



## Recent Research and Development in Porous Alumina Ceramics for Biomedical Applications

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### ABSTRACT

Alumina is a bioinert ceramic with adequate mechanical properties for manufacturing of medical devices. In biomedical field, porous alumina scaffold is used for cell loading and bone grafts due to their good biocompatibility, inertness and chemical stability. Porous alumina can be prepared by a variety of methods involving starch consolidation, extrusion, fused deposition modeling (FDM), freeze drying, gel casting, magnetron sputtering and protein foaming. These techniques will produce porous alumina bodies that closely mimic with the structures of trabecular bone. Calcium phosphate coatings are an effective way to enhance the bioactivity ability of the porous alumina. The present paper gives an overview of various recent synthetic methods used to prepare porous alumina and their applications, especially for bone regeneration.

*Keywords:* alumina; ceramic; Biomedical; Bone; Biocompatibility;

### 1. Introduction

Bone is a type of natural composite comprising of collagen (polymer) and bone mineral (ceramic), which provides framework and strength, respectively. The two most important types of bone are cortical and cancellous bone as shown in Figure 1. Cortical bone is a dense structure with high mechanical strength and is also known as compact bone. Cancellous or trabecular bone is an internal porous supporting structure present in the ends of long bones such as the femur or within the confines of the cortical bone in short bones. Trabecular bone is a network of struts (trabeculae) enclosing large voids (macropores) with 55–70 % interconnected porosity. A three-dimensional lattice of trabeculae and the porous structure in the cancellous bone are necessary for the formation of bone marrow and the growth of bone [1].

Bone also contains bone-forming cells (osteoblasts) and bone-resorbing cells (osteoclasts) and various osteoinductive growth factors and molecules. Critical physico-biochemical properties of bone include (1) interconnecting porosity (macro- and micro-porosity), (2) biodegradability (remodeling), (3) bioactivity, (4) osteoconductivity and (5) osteoinductivity. Pore size in normal cortical bone ranges from 1 to 10  $\mu\text{m}$ , and 200 to 400  $\mu\text{m}$  in trabecular bone [2]. To promote bone formation, repair or regeneration, the size and interconnection of the porosity is critical for the diffusion of nutrients, cell attachment, migration, proliferation and differentiation and tissue ingrowths to promote bone formation, repair and regeneration [2].

Osteoporosis is a disease where bone resorption occurs faster than the production of the new bone, causing the thinning of the



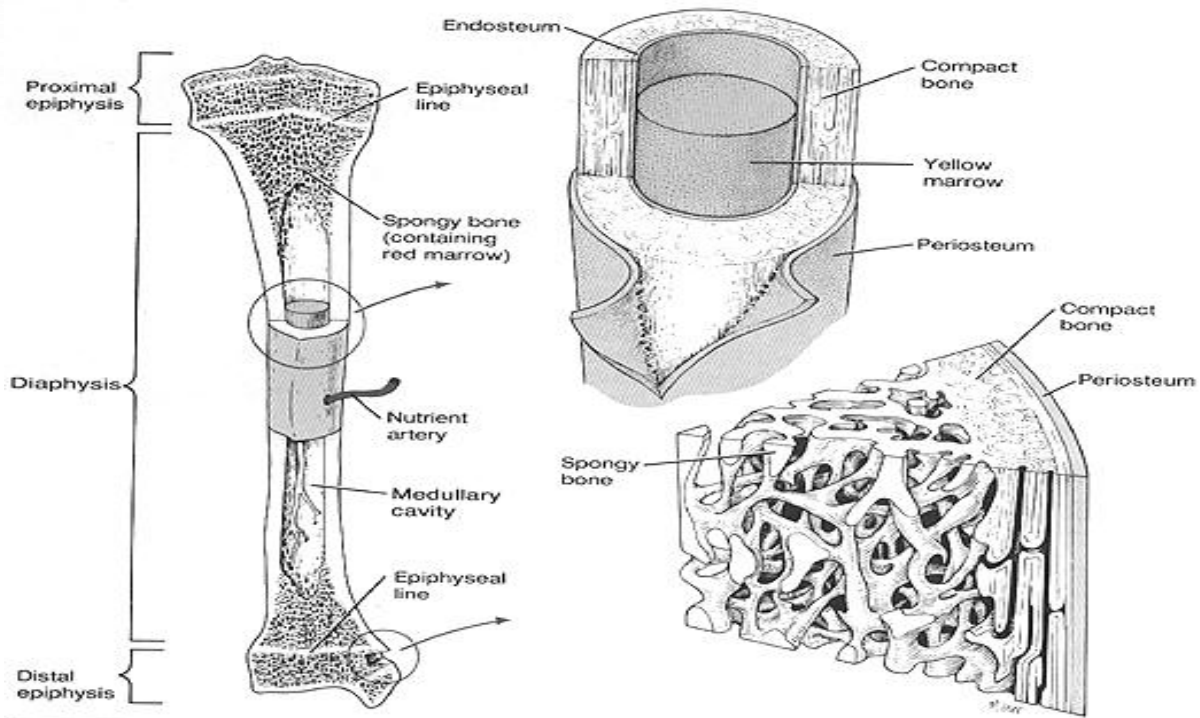


Figure 1. Structure of bone [3]

trabeculae which leads to a reduction in total bone density and strength. The disease eventually leads to fracture of bones especially in the hip, wrist, knee and spine. Hip joint replacement is often required when osteoporosis fracture occurs in knees. Millions of orthopedic prostheses made of bioinert materials have been implanted, an example of which is the Charnley total hip replacement, which was heralded as one of the most successful surgical inventions. Long term monitoring of 2000 Charnley joints has revealed that it has a survivability of 76% after 25 years implantation, i.e. 24% of hip operations required revision surgery. Improved metal alloys, special polymers and medical grade ceramics are the basis for this success, which has enhanced the quality of life for millions of patients [4].

One way to restore diseased or damaged tissues to their original state and function would be the successful tissue engineering of the tissue in the laboratory. In a typical tissue engineering application, cell would be harvested from the patient (i.e. osteogenic cells in the case of bone) and

seeded on a synthetic scaffold that acts as guide and stimulus for tissue growth in the three dimensions creating a tissue engineering construct or living biocomposite. The biocomposite would then be implanted back into the patient. Over time, the synthetic scaffold should resorb into the body as non-degradation products at the same rate that the cells produce their own extracellular matrix [5]. To regenerate trabecular bone, a construct is required that will mimic the structure of trabecular bone and stimulate new bone growth when cultured with osteogenic cells (osteoblast). An understanding of the in vitro and in vivo behavior of scaffolds must be obtained.

