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Development of Porous Calcium Phosphate Bioceramics for Bone Implant Applications: A Review

Abreeq R. Naqshbandi[1], Iis Sopyan[1,*] and Gunawan[1,2]

[1]*Department of Manufacturing and Materials Engineering, Faculty of Engineering, International Islamic University Malaysia, P.O. Box 10, Kuala Lumpur 50728, Malaysia;* [2]*Department of Mechanical Engineering, Faculty of Engineering, Sriwijaya University, Indralaya 30662, Indonesia*

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Abstract: The present review briefly outlines the most recent patents and journals on various aspects of porous calcium phosphate bioceramics including techniques of preparation, properties and bone implant applications. Bioactive ceramics are a class of materials that have capability to bond directly with the host bone. These materials can be easily assimilated by the body and are considered to be biodegradable. Researches have revealed that artificial bones made from hydroxyapatite or a combination of hydroxyapatite (HA) and tricalcium phosphate (TCP) is a perfect substitute for natural bone owing to its excellent biocompatibility and properties close to that of human bone. Bioceramics made of HA are available in dense and porous forms. Several efforts on the fabrication of porous calcium phosphate bioceramics have been carried upon in the field of clinical orthopaedics. The realisation of these efforts can be observed from the fact that numerous patents have been filed on methods of preparing porous calcium phosphate bioceramics for bone implant applications. A number of porous HA ceramics have been developed for applications in both tissue engineering and drug delivery systems. Porous bodies are decomposable in human body and provide a surface for proliferation and growth of cells that are infiltrated from the surrounding tissues so that a new bone grows into the pores and prevents any movement or loosening of the implants. Consequently, these can be used for filling the damaged bone, repair of fractured bone and even can be used as hard tissue replacements. Several processing techniques have been employed for fabrication of porous scaffolds. Among prominent techniques are gel casting, slip casting, camphene-based freeze casting and polymeric-sponge method.

Keywords: Bioactive, bioceramics, calcium phosphate, hydroxyapatite (HA), tricalcium phosphate (TCP).

1. INTRODUCTION

Bone is a hard endoskeleton tissue found in almost all vertebrates. Bones protect the vital organs of the body and are collectively known as skeleton. In addition, bones are also responsible for the production of red and white blood cells, mineral storage and facilitate body movement in conjugation with muscles. Bone has a complex structure and consists of both organic and inorganic components. Table **1** gives detailed information of the chemical composition of the most important human normal calcified tissues [1]. The inorganic composition is formed mostly of calcium phosphate whereas organic part is composed of collagen [2]. The inorganic to organic ratio of bone is approximately 75-25% by weight and 65-35% by volume.

Numerous researches have been conducted in the field of clinical orthopaedics for detecting the materials that have potential of triggering natural regeneration process of damaged or lost bone tissue. These materials have capability of being in contact with bodily fluids and tissues for prolonged periods of time. One of the key factors in a biomaterial's usage is its biocompatibility and functionality. There are 4 essential elements that are responsible for bone healing: (1) osteogenic cells (2) osteoinductive signals that are provided by growth factors; (3) an osteoconductive matrix; and (4) adequate blood and nutrient supply [3]. Biomaterials used as bone grafts are identified on the basis of osteogenicity (presence of bone forming cells), osteoconductivity (ability to function as a scaffold) and osteoinductivity (ability to stimulate bone formation) [4]. Various biological and synthetic bone substitutes have been used so far for clinical applications. Among the biological substitutes, corals have been widely used for bone implant applications since corals have skeletons similar to cortical and cancellous bone whereas among the artificial materials for biomedical purpose, calcium phosphate biomaterials have been widely used as bone substitute materials. Hydroxyapatite (HA) ($Ca_{10}(PO_4)_6(OH)_2$), is considered to be a perfect mineral replacer due to its similarity of chemical composition and crystallographic structure to the biomineral in the natural tissues [5]. It has been used widely for various bones and tooth implants and has good biocompatibility and bioactivity.

HA bonds strongly to the bone and favours osseointegration of bone implant, necessary for minifying the damages to the surrounding tissues. Calcium phosphate-based ceramics such as HA are available in porous as well as in dense form. Porous ceramic implants provide a surface for proliferation

*Address correspondence to this author at the Department of Manufacturing and Materials Engineering, Faculty of Engineering, International Islamic University Malaysia, P.O. Box 10, Kuala Lumpur 50728, Malaysia;
Tel: +603 6196 4592; Fax: +603 6196 4477; E-mail: sopyan@iium.edu.my

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Table 1. Chemical and Structural Similarities between HA, Enamel, Dentin, and Bone [1].

Composition, wt%	Enamel	Dentin	Bone	HA
Calcium (Ca)	36.5	35.1	34.8	39.6
Phosphorous (P)	17.1	16.9	15.2	18.5
Ca/P ratio	1.63	1.61	1.71	1.67
Total inorganic component (%)	97	70	65	100
Total organic component (%)	1.5	20	25	--
Water (%)	1.5	10	10	--

and growth of cells that are infiltrated from the surrounding tissues so that a new bone grows into the pores and prevent any movement or loosening of the implants. In fact porous HA ceramics are proven to mimic the porous structure of the mineral phase of the living bone [6] However, the dimensions and pore morphology of these ceramics have a considerable effect on bone prostheses [7]. Most of mammalian cells are anchorage dependent, i.e. they need a substrate for growth. Several studies suggest that ceramic scaffolds are suitable for cell proliferation, growth and cell attachment [6]. As a result, numerous studies have been conducted in the field of tissue engineering for development of porous ceramic scaffolds for bone replacement applications.

Tricalcium phosphate (TCP) is also a bio-absorbable and biocompatible material and has a crystalline structure and chemical composition similar to that of bone. Moreover its rate of biodegradation is higher than HA [8]. In comparison with other bone substitutes, TCP is characterized by well defined physical and crystalline properties, high level of uniformity of chemical composition and purity.

Several other materials have also been used as bone-graft substitutes such as bioactive glasses, glass-ceramics, crystalline phase materials etc. These substances have been used either alone or in combination with acrylic polymers or other group of polymers. These materials have been proven to be osteoconductive as well as biocompatible with host tissues. However, for being an effective bone substitute, these materials should have an appropriate structure and mechanical properties especially the porosity, pore-size and size of the interconnections between each pore [9].

2. APPLICATIONS OF POROUS CALCIUM PHOSPHATE

HA is a perfect substitute for natural bone owing to its non-toxicity, excellent biocompatibility [10] and properties close to that of human bone. A number of porous HA ceramics have been developed for applications in both tissue engineering [11, 12] and drug delivery system [6, 13-15]. This type of drug delivery system by the use of a bioactive matrix, helps in releasing a therapeutic agent *in situ* so that an anti-infection action is produced which is associated to osteoconductivity of materials. The use of bioactive porous ceramics for the delivery of antibiotics has been helpful in improving the recurrence of orthopedic infections [13]. Porous structures allow growth of tissue and bone around a supporting network and allow passage of nutrients/substances across them.

Many other applications include cell loading [6, 16] and chromatography analysis [16]. Some of the recent progresses in tissue engineering that have been achieved include therapies for regeneration of new skin as a replacement for burnt skin [17], development of bone-grafts [18], dental ligaments [19], dentin [20], dental enamel [21] and integrated tooth tissues [22,23]. The use of bio-ceramic scaffold depends upon its properties *in vivo* and *in vitro*. Bioceramics must exhibit proper mechanical strength in order to sustain *in vivo* stresses and should be mechanically stable with the surrounding tissues [24,25]. Various studies reveal that cell culture of mammalian cells *in vitro* is substrate dependant, i.e. these cells require solid substrate for growth. One of the techniques used for cell cultivation is micro-carrier culture technique. This technique offers a practical high yield culture of such cells and thus is suitable for large-scale operations. A number of micro carriers have been used so far; however use of ceramic micro-carriers has introduced new possibilities for cell culture owing to their good thermal and mechanical resistances.

In recent years, a number of porous HA ceramics have been developed to serve as graft material and scaffold for bone formation. A newly developed porous HA ceramic is NEOBONE® (Covalent Material, Tokyo, Japan). It has a porosity of about 75%, with macropores of 100-200μm that are fully interconnected by openings of about 40μm in diameter. Yoshikawa and Myoui [26] and Yoshida *et al.* [27] have successively made use of these ceramics for the treatment of bone tumours and fractures. Another newly developed HA ceramic is Apaceram-AX® (HOYA, Tokyo, Japan). It has a higher porosity of 85% and contains macropores of 50-300μm in diameter [28]. The detailed material information of NEOBONE® and Apaceram-AX® is summarized in Table **2**.

