecules and molecular clusters and, in some cases, droplets and target fragments.
Table 2. Showing the techniques, thickness, merits, demerits of Bioactive materials

<table>
<thead>
<tr>
<th>Materials</th>
<th>Technique</th>
<th>Thickness</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>HA</td>
<td>Plasma Spraying</td>
<td>50–250 µm</td>
<td>deposition rate is high</td>
<td>Coating is not uniform</td>
</tr>
<tr>
<td>HA</td>
<td>Sputtering</td>
<td>0.5–5 µm</td>
<td>Good adhesion, uniformity in coating</td>
<td>Low deposition rate</td>
</tr>
<tr>
<td>CaP</td>
<td>Pulse laser deposition</td>
<td>0.05–5 µm</td>
<td>Morphology and chemistry of coating is controlled</td>
<td>Line of sight meted</td>
</tr>
<tr>
<td>CaP</td>
<td>Electrophoretic deposition</td>
<td>0.1–2 mm</td>
<td>Deposition rate is high</td>
<td>Adhesive strength is low</td>
</tr>
<tr>
<td>Bio glass</td>
<td>Sol gel</td>
<td>&lt;1 µm</td>
<td>Chemical homogeneity, fine grain structure and low processing temperature</td>
<td>Expensive raw material, need controlled environment</td>
</tr>
</tbody>
</table>

Table 3. Costs of the bioactive materials (Listl et al., 2010)

<table>
<thead>
<tr>
<th>Material</th>
<th>Cost in €</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCP-average cost</td>
<td>55.16</td>
</tr>
<tr>
<td>DFDBA-average cost</td>
<td>57.22</td>
</tr>
<tr>
<td>HA-average cost</td>
<td>46.11</td>
</tr>
<tr>
<td>Bioactive glass (0.5 cc)</td>
<td>39.91</td>
</tr>
<tr>
<td>Synthetic resorbable membrane</td>
<td>166.29</td>
</tr>
<tr>
<td>Porcine resorbable membrane</td>
<td>124.95</td>
</tr>
<tr>
<td>EMD 0.7 mL and EDTA conditioner</td>
<td>207.30</td>
</tr>
</tbody>
</table>

Wet Deposition Technique

Wet deposition technique is the alternative of physical deposition technique. Which deals and preserves the activity of bioactive molecules. It has advantage of simple setup, minimal chemical preparations and coating of 3D implants (Rezwan et al., 2012).

Biomimetic Deposition Method

This procedure is performed under physiological temperature and pressure in which pre heated substrate is immersed in so called Simulated Body Fluid (SBF) to obtain coated with Calcium Phosphate (CaP) layer on to the substrate.

SOL–GEL Technique

Sol-Gel technique is applied to provide alternative to physical deposition techniques that enhance bone attachment to the materials and increase the process of bone healing. In this technique the layer of bioactive ceramic material is applied to form bioactive surface layer that prevents corrosion in metal. This coated material makes a bond with the existing bone and also control the release of metal ions into the tissue (Beketova et al., 2016). The first material which is used as a coating layer on the metal is synthetic Hydroxyl apatite Ca$_{10}$(PO$_4$)$_6$(OH)$_2$. During coating an adherence between the layer and the metal is also required. Electrophoresis, hot pressing and sputtering methods can deposit the coating. The Sol-Gel technique can be used as an alternative to plasma spraying process. In comparison of two methods, there are some differences in which the main one is cost effectiveness (Beketova et al., 2016).

Due to the poor mechanical strength of hydroxyapatite, it cannot be used in bulk material, instead it can be used as a coating of a thin layer on metals to achieve bioactive material properties. As compared to the melting method, Sol-Gel method is a low temperature reaction. Hydroxyapatite has the same composition of natural bone tissues and it enhance bone growth as its bioactive behavior works without any immune response from the body.

The Sol-Gel technique is based on colloidal suspension of solid particles (1-500 nm) in size in solution to make Gel (Sol). This Sol-Gel layer is applied
on the target by spraying, spin coating or dip coating methods. After drying only Sol-Gel transition is left.

**Electrochemical Deposition Techniques**

To achieve the benefits of both physical deposition and wet chemical methods, electrochemical technique is introduced in which all the particles or molecules precursor material are electrically charged and it is deposited on the target which is also conductive. This is performed in ambient temperature and pressure.

Following are the comparative chart for different techniques along with their advantages and disadvantages.

**Cost Evaluation**

Costing of bioactive materials is very important phenomena for the commercial usage. Materials should be economically feasible to access and it can be widely spread in people due to its low cost and availability.