Bioceramic is a term used to indicate ceramics used for the purpose of repairing, reconstructing and substituting of diseased or damaged parts of the body [1]. Bioceramics have structural function as joint or tissue replacement, can be used as coatings to improve the biocompatibility of metal implants and can function as resorbable lattices which provide temporary structures and a framework that is dissolved, replaced as





the body rebuilds tissue. The thermal and chemical stability, high strength, wear resistance and durability all contribute to make bioceramics good candidate material for surgical implants [6].

In general, bioceramic are classified into three broad categories that include bioinert (such as alumina, zirconia, pyrolytic carbon), bioactive (such as hydroxyapatite, bioglass) and biodegradable (such as tricalcium phosphate). A bioinert material is nontoxic but biologically inactive, whereas a bioactive material is one that elicits a specific biological response at the interface of the biological part and the material, which results in the formation of a bond between the tissues and the material. A biodegradable or bioresorbable substance can break down *in vivo* and the breakdown products are metabolized locally [1,7]. Compared with polymers and metals, bioceramics have the advantages of high mechanical strength, corrosion resistance, excellent biocompatibility, and results in no swelling or shape distortion after implantation [8].

## 2. Use of alumina in biomedical applications

Alumina is an amphoteric oxide of aluminium with the chemical formula  $\text{Al}_2\text{O}_3$ . Development of alumina ceramics was started in Germany in 1974 by the German Federal of Research and Technology BMFT in a project of producing components for artificial hip joints (total hip replacements = THR), e.g. the ball-and-socket joint of hip joint prostheses). Any artificial ball-and-socket joint consisting of a ball head in alumina and a socket should be completely made of alumina ceramics due to the basic properties of alumina ceramics [9].

Alumina, especially polycrystalline  $\alpha$ -alumina having grain size less than  $7 \mu\text{m}$ , density higher than  $3.90 \text{ g cm}^{-3}$ , and purity higher than 99.5% was required to be used clinically by the International Standard Organization (ISO) [1].  $\text{Al}_2\text{O}_3$  has been used in orthopaedic surgery for more than 20 years as the articulating surface in total hip prostheses

because of its exceptionally low coefficient of friction and minimal wear rate. The superb tribologic properties (friction and minimal wear rates) of  $\text{Al}_2\text{O}_3$  occur only when the grains are very small ( $< 4 \mu\text{m}$ ) and have a very narrow size distribution. These conditions lead to very low surface toughness values ( $R_a = 0.02 \mu\text{m}$ ). If large grains are present, they can pull out and lead to very rapid wear because of local dry friction and abrasion caused by the  $\text{Al}_2\text{O}_3$  grains in the joint-bearing surfaces [1].

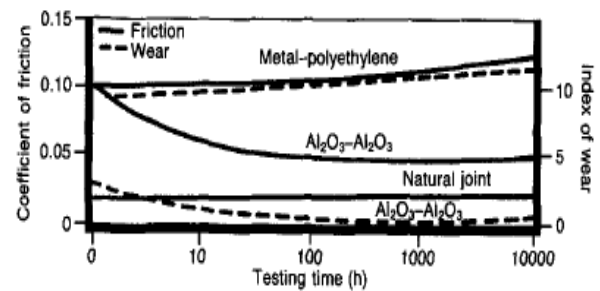


Figure 2. Time dependence of (—) coefficient of friction and (---) index of wear of alumina-alumina versus metal-PE hip joint (*in vitro* testing) [1].



Figure 3. Medical-grade  $\text{Al}_2\text{O}_3$  used in total hip replacement [1].

$\text{Al}_2\text{O}_3$ - $\text{Al}_2\text{O}_3$  load bearing wearing surfaces, such as in hip prostheses, must have very high degree of sphericity produced by grinding and polishing the two mating surface. The  $\text{Al}_2\text{O}_3$  ball and socket in a hip prosthesis



are polished together and used as a pair. The long term coefficient of friction of an  $\text{Al}_2\text{O}_3$ - $\text{Al}_2\text{O}_3$  joint decreases with time and approaches the values of a normal joint. This leads to wear of  $\text{Al}_2\text{O}_3$  on  $\text{Al}_2\text{O}_3$  articulating surfaces that are nearly 10 times lower than metal-polyethylene surfaces (Figure 2) [1].



Figure 4. Medical-grade alumina used as femoral balls in total hip replacement [1].

Low wear rates have led to use of  $\text{Al}_2\text{O}_3$  noncemented cups press-fitted into the acetabulum (socket) of the hip. The cups are stabilized by the bone growth into grooves or around pegs. The mating femoral ball surface is also  $\text{Al}_2\text{O}_3$ , which is press-fitted to a metallic stem (Figure 3). Long term results, in general, are excellent, especially for younger patients. However, stress shielding of the bone can occur. Stress shielding refers to the reduction in bone density (osteopenia) as a result of removal of normal stress from the bone by an implant. This is due to the high young patients' modulus of  $\text{Al}_2\text{O}_3$ , which prevents the bone from being loaded a requirement for bone to remain healthy and strong. The Young's modulus of cortical bone is 7-25 GPa, which is 10-50 times lower than  $\text{Al}_2\text{O}_3$ . Stress shielding may be responsible for cancellous bone atrophy and loosening of the acetabular cup in older patients with osteoporosis or rheumatoid arthritis. Consequently, it is essential that the age of the patient, nature of the disease of the joint, and biomechanics of the repair be considered carefully before any

prosthesis is used, including those made from  $\text{Al}_2\text{O}_3$  ceramics. The primary use of  $\text{Al}_2\text{O}_3$  is for the ball of the hip joint (Figure 4) with the acetabular (socket) component being ultrahigh-molecular-weight-polyethylene [1].

### 3. Properties of porous ceramics for bone substitutes

The emerging discipline of tissue engineering offers realistic alternatives to grafts and artificial implants for the repair of diseased tissues and organs. Well known examples include the replacement of skin and blood vessels with artificial substitutes grown from cells. Once removed from a patient or donor and cultured *in vitro* in the presence of growth factors, cells replicate to form specific tissues. A key element for cell culture is the scaffold, a prefabricated porous structure which is seeded with cells and provides support and shape to the tissue during its growth (Figure 5).