3. RECENT PATENTS ON POROUS CALCIUM PHOSPHATE

3.1. Method for Producing a Porous Sintered Body of Calcium Phosphate-based Ceramic

The porous sintered body of calcium phosphate-based ceramic can be used as an artificial dental root, a bone reinforcing material and a carrier for culture of cells or biological tissues. The patent US7514024 [29] issued to Matsumoto discloses a method for preparing porous calcium phosphate-based ceramic having a porosity of 80% or more. The method involves a series of steps starting with the prepara-

Table 2. Material Properties of NEOBONE® and Apaceram-AX® [28].

Sample Name	NEOBONE	Apaceram-AX
General name	HA	HA
Molecular formula	$Ca_{10}(PO_4)_6(OH)_2$	$Ca_{10}(PO_4)_6(OH)_2$
Sintering temperature	1200 ◦C	1050 ◦C
Porosity	75%	85%

tion of slurry comprising of calcium phosphate-based ceramic powder having an average particle diameter of 0.5 to 80μm, a water-soluble high molecular compound which can be preferably a cellulose derivative such as methylcellulose, carboxymethylcellulose, etc. and a non-ionic surface active agent preferably a fatty acid alkanolamide. This is followed by vigorous stirring at a temperature of 5 to 20ºC and under a stirring condition of 50W/L or more in order to froth the slurry and a gas is passed (e.g., air, nitrogen, argon etc.) during this time so as to aid the froth formation. The frothed slurry is then solidified into gel and drying is carried out at a temperature range of 80ºC to less than 100ºC. The dried green body is then degreased at a temperature of 300ºC to 900ºC so as to remove water-soluble high molecular compound and the non-ionic surface active agent. The green degreased body is then sintered at 1000ºC to 1250ºC to get the desired strength. The weight ratio of the total of the calcium phosphate-based ceramic powder, the water-soluble high molecular compound and the non-ionic surface active agent is maintained at 20 to 50 weight % based on 100 weight % of the slurry. The resulting porous sintered body of calcium phosphate-based ceramic has a porosity of 80% and an average pore diameter ranging from 5 to 1500μm.

3.2. Porous Calcium Phosphate Networks for Synthetic Bone Material

The use of resorbable and osteoconductive synthetic bone graft material comprising a calcium phosphate mineral matrix lattice interpenetrated by a substantially interconnected network of pores has been described in US7758896 [30]. The patent discloses a method for making a synthetic bone graft wherein simultaneous formation of mineral matrix and interconnected network of removable inorganic porogen takes place by controlled spinodal decomposition of a molten mixture of inorganic materials. Spinodal decomposition is a thermodynamic separation of a single-phase liquid into interconnected liquid phases with continuous networks. The patent describes a method which involves selection of calcium oxide and calcium phosphate components including a removable inorganic porogen that can be a transition metal oxide, in an appropriate ratio so as to provide a desired porosity in the product. This is followed by mixing and the mixture of the chemical components so obtained is heated in order to melt the mixture. The molten mixture is then cooled at a controlled rate so that spinodal decomposition of the mixture into a material, consisting of a primary phase of HA and a secondary phase of inorganic porogen, takes place. The inorganic porogen is then removed to leave behind a porous material having a substantially interconnected network of pores. The patent also presents porous materials having compositions of HA and TCP (as the primary phase) in which the interconnected pores are formed by the spinodal decomposition of a mixture of calcium oxide, calcium pentoxide and a removable inorganic porogen. The porosity of porous materials of such a composition ranges from 30% to about 60% and pore size from 3 to 700μm.

3.3. Porous Ceramic Composite Bone Grafts

Synthetic bone grafts have a significant advantage over natural grafts as their use limits the transmission of disease, occurrence of adverse immunological response and have relatively low costs. The patent US7875342 [31] discusses the use of porous ceramic composite comprising of a sintered porous matrix body of calcium phosphate-based compound and a biodegradable polymer and a method to prepare the same. The method involves impregnating reticulate-structured organic foam with an aqueous slurry of calcium-phosphate compound which is prepared by combining the ceramic medium with water and dispersing agent. This is followed by drying so that a green body of slurry coated foam structure is formed. It is then pyrolized and sintered at about 900-1300ºC to form a fused ceramic porous implant having interconnected pore-structure. Typical thickness of the coating varies from 10 to about 100μm. The patent also discloses the use of biodegradable coating on the external and internal surfaces of the porous structure so as to improve the physical and mechanical properties of the sintered matrix body. This biodegradable polymer can be photosensitive polymer, polycaprolactone, polyethylene glycol, polyester, polyanhydride etc.

3.4. Porous Composite Containing Calcium Phosphate and Process for Producing the Same

The use of porous body containing calcium phosphate ceramic as an implant has a little likelihood of getting rejected by the host as it is highly biocompatible. However, as these implants come in contact with soft tissues such as gum, subcutaneous tissue, internal organ etc., cells in the soft tissue tend to enter into the porous artificial bone thereby preventing the growth of a bone tissue. The patent US8039090 [32] issued to Kawamura *et al.* discusses method for the formation of a dense layer on the surface of porous body containing calcium phosphate ceramic which substantially prevents the cells of soft tissues from participating in the bone formation process. The method involves the formation of a porous composite with a porous layer containing a calcium phosphate ceramic and a dense layer formed on the part of the porous layer at a position that it comes in contact with

a soft tissue when implanted in a human body and the pore size and porosity of the dense layer being smaller than the porous layer. The method includes formation of slurry from calcium phosphate ceramic/collagen composite and collagen and pouring the same into a moulding die. This is followed by rapid freezing and drying so that a porous body is formed comprising of a porous layer and a dense layer on the porous layer. The dense layer is then removed except for a portion that comes in contact with a soft tissue when implanted in a human body. The ceramic/collagen composite used in this method is apatite/collagen composite which is produced by adding an aqueous solution of phosphoric acid or its salt and an aqueous calcium salt solution to a collagen solution. The resulting porous composite has a porosity of the porous layer of about 90-98%.

3.5. Porous Calcium Phosphate Bone Material

The use of self-hardening, porous calcium phosphate compositions that represent approximate chemical compositions of natural bone has been described in US8147860 [33]. The patent discloses a formable, self-hardening, porous calcium phosphate composition that is prepared using a calcium phosphate source, effervescent agent and a biocompatible cohesiveness agent (e.g., binder). This composition is then combined with a biological fluid and results in the production of a formable paste which hardens and reacts to form a poorly-crystalline apatite (PCA) calcium phosphate. PCA calcium phosphate remodels into bone when introduced at an implant surface. The nature of calcium phosphate powders and the presence of biocompatible cohesiveness agent allow many biological active fluids to pass through without compromising any of the mechanical properties or formability of the implant. In other words, the implant material retains its cohesiveness upon being introduced at an implant site *in vivo*.

3.6. Method for Producing Porous β-tricalcium Phosphate Granules

Biomaterials used for bone implant applications should be able to enhance the regenerative process particularly when used in conjugation with bioactive fluids. The patent US8173149 [34] describes the use of porous ceramic material having a desired composition, pore size, porosity and granule size for improving the bone regeneration process in a human or animal. The patent discloses the use of porous β-TCP granules for bone implant applications and methods for producing the same. The method involves mixing of TCP powder with a pore-forming agent that can be in the form of bead or resin. Pore-forming agent decomposes into gaseous products at high temperature without leaving behind any solid residue. It can be any thermally decomposable material such as naphthalene, polymers of polyacrylates, copolymers of methyl acrylate and methyl methacrylate or mixtures of polystyrene, cellulose powder, acrylic resins etc. This is followed by the addition of a granulating solution in order to form a friable mass which is then sieved to form granules. The use of granulating solution is to enhance the formation of granules. The sieved granules are then dried at a temperature of 90-110ºC followed by heating at 700-800ºC so as to remove the pore-forming agent. The formation of porous β-TCP takes place after sintering the granules at 1000-1200ºC. The resulting porous β-TCP consists of pores that are surrounded by the skeleton of sintered TCP. The patent also discusses an alternative method for the formation of porous β-TCP which involves blending of TCP powder and pore-forming agent in order to achieve homogeneity. The homogenized mixture is then pressed into slugs using a press, rotary tablet machine or chilsonators followed by heating and sintering. The pore diameter of β-TCP granules of this invention ranges between 50-125μm whereas total porosity of β-TCP is 70%. The patent also provides a method for inducing bone-formation in a mammal by implanting a composition of porous β-TCP and binder or a bioactive agent.

