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Porous hydroxyapatite for artificial bone applications

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Abstract

Hydroxyapatite (HA) has been used clinically for many years. It has good biocompatibility in bone contact as its chemical composition is similar to that of bone material. Porous HA ceramics have found enormous use in biomedical applications including bone tissue regeneration, cell proliferation, and drug delivery. In bone tissue engineering it has been applied as filling material for bone defects and augmentation, artificial bone graft material, and prosthesis revision surgery. Its high surface area leads to excellent osteoconductivity and resorbability providing fast bone ingrowth. Porous HA can be produced by a number of methods including conversion of natural bones, ceramic foaming technique, polymeric sponge method, gel casting of foams, starch consolidation, microwave processing, slip casting, and electrophoretic deposition technique. Some of these methods have been combined to fabricate porous HA with improved properties. These combination methods have yielded some promising results. This paper discusses briefly fundamental aspects of porous HA for artificial bone applications as well as various techniques used to prepare porous HA. Some of our recent results on development of porous HA will be presented as well.

Keywords: Porous hydroxyapatite; Preparation; Bone; Review

1. Introduction

A standard strategy applied when a bone loss occur is bone grafts which include autografts, allografts, and xenografts; each type has its advantages and disadvantages. Autografts have the advantages of no adverse immunological response and, even more importantly, it is the best for inducing new bone formation in the host due to its osteogenic capacity. However, this bone graft is usually available in limited quantity. In addition, their availability is qualitatively limited by the anatomy and physiological conditions of the donor site; they have no mechanical strength and shape which can precisely duplicate the bone being replaced. They require additional surgery for harvesting resulting in more pain for the patient. Besides additional cost for longer time of surgery, there are other disadvantages associated with the risk of donor site morbidity like fracture, long lasting pain, nerve damage, and possible infection.

Allografts, on the other hand, are available in considerable quantity, can be strong mechanically, and can duplicate the deficit; unfortunately, however, they are immunogenic and are not as osteoinductive as autograft bone thus possibly leading to non-unions. The problems of disease transmission like hepatitis and HIV are also well documented. Their storage is expensive, altering mechanical properties and biological response. Thus, with such critical arguments on applications of naturally derived bone grafts, development of artificial bone substitution materials made from metals, ceramics, polymers, and composites are of a great importance [1].

Hydroxyapatite (HA) ceramics has been widely applied as bone substitutes. Together with β-tricalcium phosphate, they have been for nearly three decades the most

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extensively used substitution materials for artificial bone grafts [2]. Their chemical composition close to the mineral phase of bone is an origin of their excellent biocompatibility to tissue bone. This meets the requirement of any materials designed for bone repair and augmentation [3]. To this aim, a high degree of crystallinity and chemical stability have been included among the desirable properties of an ideal HA [4]. Although many problems concerning infective risk, mechanical and biological stability, compatibility, storage and costs still remain, HA materials have been applied in orthopedics as block implants, granules or coating, either dense or porous [5].

In recent years, particular attention has been paid to the preparation of HA bioceramics with porous morphology. Porous HA exhibits strong bonding to the bone; the pores provide a mechanical interlock leading to a firm fixation of the material. Bone tissue grows well into the pores, increasing strength of the HA implant. It was realized that dimension and morphology of pores are crucial factors for an excellent osteointegraton [6–8]. Minimum pore size required to enable ingrowth of the surrounding bone together with blood supply, is about 100–150 μm for macropores [9,10], and even at pores of as small as 50 μm osteoconduction is still possible [11]. Some reports stated that it should be 200–500 μm for colonization of osteoblast in the pores, fibrovascular ingrowth and finally the deposition of new bone [2,12]. Other important requirements for porous implants are interconnectivity of the pores for the penetration of the osteoblast-like cells inside the pores as well surface roughness for the attachment of cells.

With larger pores strength of the implant decreases significantly. Therefore, normally porous HA implants cannot be heavy loaded and are used to fill only small bone defects. The obtained physical characteristics in development of porous ceramics for bone substitutes depend on the porous volume of the biomaterials, as well as the mean pore and interconnection sizes. A successful development of porous bone substitutes with optimal properties requires perfect control of these parameters.

2. Applications of porous HA

Porous HA have been applied for cell loading [13–17], drug releasing agents [18–31], chromatography analysis [17], and the most extensively for hard tissue scaffolds [28,30,32–43]. Various cell products are therapeutically of crucial significance including hormones, enzymes, vaccines, and nucleic acids which could improve the technology of the diagnosis and treatment of human diseases. Mammalian cells can be grown and maintained in vitro, but are generally anchorage-dependent, i.e., they need solid substrate for growth. Most of animals cell used for the production of viral vaccines, growth factors, receptors or therapeutic proteins are anchorage-dependent.

Microcarrier culture technique is one of the methods developed for cell cultivation. Owing to high surface area for cells to adhere and grow, microcarrier culture offers a practical high yield culture of anchorage-dependent cells and thus it is possibly suitable for large-scale operations. A variety of microcarriers, including those based on dextran, polystyrene or cellulose, and collagen or gelatine-based macroporousbeads have been developed [16]. Ceramic microcarriers, on the other hand, introduces new possibilities for the culture of animal cells. Ceramic microcarrier is predicted to meet the special requirements of a microcarrier technique due to good mechanical, chemical and thermal resistances. The mean diameter of microcarriers often lies in the range 130–200 μm, even though a range as wide as 100–400 μm has been described as suitable for growth [16].