An ideal scaffold would mimic the extracellular of the tissue that is to be replaced so that it can act as a template in three dimensions onto which cells attach, multiply, migrate and function. Scaffolds provide an initial biochemical substrate for the novel tissue until cells can produce their own extra-cellular matrix (ECM). The scaffolds not only define the 3D space for the formation of new tissues, but also serve to provide tissues with appropriate functions. These scaffolds are often critical, both *in vitro* as well as *in vivo*, as they serve some of the following purposes [4, 10]:

1. Allow cell attachment, proliferation and differentiation
2. Deliver and retain cells and growth factors
3. Enable diffusion of cell nutrients and oxygen
4. Enable an appropriate mechanical and biological environment for tissue regeneration in an organized way.





The criteria for an ideal scaffold for bone generation must satisfy some biological and mechanical requirements [4, 10]:

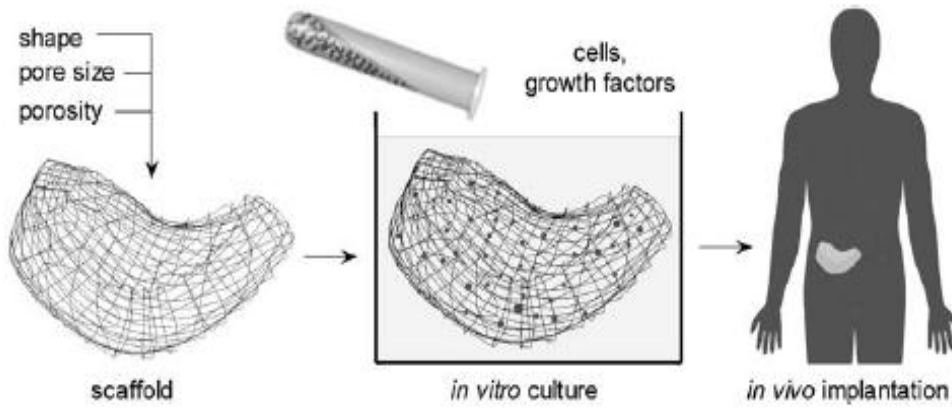


Figure 5. Scheme of scaffold based tissue engineering [49].



a) Biological requirements:

1. Biocompatibility- the scaffold material must be non-toxic and allow cell attachment, proliferation and differentiation.
2. Biodegradability- the scaffold material must degrade into non-toxic products.
3. Controlled degradation rate – the degradation rate of the scaffold must be adjustable in order to match the rate of tissue regeneration.
4. Appropriate porosity of macro- and microstructure of the pores and shape, highly interconnected pore structure and large surface area to allow high seeded cells and to promote neovascularisation. A large number of pores may be able to enhance vascularisation, while a smaller diameter of pores is preferable to provide large surface per volume ratio. Typically, desirable porosity is around 90% with pore size in the range of 20-250  $\mu\text{m}$ . Optimum pore sizes of 20  $\mu\text{m}$  have been reported for fibroblast ingrowth, between 20 and 125  $\mu\text{m}$  for regeneration of adult skin and 100-250  $\mu\text{m}$  for the regeneration of bone [10].
5. Should encourage the formation of extra-cellular matrix (ECM) by promoting cellular functions.
6. Ability to carry biomolecular signals such as fibroblast growth factor (FGF), platelet-derived growth factor, bone morphogenic protein (BMP), insulin growth factor, transforming growth factor- $\beta$ , vascular endothelial growth, etc.

b) Mechanical and physical requirements

1. Sufficient strength and stiffness to withstand stresses in the host tissue environment
2. Adequate surface finish guaranteeing that a good biomechanical coupling is achieved between the scaffolds and the tissue. Surface properties such as surface charge and surface topography can influence biocompatibility.

3. Easily sterilized either by exposure to high temperatures or by immersing a sterilization agent while remaining unaffected by either of these processes.

Pore characteristics are crucial in bone engineering due to its close correlation to the degree of bone ingrowth. Particularly porosity, pore-size distribution, pore morphology and orientation, as well as the degree of pore interconnectivity significantly affect bone penetration in macropores of implants, thus mediating implant-tissue osseointegration. Pore interconnectivity allows circulation and exchange of body fluids, ion diffusion, nutritional supply, osteoblast cell penetration, and vascularization. In this connection, closed pores do not participate in physiological events due to lack of accessibility by body fluids and cells [11,12].

An idealized cortical compact bone substitute should have an interconnected pore system with channel widths of approximately 190 to 230  $\mu\text{m}$  [13]. Pores of this size are sufficiently large to allow for migration and attachment of bone-specific cells, which establish a minimum pore size of 100  $\mu\text{m}$  for bone ingrowth into ceramic structures. Interconnected pores greater than 200  $\mu\text{m}$  are expected to be effective in osteoconduction and improved anchorage of the implant in the host bone tissue. An optimal cancellous macroporous bone graft substitute would mimic trabecular bone, containing interconnected pores of 500 – 600  $\mu\text{m}$  diameter and offer advantageous mechanical interlocking at the porous interface developing as bone grows into the pores [14]. Such bonding is a result of cell colonization from the surrounding tissue adjacent to the implant surface and cellular penetration into the porous interior ultimately leading to tissue inside the pores that is connected with the outer tissue. The porous ceramics with bimodal pore-size distribution would be favorable [15]. Pores with a diameter above 100  $\mu\text{m}$  allow for cellular colonization and vascularization, while the smaller pores with diameters in the range of 20 to 50  $\mu\text{m}$ , which will remain free from living material should provide physiological liquid exchange,

interconnectivity presumed [16]. Additionally, the porosity of an implant required to minimize stress shielding affects, and the porosity to provide mechanical fixation of implant without largely affecting overall bone morphological and metabolic properties may have to be considered. This scaling up to porosity from the bone up to the tissue-affixing level suggests the development of implants with a gradient in porosity, which is maximal at the bone/implant interface and continually scales down until it reaches either solid implant material for implants that will be exposed to high loading or 100 to 350  $\mu\text{m}$  for dental, craniofacial, maxillofacial, and osseous defects, or lesion-filling applications with exposure to less mechanical stress [16,17].

The bone ingrowth with increasing pore size reflects a dependence of bone ingrowth on the pore size. However, it has to be considered that the degree of interconnectivity might be more critical than the pore size. For resorbable materials, pore and interconnection density appeared to be more important than the pore size, whereas pore size and density were found to be of equal importance in nonbiodegradable materials [18].