3.7. Porous Materials Coated with Calcium Phosphate and Methods of Fabrication Thereof

Calcium phosphate coatings allow bone ingrowth into and around an implant device by supporting the formation of chemical bonds between the device and natural bone. The patent US20120270031 [35] describes a method of coating porous medical implants internally with a layer of Calcium phosphate. The method involves submerging a porous material in an aqueous solution that contains calcium ions, phosphate ions, carbonates, NaCl, and HCl, and has a temperature less than 100ºC and an initial pH of 6.0-7.5. The porous material to be coated generally comprises of composite material and calcium phosphate particles and has a macropore size of 0.5-3.5mm in diameter. The solution is agitated continuously at a speed of 200-400 revolutions per minute so that carbon dioxide gas is removed from the solution and the pH is increased gradually. Agitation enables the internal coating of pores extending within the volume of porous material. The thickness of the calcium phosphate coating is adjusted by controlling the contact time or immersion rate. The porous particles coated with calcium phosphate are then separated and mixed with a carrier which can be sodium alginate, gelatine, lecithin, and glycerol etc., followed by the addition of a fluid to form moldable or injectable porous material. The fluid is selected from the group consisting of water, sterilized water, blood, bone marrow aspirate etc. This moldable or injectable porous material has its individual particles coated with a layer of calcium phosphate, preferably HA. The thickness of calcium phosphate layer ranges between 0.5-50μm. The patent discusses that this moldable porous material can be used for various clinical applications including bone repair and regeneration. The patent further discloses that the porous material can be formed into sheet with a preferred thickness of 0.5-2.0mm and pore size range of 200-800μm before coating with calcium phosphate.

3.8. Biocompatible Ceramic-polymer Hybrids and Calcium Phosphate Porous Body

The use of composite material comprising HA and a biocompatible polymer for bone repair and replacement and method to prepare the same has been described in US20120136088 [36]. The patent relates to HA ceramic material with biodegradable polymer present in the pores of HAp structure. The porous HAp ceramic is prepared from slurry containing HAp fibers and carbon-beads. HAp fibers are formed by the precipitation of an aqueous solution con-

taining $Ca(NO_3)_2$, $(NH_4)_2HPO_4$, $(NH_2)_2CO$ and HNO_3. The solution is heated in the temperature range of 80-90ºC to produce HAp fibers with axes about 60-100μm in length. The use of carbon-beads is to create space between the fibers. Since carbon-beads and the HAp fibers have different densities they tend to separate out. Thus to homogenize the slurry, agar is added so that carbon-beads and fibers can be better dispersed. This slurry containing agar is poured into moulds having a porous bottom and a selected pressure of 30MPa is applied in order to form a pre-compact which is then calcined at 1200-1300ºC for about 3-5 hours. Carbon-beads vaporize leaving behind pores within HAp ceramics. The resulting HAp ceramics have an interconnected pore-structure with a pore diameter of 10μm and a porosity of about 40-70%. The patent also discloses the incorporation of poly-L-lactic acid esters into the pores of porous HAp ceramics by enzyme catalysis. HAp, lactic acid and lipase are mixed in a reaction container and then degassed by freeze-thaw and vacuuming. This is followed by flushing with an inert gas while maintaining a proper temperature so as to allow polymerization of the reaction mixture. The resulting HAp-PLLA hybrid is polished into the final product. PLLA is found to improve the mechanical properties of HAp ceramics.

3.9. Ion Substituted Calcium Phosphate Coatings

Ion-substituted calcium phosphate plays an important role in bone formation. The patent US20120087954 [37] describes a method for the formation of a surface coating of an ion-substituted calcium phosphate on a substrate. The method involves a substrate that is pre-treated so as to activate its surface. Pre-treatment is carried out with the help of heat treatment, hydrolysis, oxidation, acid or base treatment, UV radiation etc. A portion of this substrate is then immersed in the aqueous solution comprising calcium ions, sodium ions, magnesium ions, phosphate ions, Sr^{2+}, F^- etc. at a temperature of 20-100ºC with pH of the solution being maintained in the range of 6.0-8.0. The incubation or immersion time is around 1-3 days so that a coating of desired thickness is formed on the substrate. The patent also describes the use of two aqueous solutions in order to create additional layers of different chemistry and morphology. The obtained surface coating has about 25-60% cationic substitution of calcium and 10-25% anionic substitution of phosphate and hydroxide and a composition comprising 1.5-3% fluoride, 3-8% strontium and 0.5-2% silicon. The morphology of coating is in the form of sheets, flakes, porous structures, spikes and rods. The invention claims that thickness of the coating can be controlled between 10nm-100μm.

3.10. Delayed-setting Calcium Phosphate Pastes

The use of delayed-setting calcium phosphate pastes in the preparation of delivery vehicles for biologically active agents is described in US8216359 [38]. The patent discusses the use of calcium phosphate pastes for delivery vehicles and discloses the method to prepare the same. The paste that is used consists of a calcium phosphate material, an osteogenic protein which acts as a biologically active agent and a non-aqueous liquid which contains less than 5% water. Optionally, a bioerodible material is also added so as to introduce porosity in the paste. This paste is then exposed to moisture either before or after implantation and turns into a hardened calcium phosphate material upon hydration. This is followed by applying the delayed-setting paste to the surface of a bone implant so as to promote bone growth thereof. The patent also relates to an implant device comprising of delayed-setting calcium phosphate pastes which can be combined, mixed, and stored without setting or hardening for years together depending upon the application involved.

3.11. Bioactive Bonegraft Substitute

The use of calcium phosphate, resorbable collagen and bioactive glasses for the preparation of bonegrafts is discussed in US8303967 [39]. The method involves forming a homogeneous mixture of calcium phosphate, collagen and bioactive glass in a weight ratio of 75:10:15. Bioactive glass is present either in the form of coating on collagen or as a separate component in the mixture of collagen and calcium phosphate. The pH of the mixture is monitored so that bioactive glass does not undergo premature leaching necessary for osteoactivity. The mixture is then made to undergo heating, freeze-drying and many cross-linking techniques to yield a porous bonegraft with a total porosity of 65-95%.

4. PROPERTIES OF POROUS CALCIUM PHOSPHATE

For developing porous scaffolds, it is important that they meet certain requirements of bone tissue engineering and integrate well with the bone healing process. Some of the important aspects that need to be considered while developing these scaffolds are: appropriate micro- and macroscopic structural morphology including pore size, pore interconnectivity, biocompatibility, osteoconductivity, mechanical strength and biodegradability [40]. The idea is that if an implanted porous ceramic is progressively replaced by natural bone, its biomechanical properties should more and more resemble with natural bone. Extensive research efforts have been done in order to make use of synthetic HA/calcium phosphate as a bone substitute material in biomedical applications [41, 42].

Some of the physical and mechanical characteristics of porous calcium phosphates include biocompatibility, osteoconductivity, adequate mechanical strength and porosity degree. Biocompatibilty enables new cells to grow and proliferate on the implant surface and also ensures their adhesion to the surface. Osteoconduction and osteoinduction is another characteristic which comes from strong bonding between adjacent bones. Mechanical strength should be considerable so as to provide mechanical constancy in load bearing sites prior to regeneration of new tissue. It has been observed that the values for bending, compressive and tensile strengths of dense calcium phosphate bioceramics lie in the range of 38-250MPa, 120-900MPa and 38-300MPa, respectively whereas for porous calcium phosphate bioceramics, in the range of 2-11MPa, 2-100MPa and ~3MPa, respectively [43]. The variation in the values can be attributed to the difference in manufacturing processes of both the structures and innumerable structural variations. Furthermore, strength of porous calcium phosphate has been found to have an inverse exponential dependence on porosity, i.e. strength decreases

Table 3. Pore Size Distribution for an Ideal Scaffold in Bone Tissue Engineering Applications [46].

Pore Size (μm)	Biological Function
< 1	Protein interaction, responsible for bioactivity
1-20	Cell attachment, their orientation of cellular growth (directionally)
100-1000	Cellular growth and bone ingrowth
> 1000	Shape and functionality of implant

almost exponentially with increasing porosity [44, 45]. However, by changing the pore geometry, it is possible to influence the strength of porous bioceramics. The compressive strength of porous calcium phosphate bioceramics is reported to increase from 2MPa to 20MPa after 3 months of implantation [26].