Among various bioactive materials, Bioactive Glass materials are the most cost effective. These materials have reasonable cost (see table below). The cost difference has wide range from other materials to bioactive glass. Tricalcium Phosphate is also cost effective used in Sol-Gel technique (Listl et al., 2010).

**Methodology**

The review article about bioactive materials is carried out after the reviewed of more than 70 articles including clinical research articles and reviewed articles. All these articles are categorized in four sections.

First of those related to the history and background of the bioactive materials and also includes those who discuss the physiological process of bone healing in human beings, the basic structure and natural remodeling process.

Second category includes those research papers which discussed different types of bioactive materials, structure of those materials and their basic properties.

Third category discussed different techniques and methods of applying these techniques on materials especially on to the implants. Last but not least this category describes and discussed the cost evaluation of these materials.

The articles are mainly selected which published in peer-reviewed journals from 1961 to 2016. Bibliography of these selected articles is also included as a reference study. These bibliographic articles are not chosen as year limitations, especially which described history and background of materials, but for describing techniques it is consider that the article should be as recent as possible. In this reviewed article it is tried to mention the latest researches that have been carried out and that could help us in the understanding of their potentiality for their clinical and commercial use.

**Discussion**

Biomaterials were used to replace damaged bones since several years. The materials used in the early years have been chosen to be bio inert and not interacting with bone tissues. Further on, bioactive materials were introduced. The big difference was to make chemical and mechanical interactions with the bone tissue (Apicella et al., 1993; Schiraldi et al., 2004; Apicella et al., 2010; 2011; 2015; Aversa et al., 2009; 2016).

Bone tissue is the combination of inorganic component and organic matrix. Bioactive material structure is similar to the inorganic component of bone, such as CaP and HA. These materials, after degradation in aqueous medium, releases ions that help in bone repair. Polymers and bio glass are main types that took the main attention of researchers. Polymers are has their own physical properties and degradation process and has strength related to its molecular weight. Bio-glass seems to be the favorite material among researchers due to its bioactive property and also gene activation property that make it revolutionary material among the latest technology.

Techniques through which bioactive materials are deposited on the implant is remarkably the revolution, in the field of implantology. Bioactive materials can be deposited on the metal to achieve bioactive surface bonding, the bone with the advantages of strength of metal. Different techniques were discussed and advantages and disadvantages were also discussed but Sol-Gel technique is the latest technology with good prognosis.

Cost evaluation is the most important part to describe material efficacy. The material might be very beneficial to the human and it can be practically useful until the cost for commercial availability is low. The researches on the bioactive materials are in evolution, which bring new techniques and technology about it.

In term of cost evaluation, if Bioactive material is compared to other natural or synthetic materials and techniques, it is widely appears big difference costing of materials. Bioactive materials are most cost effective materials.

**Conclusion**

The earliest bioactive materials which were used within the body were identified as called Prostheses. These Prostheses had to be standardized according to the physical properties of living tissues. Professor Bill Bonfield et al. (1981) was the pioneer of researching mechanical properties of living tissues, its skills were especially centered on bone to make Prosthesis. The basic objective of making the Prosthesis was to achieve a combination of physical properties of living tissue with minimal toxic response to the surrounding structures. These prostheses had the limitation of stress shielding and bone resorption.
Bioactive materials are most latest materials which are still undergo in research and bring new technology to make it commercial material and give benefit to humanity with its low cost and easy availability. Bioactive materials have been used since decades but the researches on these materials are still continuing in phase. This material got extra ordinary attention by the scientist and researchers. Bioactive material has ability to bind itself chemically with natural bone tissues. Bioactive materials bring revolution in the field of bone repair and implantology. Bioactive materials have also ability to effect on gene activation of Osteoblastic cells that enhance proliferation, resulting rapid bone formation. At last the techniques through which bioactive materials are used to deposits on the implant, to create bond between implants and the bone. Cost evaluation is the very essential part that classifies the use of material commercially.

Polypropylene fumarate is an unsaturated polyester. Its degraded products, propylene glycol and fumaric acid, are biocompatible and also removed from the body. The double bond at the back-bone of polymer that become cross linkage causes hardening in it. Its mechanical properties depend on its molecular weight. Titanium is biocompatible to human body tissue. It has its physical properties which makes it more desirable material than other alloys. As compared to the gold alloy its four specific gravity is four time less. Titanium is a light metal and has resistant to corrosion. It is strong and ductile metal. Titanium has high strength and weight ratio that makes it popular among all. It has low thermal conductivity and low weight due to which patient can use it comfortably without experience of hot and cold sensation. It is biocompatible and hypo allergic. It helps and encourage surrounding bone to grow that enhance rapid healing.

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All the authors contributed equally to prepare, develop and carry out this manuscript.

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