The mechanical properties of highly porous ceramics can be described based on the model of an elastic-brittle foam and depend strongly on both the apparent density and the structural texture [19, 20]. Thus, if pore connectivity is maintained, implants with larger pore sizes will inherently show lower mechanical strength as a result of an associated reduction in density [21].

Although the compressive strength of highly porous ceramics implants can reach low levels in the range of 0.5 to 10 MPa [21,22], bony ingrowth has a strong reinforcing effect on porous implants. This phenomenon is more pronounced in lower-density implants as a result of a greater relative degree of bone ingrowth [21]. Compared to ceramics with identical pore structure that had not been loaded with cement, no significant difference in osseointegration could be observed [23]. Histomorphometric measurements indicated that osteoblasts attached with similar avidity onto the ceramic and the cement surface. The amount of newly formed bone and the ossification rate were

found to be similar in the cemented ceramics at 60 days post-implantation [23,16].

#### **4. Preparation methods of porous alumina ceramics**

In order to fulfill the different demands of many applications, various techniques have been developed, allowing design and fabrication of porous alumina ceramics with tailored porosities, interconnectivities, mechanical properties, and surface chemistry. Typically, most synthetic bone-replacement materials aim to mimic the macrostructure of the inorganic matrix of natural cancellous bone.

##### **4.1 Pore generation**

###### **4.1.1 Generation of porosity by burnout of volatile particles**

One method to obtain porous alumina ceramics is by mixing appropriate amounts of particulate organic substances with alumina as powder and dispersed in a slurry in the case of wet-forming procedures like drip casting, slip casting or tape casting. This approach allows direct control over the pore characteristics since their fraction, size, morphology, and distribution are controlled by the amount and properties of the added volatile phase. Among pore forming agents (PFAs) are carbon [24,25], spore [26], starch [27], gelatin [28], wheat [29] or synthetic polymers, such as polyvinyl acetate [30], polymethylmethacrylate (PMMA) [31] or polystyrene [32,33]. After controlled burnout of the organic particles and after sintering, a stable porous ceramic structure can be obtained. Removal of the PFAs can either be brought about by physical effects, for example sublimation or vaporization; or chemical reaction, for example pyrolysis or combustion. By using large amounts of PFA particles, it is possible to achieve percolating open pore networks in the green body and the sintered ceramic. Typically, the macrostructure represents



spherical voids communicating by narrow-necked apertures [16].

#### **4.1.2 Generation of porosity by burnout of thermally unstable sponge structure**

Similar to the burnout of organic PFA particles, reticulated open-celled porous ceramics can be produced via replication of polymeric sponge structures. A flexible sponge made, for example, of polyurethane, is impregnated with a ceramic suspension and after drying, the organic sponge is removed by pyrolysis and the ceramic material is sintered, resulting in an open porous replica of the initial foam. Luyten et al. prepared porous alumina ceramics (25% porosity) by coating a polyurethane-based template with the powder slurry and after squeezing out the excess slurry, the structure was dried following sintering [34]. Costa et al. fabricated porous alumina body by immersing the struts of polyurethane (PU) (50 pores per inch-ppi) foam in alumina slurry. After drying, burnout, and sintering, a ceramic with an interconnected macroporous structure of a compressive strength between 1.9 – 3.3 MPa and porosity of over 65% was obtained [35]. Han et al. produced sintered bimodal porous alumina ceramics with a final porosity of 86%, using combining the sponge method and the pore-former method. The pore sizes of the sintered porous alumina varied over a range of 24 to 80  $\mu\text{m}$  [36].

#### **4.1.3 Generation of porosity by foaming**

Another common technique is foaming, which involves the creation of a gaseous phase dispersed in a ceramic green body or in a suspension typically containing the ceramic powder, water, polymeric binder, surfactant, and gelling agents. Foaming of the suspensions can be achieved by gas formed, for example, by thermal decomposition of hydrogen peroxide  $\text{H}_2\text{O}_2$ , ammonium carbonate  $(\text{NH}_4)_2\text{CO}_3$  or calcium carbonate  $\text{CaCO}_3$  [37,38]. Subsequently, the ceramic foams are consolidated at high temperatures to obtain high-strength porous ceramics. The total porosity of directly foamed ceramics is proportional to the amount of gas

incorporated into the suspension or liquid medium during the foaming process. The pore size, on the other hand, is determined by the stability of the wet foam before setting takes place. Wet foams are thermodynamically unstable systems which undergo continuous Ostwald ripening and coalescence processes in order to decrease the foam overall free energy. The destabilization processes significantly increase the size of cellular microstructure. Therefore, the most critical issue on direct foaming methods is the approach used to stabilize the air bubbles incorporated within the initial suspension or liquid media.

Related novel processing techniques have been introduced recently: protein foaming [39] which enabled the production of foamed ceramics with high interconnected porosity (up to 80%) and pore dimensions over a wide range from 10- to 1000  $\mu\text{m}$ .

#### **4.2 Fabrication of porous bulk alumina ceramics**

For the fabrication of porous bulk alumina ceramic a variety of different methods have been developed that will be presented in detail. Each method has its advantages and potential uses. The control of processing, consequently the ultimate material properties in terms of pore structure and component dimensions is a general problem, however.

##### **4.2.1 Starch consolidation**

Bioinert porous alumina materials were manufactured by using starch that act both as binder and as a pore-forming agent. Water based slurries were prepared from ceramic powders and cast into an impermeable plastic mould. The only restriction for this technique is the requirement for water-based processing, because the process is based on the gelling ability of starches in water. Other properties that make starch so widely used are that they are environmental friendly, easy to burn and very cheap. The porous alumina with porosities between 23 and 70% were obtained after drying, burning out the starch and sintering. The





overall pore structures were dominated by large spherically shaped pores (10 to 80  $\mu\text{m}$ ) left by the starch particles (the initial average particle size of the starch being 55  $\mu\text{m}$  in diameter) with interconnecting smaller pores in between. The average size of the small pores was controlled by the total solids loading and starch content in the originally prepared ceramic slips and varied between 0.5 and 9.5  $\mu\text{m}$ . Chemically modified starch was found to give better dimensional control and regularity regarding the average size of the connecting pores than native starch owing to its higher stability during water processing [27].