Pore characteristics are crucial in bone engineering due to its correlation with the degree of bone in-growth. Porosity determines the movement of cells across pores. A good bioceramic should have an interconnected porosity ranging between 55-70% and the pore size should range from 150-700μm as in natural bone [30]. Pore size distribution for an ideal scaffold [46] is given in Table **3** as under:

5. PREPARATION METHODS OF POROUS CALCIUM PHOSPHATE BIOCERAMICS

5.1. Fabrication of Porous HA Ceramics with Controlled Pore Characteristics by Slip Casting

Porous HA ceramics with controlled pore characteristics were fabricated using slip casting method by Yao *et al.* [47]. HAp powders with dispersant are milled in a ball jar followed by the addition of Spherical polymethyl methacrylate (PMMA) particles and polyvinyl alcohol (PVA). In this method (PMMA) is used as a porosifier. The so formed slurries, free of foam, are cast into plaster molds. After demolded and dried at ambient temperature for 72h, the green blocks are heated to burn out the PMMA particles and other volatiles, followed by the treatment at 1200ºC for 2h for densification purpose. The pore characteristics of sintered porous HA bioceramics can be controlled by changing the size and content of PMMA. For an average particle size of added PMMA of 305, 134 and 62μm, the average pore size of porous HA ceramics is 290, 96 and 45μm respectively.

5.2. Fabrication of Porous Silicon-incorporated HA Using Natural Coral as a Calcium Source

Natural coral has a porous structure with all its pores interconnected throughout the skeleton as depicted in Fig. (**1**) [48]. its microstructure resembles that of bone and can be used as an excellent starting material for synthesis of porous HA.

Moreover, it has been suggested that the incorporation of silicate ions creates defect sites in HA and are favourable to dissolution [49]. In this method porous silicon doped HA has been prepared by hydrothermal treatment and solvo-thermal treatment of the natural coral in silicon acetate saturated

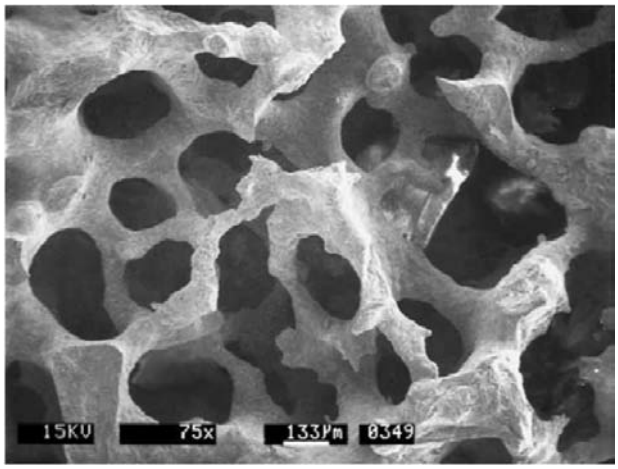

Fig. (1). SEM micrograph of natural coral [48].

acetone solution [48]. The resulting porous silicon doped HA possessed uniformly permeable micropores and uniform pore volume of about 70% with pore size distributions ranging from 200-300μm. The compressive strength of the porous silicon doped HA was found to be 5.5 MPa.

5.3. Highly Porous HA Bioceramics with Interconnected Pore Channels Using Camphene-based Freeze Casting

In this method, HA/camphene slurries are prepared through ball milling. The slurries are prepared with different (as received and calcined) HA contents (10, 15, and 20 vol %) and the temperature during milling is maintained at 60°C followed by casting into the moulds at room temperature. By removing the frozen camphene network via sublimation, a well defined three-dimensional interconnected pore channel system is easily produced [50]. Camphene can be frozen and easily sublimed near room-temperature and hence can be used to produce highly porous HA bioceramics with completely interconnected pore channels. Freeze casting method has been considered a preferred method since it can produce well defined pore structures on a finer scale [51-53]. In addition to it, the use of calcined HA powders produces homogeneous slurries with different HA contents. Thus this method allows the fabricated samples/bodies to have completely interconnected pore channels with porosity being controlled by the initial HA content. Moreover these porous bodies have higher strength and smaller pore size due to the densification of the HA walls resulting from sintering of highly packed HA powder networks at 1250°C for 3 h.

5.4. Preparation of Porous HA Through Polymeric Sponge Method

Yet another method to fabricate porous ceramics is through replication of the polymeric sponge substrate [54]. Ceramics developed this way have controllable pore size and can be made into various complex shapes useful for different applications [55]. This method is carried out by impregnating the cellulosic sponges with prepared HA slurry. Porous HA prepared by the polymeric sponge method has shown to have interconnected pores but poor mechanical strength for load bearing applications. However, this method results in an adequate pore size distribution as is required for osteoconduction to take place. The slurries are made from commercial HA powders while making the use of cellulosic sponges for impregnation. All porous samples contained micropores of 0.2-1μm and macropores of 100-500μm in diameter. The effect of processing parameters viz; sintering rate, stirring time and HA concentration on the physical properties was studied. Higher sintering rates resulted in a higher apparent density and higher compressive strength and thus better mechanical strength. The average compressive strength of the porous bodies varied between 1.8 and 10.5MPa for a decrease in porosity from 59.8% to 34.3%; concluding that compressive strength is inversely dependent on porosity. Stirring slurry for a prolonged period of time also resulted in higher compressive strength due to its better homogeneity.

5.5. Spark Plasma Sintering of Macroporous Calcium Phosphate Scaffolds from Nanocrystalline Powders

Macroporous β-TCP scaffolds are fabricated via Spark plasma sintering (SPS) technique using nanocrystalline powders [56]. SPS is a new technique used for the fabrication of various solid nanostructured materials viz; ceramics, cermets and alloys [57]. In this technique nanocrystalline β-TCP powders are first synthesized by a chemical precipitation reaction. The precipitates so obtained are dried at 80°C for 24h followed by calcination of powders at 700 and 800º C for 2h. The obtained nanocrystalline β-TCP powders are then mixed with polyethylene glycol particulates and the mixtures are pressed in a stainless steel die. The prepared green disks are heat-treated at 400°C to remove the organic substances, and then they are presintered. The presintered sample is then placed into a graphite die for spark plasma sintering. The obtained macroporous scaffolds were found to have a porosity of 55-70% and macropore size of (300-500μm) whereas, the compressive strength and elastic modulus improved by 50-100%.

5.6. Manufacturing of Highly Porous Calcium Phosphate Bioceramics Via Gel-casting Using Agarose

Gel-casting technique is the method resulting in the production of scaffolds most closely mimicking the structure of trabecular bone [58]. This method uses agarose as gelling agent [59]. Agarose solution is prepared by adding agarose powder to distilled water followed by heating at 12°C and 1.4 bar in an autoclave. Meanwhile, HA slurries are prepared from HA powders synthesized by precipitation method. Prior to foaming, agarose solution is added to HA slurry while maintaining the temperature at 60°C. The foaming suspension containing agarose is then poured into a mould which is further cooled by water to transform the liquid state to a gelled state. The whole process is followed by de-moulding, drying and sintering. Characterization of the ceramic foams was carried out using different techniques in order to monitor cellular microstructure of the sinters by analyzing in terms of estimation of cell sizes (spherical pores) and window sizes (interconnected pores). XRD study revealed that additives used in the gel-casting process did not influence the phase composition of the investigated materials. The obtained porous (P = 90%) CaP scaffold had macropores (spherical~500μm and interconnecting windows~100μm in diameter) and a small amount of micropores (0.2-0.9μm) as seen in Fig. (**2**). The advantage of this technique is that it is environmental friendly.

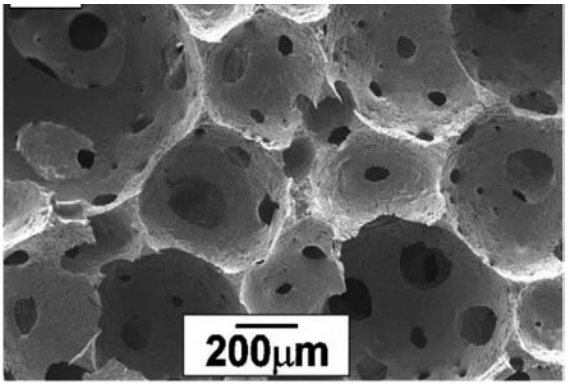

Fig. (2). SEM micrographs of the cross-section of sintered CaP foam [59].