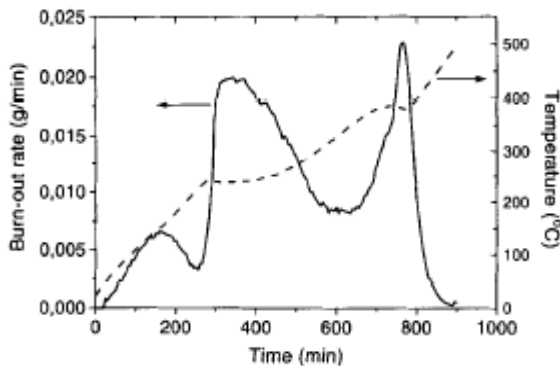


Figure 6. Burn-out rate and temperature versus time in a rate control burn-out operation for an alumina sample containing 66.2% vol.% [27].

The burn out rate in this method can be optimized, both regarding time efficiency and avoidance of cracks. Figure 6 shows burn out process, in which the maximum weight loss was set at 0.23% (of the starch content) per minute and the maximum temperature increased at 1°C. Figure 6 shows that under these conditions absorbed water is removed in the range 100-200°C, whereas the starch is removed in two sequences at 240 and 380°C, respectively [27]. Almeida et al. (2009) reported that the densities and porosities of porous alumina prepared via starch consolidation were a function of starch contents and sintering temperature [40]. The relative thermal conductivity ( $k_r$ ) of porous alumina prepared using starch as a

pore-forming agent is well described by a model;  $k_r = \exp(-1.5\phi/(1-\phi))$ , where  $\phi$  is the porosity [41].

Gregorova and Pabst (2007) reported that alumina ceramic with porosity control between 25 and 50% is feasible, while lower and higher porosities are difficult to achieve by starch consolidation method. The main factor of pore size control is the selected starch type, although swelling should be taken into account for a more precise control. The potato starch is the largest (resulting in pore sizes of 50  $\mu\text{m}$  and higher) and corn starch is the smallest (14  $\mu\text{m}$ ), while wheat starch is intermediate (20  $\mu\text{m}$ ) [42].

#### 4.2.2 Extrusion method

This method produces porous alumina with unidirectionally aligned cylindrical pores using combustible fibers as a pore former. The paste for the extrusion is prepared by mixing alumina powder and combustible fibers with binder and dispersant. The resulting paste is extruded and the fibers in the paste are oriented during the extrusion process, and the desired porous alumina ceramics are obtained after firing. An extruded paste is elongated in the extrusion direction after passing through the convergent region of the extrusion die. When the paste contains secondary phases, these also elongate in the extrusion direction, as shown schematically in Figure 7. The secondary phases may be solids, liquids or gases, if they have plastic properties. Thus, water and/or air can be used as pore formers and their usage makes the process eco-friendly, since harmful gases are not generated during production [43].

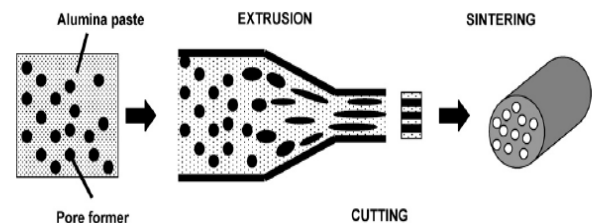
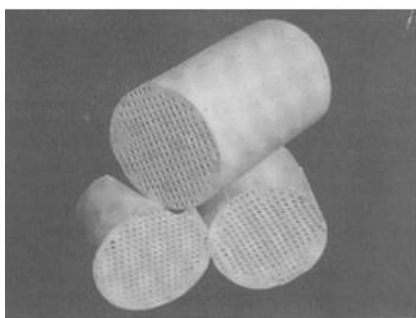


Figure 7. Schematic of the preparation of porous alumina ceramics by the extrusion method [43].

For porous alumina using carbon fibers and nylon 66 fibers as the pore formers, the porosity and pore size could be changed strongly by modifying the fiber content and diameter, respectively [43]. The porous alumina prepared by the extrusion method using nylon fibers as the pore former shows excellent orientation of cylindrical pores with 39% porosity and bending strength of 106-156 MPa as well as pore sizes are in the range of 8.5 - 38  $\mu\text{m}$  obtained [30].



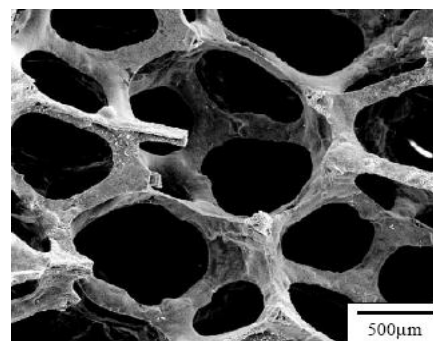
**Figure 8. Photograph of porous alumina with multihole structure [44].**

Optimization of the rheological properties of the paste is one of the most important factors for high fiber orientation and the microstructure with more highly oriented cylindrical pores obtained when the paste showed optimum rheological properties [43]. Porous alumina ceramics with single tube and a multihole have been prepared using a screw-type extruder with a vacuum system for extrusion (Figure 8). The properties of the produced alumina ceramics satisfy the requirements of membrane supports for gas separation process [44].

#### 4.2.3 Polymeric sponge method

In the polymeric sponge method, a highly porous polymeric sponge (typically polyurethane) is initially soaked into a ceramic suspension until the internal pores are filled in with ceramic material.

The impregnated sponge is then passed through rollers to remove the excess suspension and enable the formation of a thin ceramic coating over the struts of the original cellular structure. The ceramic-coated polymeric template is subsequently dried and pyrolysed through careful heating between 300 and 800°C. Heating rates usually lower than 1°C/min are required in this step to allow for the gradual decomposition and diffusion of the polymer material, avoiding the build-up of pressure within the coated struts [45]. Binders and plasticizers are added to the initial suspension in order to provide ceramic coatings sufficiently strong to prevent cracking the struts during pyrolysis. After removal of the polymeric template, the ceramic coating is finally densified by sintering in an appropriate atmosphere at temperatures ranging from 1100 to 1700°C depending on the material [46]. To control the porosity, the sintered bodies are impregnated with the slurry and densified repeatedly. This multiple coating technique results in ceramic bodies with pore size in the range 800-1000  $\mu\text{m}$  and a porosity of 75-95% as well as compressive strength of 0.5 – 11 MPa as shown Figure 9 [47].