5.7. Biphasic Calcium Phosphate Macroporous Scaffolds Derived from Oyster Shells

Oyster shells are considered to be biocompatible and bioactive materials for bone grafting applications [60]. This method uses HA powders obtained from the hydrothermal treatment of oyster shells for the fabrication of porous scaffolds [61] via polymeric replication method as reported in previous works [62, 63]. The overall process flowchart of the method is shown in Fig. (**3**).

The resulting scaffolds, comprised of a biphasic structure of HA/β-TCP, and open macropores with pore size in the range of 200-500μm and interconnected micropores from 100nm to 500nm. In addition, O-HA scaffolds showed excellent permeability and a high porosity upto 91.4% $\pm$ 1.2%. Cell-culture results confirmed their non-cytotoxic behavior and a better biocompatibility.

5.8. Fabrication of Mesoporous Carbonated HA Microspheres by Hydrothermal Method

One of the major inorganic constituent of natural bones and teeth that is native to the human body is carbonated HA (CHA). A number of corresponding synthetic materials, possessing excellent biocompatibility, nontoxicity, bioactivity and non-immunogenecity, have been synthesized for bone substitute applications [64-66]. However, porous biomaterials have been considered to be the most suitable materials for bone reconstruction and replacement. It has been found that macropores (greater than 100μm) allow the bone in-growth [67]. The mesopores (2nm < pore size < 50nm) or micropores (< 2nm) help in enhancing cell adhesion, adsorption of

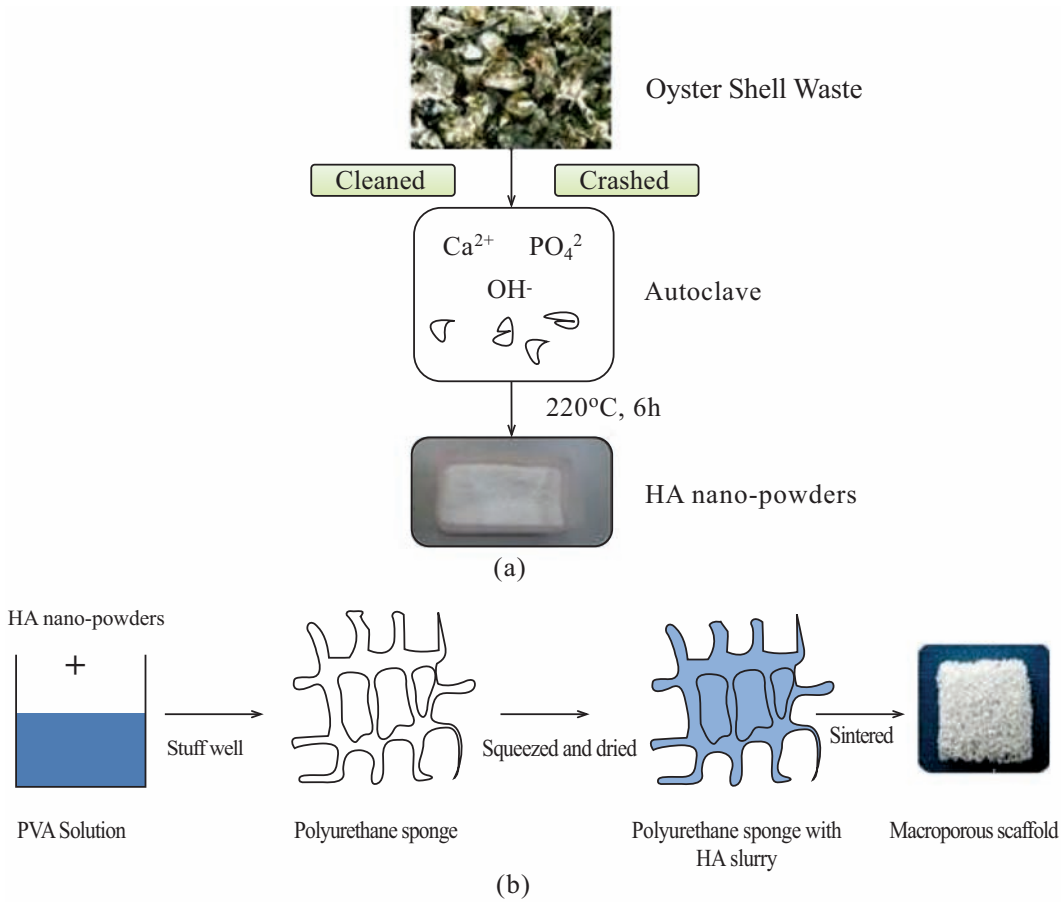

Fig. (3). Schematic of the basic process: (**a**) Hydrothermal conversion of oyster shells to ha nano-powders and (**b**) Polymer replication technique, which is used to fabricate the macroporous scaffolds [61].

biological fluids, resorbability and formation of bone-like apatite after soaking in simulated body fluids (SBF) [67-69]. A number of natural sources have been used as starting materials for the preparation of porous HA by hydrothermal method or by treatment with phosphate buffer solution [70-72]. Some of them include corals [73], algae [74], cuttlefish [75], and nacre [76, 77]. In this work calcium carbonate microspheres (CCMs) (prepared from nacre) are used as starting materials for the fabrication of mesoporous carbonated HA microspheres (MCHMs) via hydrothermal method [78]. The chemical elements of nacre mainly include O (48.026 wt.%), Na (0.281 wt.%), Al (0.215 wt.%), Si (0.058 wt.%), S (0.022 wt.%), Ca (40.957 wt.%), Sr (0.083 wt.%), and other elements such as C, H, and N (10.4 wt.%). The preparation of CCMs from nacre is mentioned elsewhere [79]. A schematic diagram of the overall method is shown in Fig. (**4**).

The resulting MCHMs have a diameter of ~5μm and are composed of many nanoparticles within the whole microspheres. These nanoparticles aggregate to form mesopores with a pore size of 4.5-14.0nm among them.

5.9. Production of Porous Calcium Phosphate (CaP) Ceramics with Highly Elongated Pores Using Carbon-coated Polymeric Templates

This method produces porous calcium phosphate ceramics with highly elongated pores. The elongated pore structure ensures good compressive strength of these ceramics. CaP/camphene slurry is cast into stretched polymeric sponges, precoated with a very thick carbon coating layer used as a template. This is followed by heat treatment at 800°C for 3h in order to remove the carbon-coated template and then at 1250°C to sinter CaP walls. The resulting sample has a highly elongated pore structure with a pore size of 512 ± 96μm and a porosity of about 38 vol% where as compressive strength values are as high as 22 MPa in the direction parallel to the pore elongation [80].

5.10. Porous Alumina-HA Composites Through Protein Foaming–consolidation Method

Porous HA ceramics have been commonly used for bone implant applications due to their excellent bioactivity and compatibility. However, these ceramics have a disadvantage of being mechanically weak thereby have limited use in load-bearing applications [6]. Various attempts have been made to improve the strength of porous HA ceramics one of them being incorporating alumina into HA powders. Jun *et al.* [81] successfully fabricated porous alumina-calcium phosphate composites using polyurethane sponges. The resulting porous bodies were found to have a porosity of 75-90% and a compressive strength of 6MPa.