**Figure 9. Porous alumina with a porosity of 94% prepared by a polyurethane sponge method [47].**

#### 4.2.4 Fused Deposition Modeling (FDM)

Fused Deposition Modeling (FDM) can be used to obtain porous alumina scaffold by a lost-mold technique. First, sacrificial wax models



representing the inverse configuration of the desired ceramic structure are built-up layerwise by extruding a semimolten filament through a heated nozzle in a prescribed pattern onto a stepwise lowering platform. The wax models are infiltrated with a water-based stabilized alumina ceramic suspension that fills the open spaces in the wax model. After drying, the molds are burnt out together with the binder and the green alumina ceramic structures sintered. A variety of porous alumina scaffolds with uniform pore channels is produced, including three-dimensional honeycomb structures with interconnected and continuous cylindrical pore channels along the x-, y- and z-directions (Figure 10).

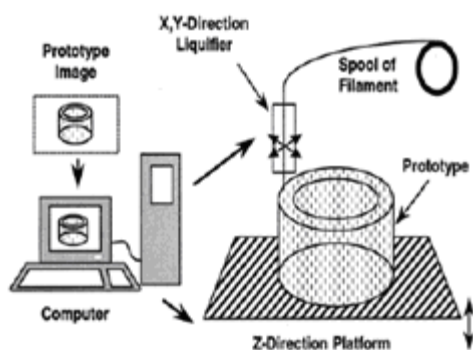


Figure 10. Schematic of the FDM process [48].

Bose et al (2002) produced sintered porous alumina with final porosity values of 27 to 450%, and pore sizes in the range of 200 – 600  $\mu\text{m}$  by using FDM [48]. The FDM process allows a control a microgeometric properties (porosity, pore size) and mechanical strength of the scaffolds through a proper choice of laydown strategies for the deposition process [49].

#### 4.2.5 Freeze drying method

Freeze drying method has several advantages, including small sintering shrinkage, simple sintering control, widely controllable porosity, relatively good mechanical strength and environmentally friendly

The technique consists of freezing a liquid suspension (aqueous or otherwise), followed by sublimation of the frozen phase and subsequent sintering, leading to a porous structure with unidirectional channels in the case of unidirectional freezing, in which pores are a replica of the ice crystals in case of aqueous slurries as shown in Figure 11 [50]. Fukasawa et al., (2001) used controlled crystallization of ice for consolidation of aqueous powder suspensions into bodies and sublimation of the ice crystals under reduced pressure resulted in porous structure. The resulted porous alumina ceramics have a complex pore structure with pore size distribution of 0.1-10  $\mu\text{m}$  and porosity in the range 36-50% as well as aligned macroscopic open pores that contain minute pores in their internal walls [51]. Deville et al., (2007) demonstrated that the morphology of the porous structures like the content, dimension, shape and orientation of porosity, can be controlled to some extent by the initial slurry composition and the freezing condition [50].

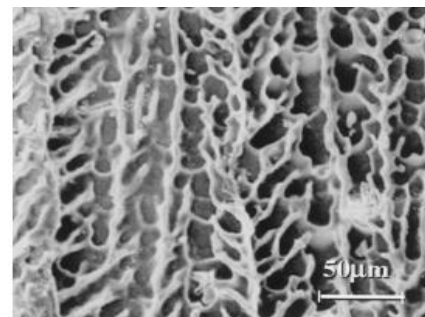


Figure 11. SEM micrograph of porous alumina produced by freeze drying method [50].

Nakata et al., (2005) reported a gelate-freezing method, in which ice crystals grew in the polymer during the freezing process and resulting in a porous alumina with pore size between 20 to 200  $\mu\text{m}$  and porosity of 30-70% [52]. Chen et al., (2007) prepared porous alumina by combining the merits of freezing-casting and gelcasting using tert-butyl alcohol as a template. This new technique resulted



in porous alumina with high porosity (over 65%) at the bottom and low porosity (<10%) at the top as well as a compressive strength of 150 MPa [53]. Yoon et al., (2008) used camphene dendrites as the freezing vehicle instead of water for the production of highly aligned porous alumina ceramics with pore size of > 100  $\mu\text{m}$  and compressive strength in the range of 11 – 95 MPa [54]. Zhang et al. (2010) reported that the addition of glycerol into aqueous alumina slurries will improve the mechanical properties of porous alumina with the optimum percentage of 30 vol.% alumina slurry with glycerol. The axial and radial compression strengths reach 255.1 MPa and 105.8 MPa respectively [55]. According to Jing et al. (2010), by using alumina sol to replace water, the microstructure and pores' morphology of porous alumina can be easily modified because the sol is helpful to control the ice growth method. The porous alumina ceramics prepared from 70 wt.% to 90 wt.% solid loading sol-contained alumina slurries and sintered at 1500°C for 2 h have open porosities from 81.7% to 64.6% [56].

#### 4.2.6 Gel casting method

In gel casting, a ceramic powder suspension containing organic monomer and cross linking agent are foamed by using a blowing agent followed by setting in situ polymerization of the monomer. Gel casting can be used to form simple or complex shaped components in a single step or by machining of simple disks, blocks etc. Features such as steps, through and through holes can be incorporated after net shape forming. Thus, complexity in mold design is minimized and mold release is made easier. There is almost no limitation to the size of the parts formed and it can be used with a range of materials as long as the material forms a stable suspension. The gelcasting process can also be used to form highly porous ceramic shapes by direct foaming technique [57]. Gel casting of foams is a common technique for fabricating ceramic scaffolds with combination of open and closed pore microporosity, high mechanical strength, but it usually results in a structure of poorly

interconnected pores, and non-uniform pore size distribution. The process, however, has limitations with respect to the control of pore size.

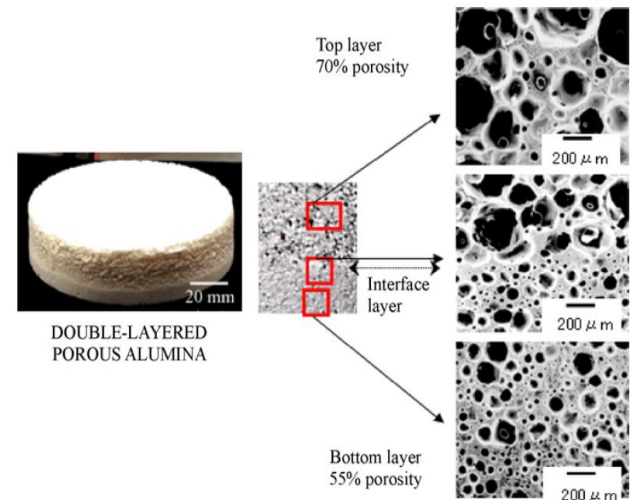


Figure 12. Porous alumina filter with a double-layered structure [58].