We have reported the fabrication of porous alumina ceramics using egg yolk as a pore forming agent via protein

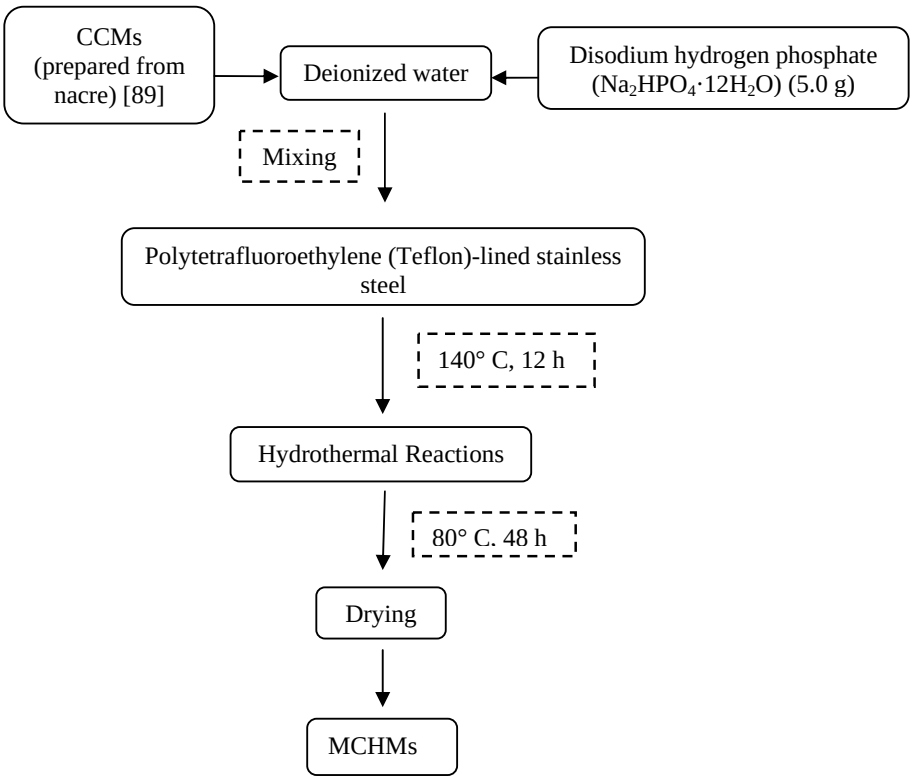

Fig. (4). Schematic diagram of Fabrication of mesoporous carbonated HA microspheres by hydrothermal method.

foaming-consolidation method [82]. The obtained porous bodies showed good pore connectivity with a pore diameter of approximately 100-500µm. However, in the present method, protein foaming-consolidation method has been used to fabricate porous alumina-HA composites [83]. The flowchart of the method followed is given in Fig. (**5**).

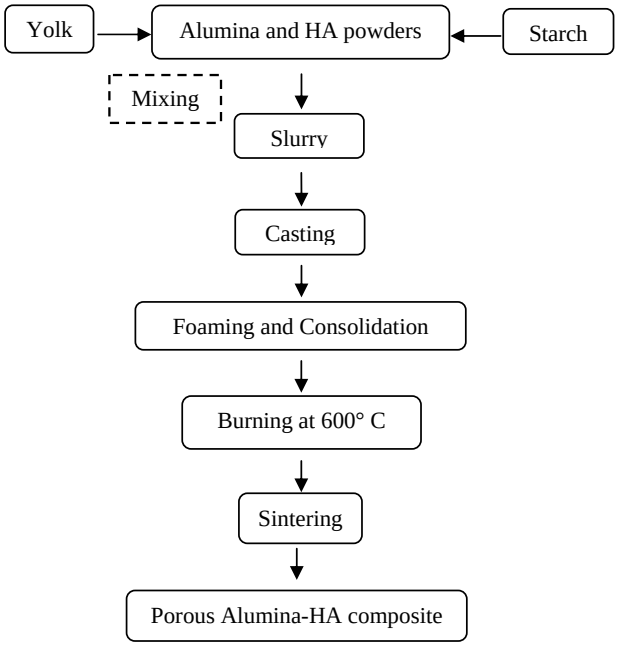

Fig. (5). Flowchart of fabrication of porous alumina-HA composites through protein foaming-consolidation method.

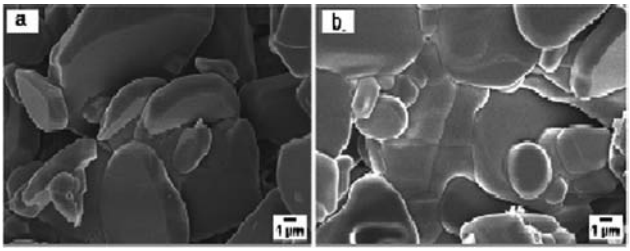

Fig. (6). SEM micrograph of porous alumina-HA ceramics sintered at (**a**) 1350 and (**b**) 1550°C [83]. Reproduced by the permission of authors.

Alumina and HA powders, obtained via sol-gel technique [84] are mixed with yolk and starch in a proportionate ratio in order to make a slurry. Yolk, used as the protein source for foaming, is taken from chicken egg. It consists of 25 wt% protein and 24 wt% lipids. Starch flour acts as a binder whereas Darvan 821A (40 wt% aqueous solution of ammonium polyacrylate; R.T. Vanderbilt, USA) as the dispersing agent. The resulting slurries are cast into cylindrical open stainless steel molds followed by foaming and consolidation at 180°C for 1 h. The green bodies obtained after consolidation are burnt at a temperature of 600°C for removal of yolks and then sintered between 1200-1550°C for 2h.

This method produces porous composites with 26-77 vol% shrinkage and 46%-52% porosity. The micrograph of porous alumina-HA ceramics sintered at 1350 and 1550°C respectively, shows that with an increase in sintering temperature the grains get strongly bonded together as a result of progressive fusion of particles as depicted in Fig. (**6**).

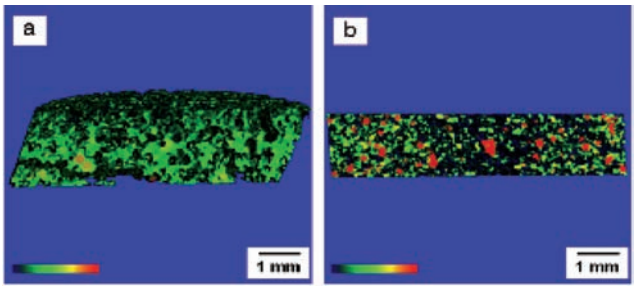

Fig. (7). Micro CT cross-sectional images of HA thickness with color coded porous bodies having HA-to-alumina mass ratio of (**a**) 0.30 and (**b**) 1.0 w/w [83]. Reproduced by the permission of authors.

The effect of HA loading and yolk addition on the properties of porous samples was also studied. Fig. (**7a-7b**) shows Micro CT images of HA thickness with HA-to-alumina mass ratio of 0.3 and 1.0 w/w respectively. The thickness of HA increased with an increase in HA loading in the slurry. Sample of 0.3 w/w ratio shows thicker HA layer in the middle part of porous body than the upper part, whereas in 1.0 w/w ratio sample, HA particles precipitate only in the surface part.

It was also observed that an increase in HA content in the slurry led to a decrease in pore size. The 3D images of colour coded porous bodies with corresponding pore size distributions is shown in Fig. (**8**). The pore size of 0.3 ratio sample was found to be in the range of 10-460µm and of 1.0 ratio sample in the range of 10-350µm as seen in Fig. (**8b**) and Fig. (**8d**) respectively.

On contrary an increase in the yolk amount in slurry leads to an increase in pore size due to higher foaming capacity of slurry. This result is attributed to the fact that amphiphilic character of protein decreases the surface tension of slurry and leads to better foaming property [85].

Biocompatibility tests revealed good compatibility of the cells to the porous microcarriers as the cells attached and grew at the surface of microcarriers at 8-120 cultured hours which is depicted in Fig. (**9**). The cell growth on porous alumina microcarrier has been observed to be 0.015 h-1 which increased with an increase in HA-to-alumina mass ratio. Figure **9a** shows the microstructure of porous alumina after being sintered at 1550°C without cell seeding. Figure **9b** shows an initial stage of attachment and proliferation of the cells on porous alumina surfaces only in 12 cultured hours. After 120 hours, Vero cells have started to respond in different manners to every sample. The Vero cell density for pure alumina samples was lower Fig. (**9c**) than that of the 1.0 w/w ratio sample Fig. (**9d**).