Figure 12 illustrates the gelcast green body of double-layered porous alumina fabricated by the two surfactants. The top layer with 75% porosity uses the dioctyl sodium sulfosuccinate as surfactant and the bottom layer (55% porosity) uses the ammonium lauryl sulphate. Microscopic investigation into the porous interface revealed that the two gelled slurries joined well, proving that the sample casting of slurries with different foam characteristics is an attractive shaping route. With the inclusion of double-layered porosity in the filter, the pressure drop is essentially minimized [58]. Wang et al. prepared  $\alpha\text{-Al}_2\text{O}_3$  ceramics by gelcasting, the porous ceramics with open porosity and mean pore size in the ranges of 40.0-42.5% and 1.92-3.65  $\mu\text{m}$ , respectively were obtained [59]. Expandable microspheres have been used as a sacrificial template to produce porous alumina by a gelcasting process and resulting porosity up to 86% and pores size distribution from 15 up to 150  $\mu\text{m}$  [60]. Potoczek (2008) prepared porous alumina

foams using agarose solutions as gel-formers via gelcasting method; with the mean pore size ranged from 527 to 375 and the mean window size varied from 113 to 77  $\mu\text{m}$  as well as the compressive strength between 2.71-5.50 and 4.01-8.18 corresponding with porosity level of 86-90% [60]. The porous alumina tubes with spherical pore about 10  $\mu\text{m}$  have been prepared through centrifugal molding technique using PMMA as pore-forming agent [31].

#### 4.2.7 Biotemplating method

The biotemplating technology has been developed for conversion of naturally grown plant structures into biomorphic, highly porous ceramics with undirected pore morphologies in the micrometer range [62]. This technology offers a possibility to use the large variety of nature developments to produce microcellular ceramics, which are so far difficult to manufacture by conventional techniques. Biomorphic oxides are prepared by infiltration of metal salt as well as alkoxide into open cellular biological materials. A macromolecular oxide network is formed inside the porous templates after hydrolysis and condensation reaction. Annealing in air causes the burning out of the biocarbon, leaving an oxide ceramics with biomorphic morphology. Therefore, the technique can be viewed as a micro-reflection method of the biological reform. Cao et al, (2004) reported on the preparation of porous alumina with porosity of 90-94% and pore size in the range 1-500  $\mu\text{m}$  (from SEM micrographs) via the sol-gel route by repeated infiltration of low viscous alumina sols into woods and subsequently annealing in air (Figure 13) [62].

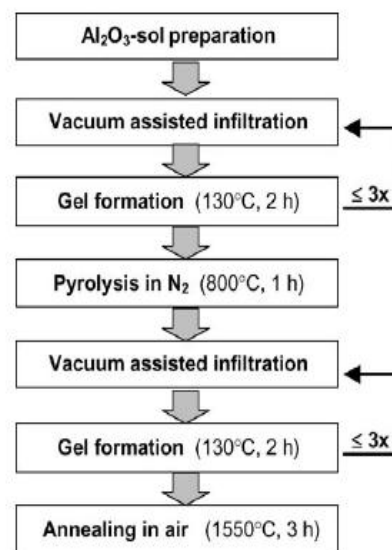


Figure 13. Flow chart for the manufacturing of biomorphic  $\text{Al}_2\text{O}_3$  from wood [62].

Mizutani et al., (2005) reported porous ceramics were prepared by mimicking silicified wood. In this process, ceramic woods were prepared by the sol-gel method, using natural woods as templates. The pore size distribution of wood-derived porous alumina ceramics is determined by the microstructure of the original wood template used as wood structures may exhibit cell sizes down to a few micrometers, porous ceramics obtained within the range 10 to 70  $\mu\text{m}$ , and the major pores being unidirectionally connected. The anisotropic nature of cellular ceramics produced using wood as template might be very advantageous in applications that require open and highly oriented porous structures. The drawback of the wood-replica approach is the tedious steps involved, which might add considerable cost to the process and very time consuming [63].

#### 4.2.8 Magnetron Sputtering

Magnetron sputtering has been used in the electronic and device industries for many years, but



its potential for bioactive on medical implants has only recently been recognized. Sputtering offers the potential to produce dense, uniform and well-adhered coatings on metallic, ceramic or polymeric substrates and the ability to produce thin coating (< 1  $\mu\text{m}$  thickness) with controlled microstructure also reduces the risk of third body wear and osteolysis [64].

Uniform porous alumina materials with the mean pore size of 530 nm and porosity of 70.65% were fabricated successfully by depositing alumina on polystyrene template by Radio Frequency (RF) magnetron sputtering. Compared with the diameter of polystyrene microspheres, the pore diameter of porous alumina materials has 11% shrinkage. This method could be adapted for commercial production, and obtained from a series of uniform porous materials with tunable pore size. Furthermore, these porous materials with uniform pore size have potential applications in photonics, nanocatalysts, and separation, especially in cell separation [65].

#### 4.2.9 Foaming method

Preparation of porous alumina by protein foaming method has been investigated by Garn et al., (2004). This technique is based on the denaturation of a protein (Bovine serum albumin) when heated at 80°C. The alumina ceramics prepared were found to have fine cellular foam structure with cell diameter of 50-300  $\mu\text{m}$ , and densities in the range from 8 to 20% t.d [66]. There are also three dimensional (3D) interconnectivity porous alumina ceramics with average density of 0.5  $\text{g cm}^{-3}$  and porosity 87% as well as compressive strength of 8 MPa prepared by a direct protein foaming using egg white protein and whey protein isolate [39]. A simple direct foaming and casting process using ovalbumine based slurries for fabricating defect-free alumina foam with porosity exceeding 95% is demonstrated by Dhara and Bhargava [67]. On the other hand, a viscous resin obtained by heating acidic aqueous sucrose solution containing aluminum nitrate on drying in an oven

produced alumina foams with porosities and pore size of 0.48-2.69 mm [68].

Eckert et al., (2000) reported on preparation of porous alumina ceramics using hot plate molding (HPM) method and resulting alumina body with open, interconnected system with pore distribution ranging from 20 to 100  $\mu\text{m}$  as well as porosity of 56 $\pm$ 8% [69]. In addition, sintered cellular alumina using a polyurethane foaming system was prepared by Peng, et al., (2000). The ceramic foams obtained had fine cell size ( $\sim$ 150  $\mu\text{m}$ ) and porosity in the range of 91-93% as well as compressive strength of 400 – 800 KPa [70].

#### 4.2.10 Protein Foaming-Consolidation method

Sopyan and Fadli (2009) have successfully developed protein foaming-consolidation method for preparation of porous ceramics using egg yolk both as consolidator and foaming agent [71]. The flow chart of the process can be shown in Figure 14. The benefits of the method are simplicity and fast process as well as the low-cost processing/materials that were needed to produce porous ceramics with controllable physical properties. In addition, the temperature of pore creation can be reduced to very low temperature (110-180°C) compared to conventional method (normally 500-600°C) [72].

Recently, floating porous ceramics were successfully manufactured via protein foaming-consolidation method [73]. The physical properties of ceramics were controlled by varying yolk and dispersant concentrations. Subjection to heat treatment resulted in porous ceramic with shrinkage in the range of 29 – 40 vol.% and pore sizes of 250-500  $\mu\text{m}$ . The compressive strength of the ceramic was 1.1 MPa at 70.6% porosity and it increased to 1.7 MPa at 52.8% porosity. The density of the porous ceramics was in the range of 0.85 – 1.11  $\text{g/cm}^3$  and they can float on water (Figure 15a) or any common media for cell culture. The pore interconnectivity and struts like structure of bone can be seen using micro-CT scan as shown in Figure 15b.





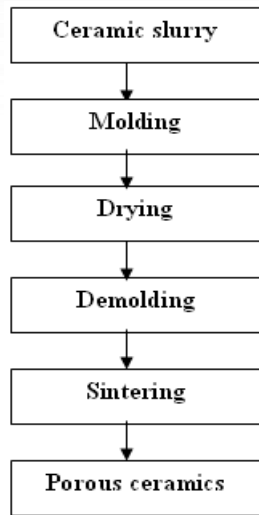


Figure 14. Flow chart of process for porous ceramics by protein foaming-consolidation method [71].

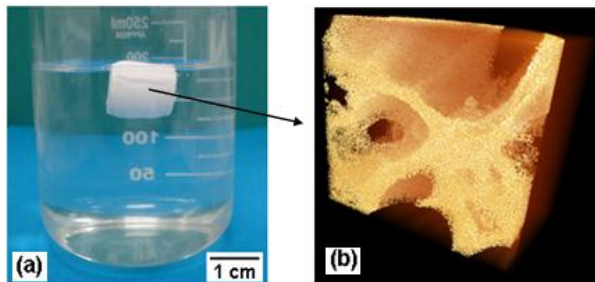


Figure 15. (a) A porous alumina floats on water and (b) CT-scan image of the body [73].

The floating ceramics obtained using the protein foaming-consolidation technique are non-toxic after processing and the ceramic pores provide favorable sites for attachment and growth of DF-1 cells [73]. Therefore, the porous ceramics can be a potential candidate for floating microcarrier application, especially in a bioreactor cell culture. The main advantage of the porous ceramic microcarrier is cells with 20 – 30  $\mu\text{m}$  sizes can be entrapped in pores with size in the range of 250-500

$\mu\text{m}$  and grow without damaged by fluid turbulence and vibration.

## 5. Porous Bioactive Ceramic-Alumina Composites

Porous alumina is relatively strong and tough compared to other porous bioceramics such as hydroxyapatite,  $\beta$ -tricalcium phosphate and biphasic calcium phosphate. However, the drawback is on biological inertness to bone tissues. Therefore, it is desirable to combine the mechanical properties of alumina with the bioactivity of calcium phosphate ceramics. The porous bioinert ceramic has also been known to form a thinner fibrous layer with faster hilling in surrounding muscles and connective tissues with the dense ones.

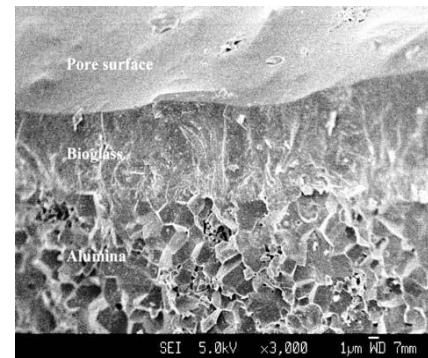


Figure 16. SEM micrographs showing the fracture surface of a bioglass coating layer on porous alumina surface [8].

A number of surface modification techniques (hydrothermal-electrochemical deposition, plasma spraying, spraying-and-sintering, ion beam assisted deposition, and biomimetic deposition) have been used to improve the osteoconductivity of scaffolds [74]. Liu and Miao (2005) reported that a bioactive 58 S bioglass layer (12-15  $\mu\text{m}$ ) was successfully coated on the porous MgO-doped alumina, resulting in a desirable combination of both high mechanical strength (5.5-7.5 MPa) and good bioactivity (Figure 16) [8].

Impregnation of alumina porous body using bioactive ceramics such as hydroxyapatite (HA) [75,47,76] and  $\beta$ -TCP slurry [47] has been conducted to improve its biocompatibility. The HA coated alumina bodies indicated that the alumina struts were uniformly coated with HA, and the HA layers with 10-20  $\mu\text{m}$  thickness were well adhered to the alumina substrates. In addition, the calcium phosphate coating did not improve the strength of the alumina porous body [47]. A porous alumina-tricalcium phosphate ( $\beta$ -TCP) composite with a compressive strength in range of 4 -12 MPa was prepared through infiltration of the polymer foam by Gremillard et al (2006) [77]. Various studies indicated that the difficulty in obtaining dense bioinert-hydroxyapatite composites is due to poor sinterability and the decomposition of hydroxyapatite [74]. Costa et al (2008) have developed alumina with tri-dimensional porous structure. Subsequently, the alumina was covered with a biocompatible coating of calcium phosphate/polyvinyl alcohol (CaP/PVA) resulting in alumina scaffolds with an average compressive strength of 3.3 MPa as well as the average thickness of the CaP/PVA coatings varied between 9 and 15  $\mu\text{m}$  [35].

The alumina reinforced hydroxyapatite porous implants had a higher strength than the hydroxyapatite porous implants and exhibited a similar bioactivity and osteoconduction property to the hydroxyapatite porous implants [47,76]. Ruano et al., (2000) reported that hydroxyapatite supports cell growth and fibroblast metabolism including collagen production, and hence is biocompatible [78].

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