5.11. Fabrication and Properties of Porous β-TCP Ceramics Prepared Using a Double slip-Casting Method Using Slips with Different Viscosities

This method produces porous β-TCP scaffolds with enhanced mechanical properties and has a better control over the microstructures of the scaffolds [86]. Scaffolds are produced by combining two methods viz; double slip-casting and polymer sponge method. In step 1, Slurry 1 has been obtained by adding a solution of 1.5 wt% deflocculant to β - TCP1 powder with a solid content of 58.5 wt% followed by dilution with water. After that 0.5 wt% of foaming agent has been added to it to make a slip-1. The specimen is obtained

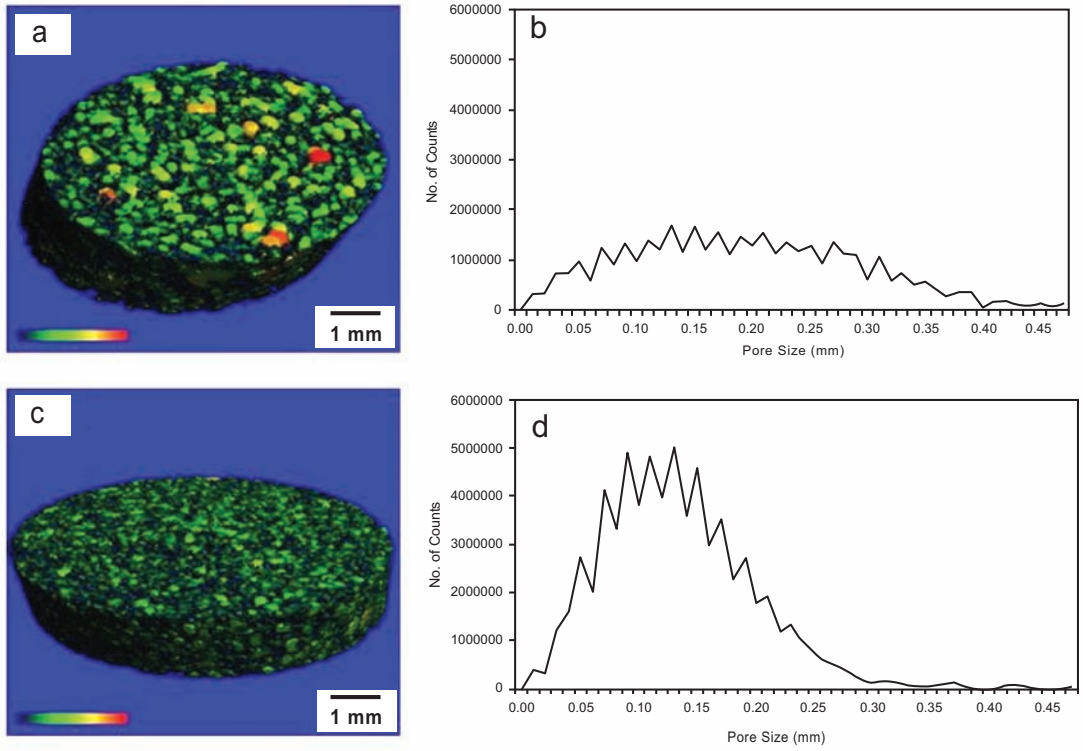

Fig. (8). 3D images of color coded pores with corresponding pore size distribution of bodies with HA-to-alumina mass ratio of (**a**, **b**) 0.30 and (**c**, **d**) 1.0 w/w [83]. Reproduced by the permission of authors.

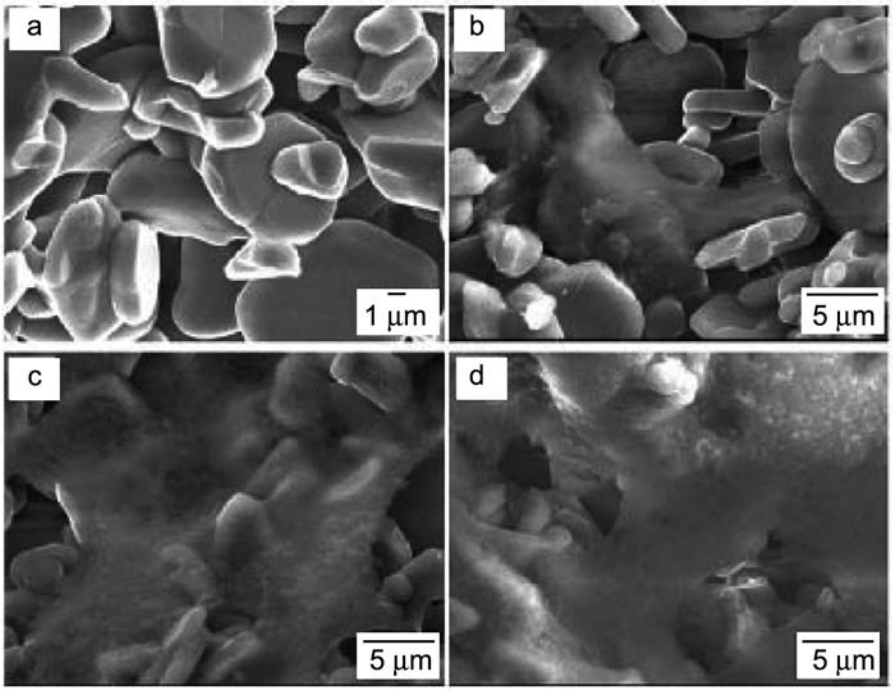

Fig. (9). The morphology of surface of (**a**) Porous alumina without cell seeding (**b**) Initial attachment and proliferation of Vero cells on surfaces of the alumina-HA porous bodies (**c**) Vero cell density of Pure alumina sample (**d**) Vero cell density of 1.0 w/w ratio sample [83]. Reproduced by the permission of authors.

by dipping a polyurethane block into slip-1, after which it's dried under vacuum for 5 min to yield dried specimen-1. Slip-2 has been obtained by adding β-TCP 2 powder with a solid content 62.5 wt% to a solution of 1.5 wt% deflocculant followed by dilution with water to make slurry-2. After that dried specimen-1 has been dipped into slip-2, and then the sample is dried under vacuum for 5 min followed by heating at a rate of 0.5°C / min to 250°C and then incubated at 250ºC for 30 min to decompose the deflocculant and the polyurethane template. The samples are again heated at a rate of 3°C /min to 1200°C, incubated for 3h at 1200°C, and cooled down to room temperature at a rate of 3°C/min to yield the final samples. The series of steps involved in this method are shown in Fig. (**10**) as under:

The resulting scaffolds have a porosity of 61.4% and an open, uniform, interconnected porous structure with a bimodal pore size of 100-300μm and a very high flexural strength of 56.2MPa.

6. CURRENT & FUTURE DEVELOPMENTS OF BIOCERAMIC BONE IMPLANTS

A well designed bioceramic scaffold in terms of structure and properties plays an important role in directing and enhancing cell growth and cell proliferation to surrounding tissues [14, 87-89]. Porous HA ceramics have been extensively used as bone graft substitutes [90, 91]. Moreover their interconnected structure favors bone ingrowth and osseointegration [58]. The strength of these ceramics/scaffolds depends upon various factors e.g., pore size, pore shape, and pore orientation [92]. Variation in preparation technique allows production of porous HA with different porosity, pore connectivity, surface and mechanical properties. Several

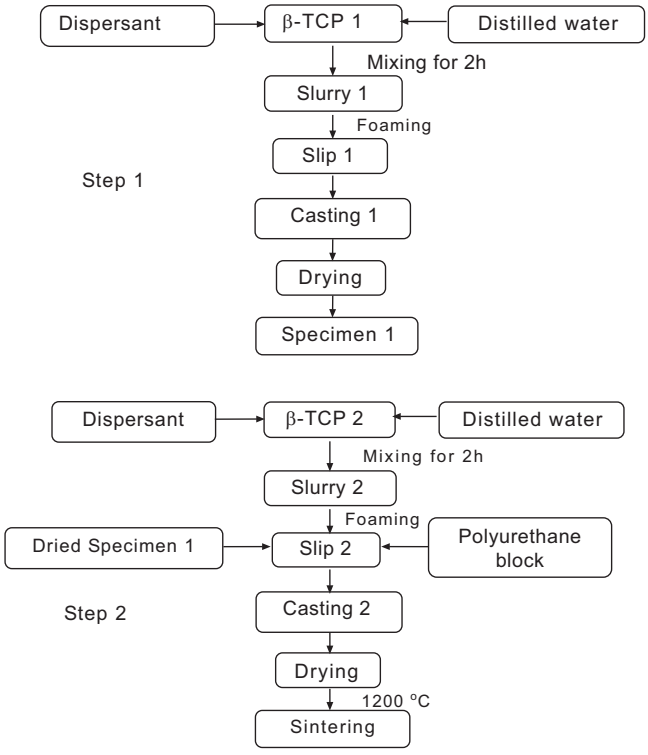

Fig. (10). Series of steps involved in fabrication of porous β-TCP ceramics [86].

methods for the preparation of porous HA have been highlighted in this article through a thorough review of the most recent patents and journals. Some of the methods are tabulated in Table **4** below:

Table 4. Porosity and Pore Size of Porous Samples Produced by Different Methods.

Method	Porosity (%)	Pore Size (μm)
Fabrication of porous HA ceramics with controlled pore characteristics by slip casting [47]	25 - 40	45 - 290
Fabrication of porous Silicon-incorporated HA using natural coral as a calcium source [48]	70	200 - 300
Highly porous HA bioceramics with interconnected pore channels using camphene-based freeze casting [50]	56-75	~100
Preparation of porous HA through polymeric sponge method [54]	0.2-500	34 - 60
Spark plasma sintering of macroporous calcium phosphate scaffolds from nanocrystalline powders [56]	55-70	300 - 500
Manufacturing of highly porous calcium phosphate bioceramics via gel-casting using agarose [59]	90	100 - 500
Biphasic calcium phosphate macroporous scaffolds derived from oyster shells [61]	91	200 - 500
Fabrication of mesoporous carbonated HA microspheres by hydrothermal method [78]	-	-
Production of porous calcium phosphate (CaP) ceramics with highly elongated pores using carbon-coated polymeric templates [80]	38	416 - 608
Porous alumina-HA composites through protein foaming–consolidation method [83]	46-52	10 - 460
Fabrication and properties of porous β-TCP ceramics prepared using a double slip-casting method using slips with different viscosities [86]	61	100 - 300

However, due to the poor mechanical properties of the porous HA bioceramics, their use for load bearing applications is severely restricted [93, 94]. Several attempts have been made to improve the mechanical strength of porous HA bioceramics e.g., doping with metals or blending with high performance reinforcing materials or organic polymers, including introducing secondary phase [95, 96] and optimizing sintering techniques [97] etc. Kim *et al.* [98] used poly (ε-caprolactone) (PCL) and HA composite coatings on the surface of the porous HA scaffolds to improve the mechanical properties of the scaffold. Yook *et al.* [99] used polystyrene (PS) polymer as a binder to HA/camphene slurries. The PS binder increased the green strength of the sample thereby preventing the sample cracking. The compressive strength was significantly increased from 1.1±0.2 to 2.3±0.5 MPa, while the pore size was decreased from 277±47 to 170±29μm. Zhang *et al.* [100] developed a novel method for the fabrication of porous bodies. The method was developed by combining the conventional freeze casting and gel casting. Hydantoin epoxy resin was used in the freeze casting which promoted the gelation process and led to a higher compressive strength of the green body. However, after sintering freeze-gelcast samples exhibited a twice higher compressive strength and 15.6% higher porosity. Lee *et al.* [101] used bone ash for the fabrication of biphasic calcium phosphate bioceramics. Bone ash, used as a raw material for bone china, was treated with NaOH solution and then calcined to obtain calcium phosphate powders. The bone ash derived-biphasic calcium phosphate ceramics showed high biostability in liquid environment when -compared with commercial calcium phosphate ceramics. Yang *et al.* [102] developed a strong layered HA/TCP-zirconia scaffold composite by employing newly developed slip-deposition and coating-substrate co-sintering technique. The developed scaffolds exhibited a bending strength of 321 MPa. Also from the *in vitro* cell culture study, it was indicated that the coatings had no cytotoxicity.

For developing a bone graft, its *in vivo* resorption rate becomes a matter of concern since bone graft should be rapidly resorbable and replaced by new bone. In a recent patent application, Yang *et al.* [103] related to a composite of α-calcium sulfate hemihydrates and amorphous calcium phosphate having resorption time of 3-6 months. The composite consists of calcium sulfate which has a bone regeneration and angiogenic effect. The preparation method involves dissolving the solutions containing calcium ion and sulphate ion separately in calcium chloride solution. The process is followed by heating and mixing of two solutions to produce α-calcium sulphate hemihydrates (α-CSH). Solid α-CSH is separated from the solution after filtration. Amorphous calcium phosphate (ACP) is formed by adding a phosphate compound to the solution of calcium chloride. α-CSH and ACP are further mixed to produce the desired composite (α-CSH/ACP).

Recently, attention has been paid to the development of resorbable tissue scaffold that can have load bearing strength and at the same time sufficient porosity so that growth of bone tissue is promoted effectively. In a patent of Liu *et al.* [104], one such prosthetic device is described. The patent discloses the use of bioactive glass fibers comprising of calcium carbonate, phosphorus pentoxide, silica and sodium carbonate, bonded into a porous matrix having a pore size distribution in order to facilitate the growth of bone tissue for the treatment of bone defects. Bioactive glass fibers of such a composition have capability to form silica-rich layer and a calcium phosphate film on the surface that readily bonds glass material to bone. The rigid three-dimensional matrix of bioactive tissue scaffold is formed by heating the mixture of bioactive glass fiber, binder, pore forming agent and liquid.

Preparation of calcium phosphate particles in the nano to micrometer range with controlled morphology without the use of surfactant or template has been proposed by Engqvist and Xia [105]. The invention presents a method for the

manufacture of ion-substituted calcium phosphate particles with controlled morphology and structure via a surfactant-free biomineralization process. Calcium phosphate particles are synthesised with mineralisation and precipitation methods comprising the basic steps of preparing a salt solution and precipitating calcium phosphate particles from the salt solution. The solution comprises calcium, and phosphate ions and one or more of magnesium, sodium, potassium, chloride, carbonate or sulphate ions. The morphology of calcium phosphate particles is controlled by adjusting the concentration of substituted ions. Use of such particles with controlled morphology is helpful in stimulating regeneration of damaged bone by inserting ion-substituted calcium phosphate into the body.

In a recent patent, Kjellin and Andersson [106] provided highly crystalline synthetic nano-sized HA with a specific area in the range of $150m^2/g$ to $300m^2/g$. It is the highest specific area ever presented. The patent discloses that nano-sized HA crystals resemble HA particles that are present in the living body and are suitable in the biomimicking of body tissue for the making of body implants. Thus HA of this invention is suitable for being deposited on the surface of an implant to make it bioactive in order to stimulate bone growth process.

A patent based on the fabrication of an implantable device comprising of bioceramic particles has been published recently by Gale *et al.* [107]. The patent relates to a method for fabricating a stent comprising of biodegradable polymer and bioceramic particles. Bioceramic particles are made from biodegradable bioceramics such as tetracalcium phosphate, amorphous calcium phosphate, α-TCP, β-TCP and various types of bioglass materials. The use of bioceramics is aimed at inhibiting infection that may result during implantation and to increase the fracture toughness of the stent. Bioceramic particles disperse the strain over a large volume of the stent and increase its flexibility and resistance to cracking during deployment.

In addition to the efforts made in developing bioceramic implants as a replacement for fractured or diseased bones, several techniques have been introduced to form bioceramic coating on the metal implants as well. In a patent appeared on February 2013, Liu *et al.* [108] indicated a method to develop a gradient bioceramic coating on the surface of titanium alloy which can be implanted in order to restore defects in human sclerous tissues. The method involves mixing of powdery composite ceramics of calcium phosphate and calcium carbonate with rare earth oxide and powdery titanium on the surface of a titanium alloy. This is followed by cladding treating the surface with carbon dioxide laser processing system so that synthesis and coating of HA on the surface of titanium alloy are completed in one step.

In a patent published in January 2013 by Betz *et al.* [109], the use of coherent aggregate of elongate bone particles was made for the preparation of osteoimplant. The object of the invention was to provide a low density implant which possesses an open pore structure to allow the passage of blood and other bodily fluids and yet retain its original shape. The implant was prepared by mixing elongate demineralised bone particles with an aqueous wetting agent followed by moulding into a desired shape. The excess moisture was removed through heating at elevated temperature in absence of pressure. The osteoimplant formed from such a process does not require time-consuming rehydration prior implantation and can attain any shape and configuration.

In yet another recent patent issued to Burkinshaw [110], a composite bone graft kit comprising of an allograft bone component and a synthetic bone substitute (such as β-TCP, HA and poly-lactic acid) is disclosed. The composite is arranged in a core/outer layer structure and consists of a mesh casing wherein allograft bone component and synthetic bone substitute are in contact with each other. The patent also describes the use of a bone graft syringe with composite bone graft disposed within the syringe. This bone graft syringe is further claimed to be connected with a delivery syringe for delivery of an injectable component such as cell concentrate, platelet rich plasma or a bone marrow aspirate.

A great progress has been accomplished in the field of bio-ceramics so far; however major advances are needed to be done in order to develop ceramics with improved properties depending upon the specificity of disease and demand. A large increase in active elderly people has alarmingly raised the need for load-bearing bone graft substitutes. Owing to this demand, new strategies for enhancing the mechanical properties of porous scaffolds have to be proposed and developed.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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