In drug delivery systems, it has been recognized that a system for the slow, local and continuous release of drugs would be a decided advantage for the treatment of many ailments. One of potential candidates for such controlled drug delivery systems is porous ceramics; much attention has been paid to porous HA. Owing to their physicochemical and biological properties, porous HAs have been proven as a potential candidate for bone drug delivery system [41]. This type of drug delivery system, via use of a bioactive matrix, can release a therapeutic agent in situ to produce an anti-infection action associating the osteoconductivity of materials. For example, chronic disease or localized surgical intervention, relying on a sustained local drug delivery, needs ceramic capsulae suitable to release drugs at a controlled rate [31].

The flux of a substance across a porous layer is connected to two main parameters: its solubility in the physiological body fluids and the possible physical or chemical bonds formed by its molecules with the walls of the pores of the delivery device [25]. Several groups have designed different types of porous calcium phosphates for drug delivery accordingly. Palazzo et al. [21] tested their porous HA device with a bimodal porosity degree (60% and 40%) as controlled drug delivery devices for anti-inflammatory drugs. Another device with a bimodal porosity have been introduced for a controlled delivery of an anti-phlogistic, hydrocortisone acetate [29]. An interesting approach has been done by Komlev et al. [41] who developed porous spherical HA granules and fluoroHA granules applicable for bone drug delivery system. As well known the incorporation of fluoride ions into the structure of HA can stimulate bone cell proliferation and increase new mineral deposition in cancellous bone. FluoroHA also showed good integration in the bone tissue and much longer resorption time than classic calcium phosphate [41]. On the other hand, for biomedical applications spherical geometry is much preferable than irregular one to eliminate non-desirable inflammation reactions from the body soft tissues. Granules of diameter range from 50 to 200 μm with open pores content of 43–62% were successfully prepared (see Fig. 1). Bone drug delivery systems were also developed using porous calcium phosphate ceramics bonded with antibiotics through a biodegradable polymeric

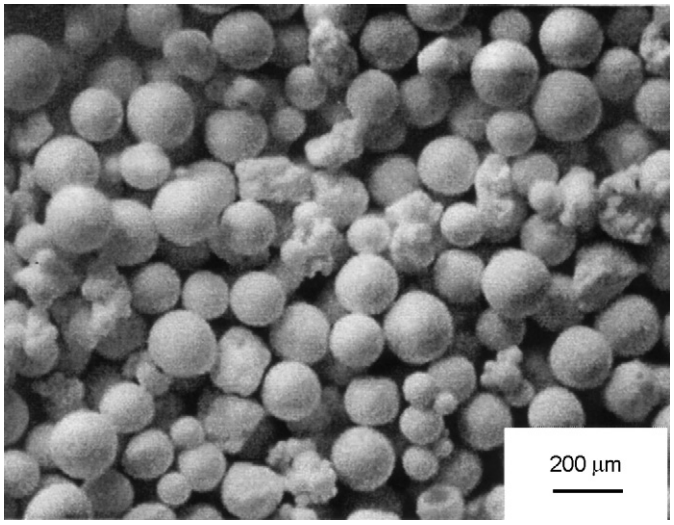

Fig. 1. A photomicrograph of porous spherical hydroxyapatite granules [41].

matrices. Usage of biodegradable polymers is to obtain a controlled release bone drug delivery device. Many types of biodegradable polymers have been used for this purpose including gelatin, albumin, and PLGA [44,45].

Porous HA has been extensively applied for artificial bone substitutes. The primary purpose of tissue engineering is repair, regeneration, and reconstruction of lost, damaged or degenerative tissues. Although bone tissue itself shows an excellent ability of bone regeneration, for big bony defect or for such situations that bone healing process is difficult bone grafts are required. At this point, it is very crucial to match the osteoconductive properties of porous ceramic scaffold in one side with the osteoinductive or osteogenic properties of living bone cells in the other side. Theoretically, a degradation rate of the implant similar to the rate of tissue formation is expected. Therefore one of important aspects in the development of bone and organ substitute materials is the fabrication of supporting matrices or scaffolds with an appropriate micro- and macroscopic structural morphology including pore size, pore interconnectivity, biocompatibility, osteoconductivity, mechanical strength, and biodegradability.

Results on histological analysis of osteoconduction in vivo of porous HA showed that within six weeks after implantation mature bone ingrowth was observed in the whole parts of the porous HA [8], followed by an increase in compressive strength of porous HA. Besides via osteoconduction in vivo, bone tissue regeneration can be conducted using carrier-scaffold system using biologically active bone morphogenetic protein (BMP) as the carrier. Embedding BMP on porous HA has enhanced bone formation and reduced the amount of BMP used in comparison with the cases in conventional studies [46]. Mesenchymal stem cells are also used as a source of bone-producing cells [47]. Studies showed that initial bone formation inside the pore areas can be seen after 2 weeks implantation, and even at 8 weeks after implantation extensive bone volume was detected in the center areas of the implants. The combination of porous HA and mesenchymal stem cells are a potential candidate for an excellent bone graft substitute accordingly due to mechanical properties and capability of inducing bone formation [47,48].

3. Physical characteristics requirements of porous HA for bone substitutes

Development of porous bone replacement materials are addressed to mimic the micro- and macroporous architecture of the mineral phase of living bone [2,25,39,49]. Macro- and microporous bioactive ceramics shows high true surface area which facilitates appropriate contact osteogenesis. This prevents interference of connective tissue formation which will obstruct the long-term stability of the implant. In the case of bioresorbable calcium phosphate ceramics biodegradation rate can be even increased.

Physical characteristics of porous HA which include porosity degree, pore-size distribution, pore morphology and orientation, and pore interconnectivity influence bone penetration in implants [2]. 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 [31].

Porous ceramic implants with a wide range of pore size is necessary to meet all the functions involved in osseointegration. Pores of 20–50 μm diameter may give a favorable function for physiological liquid exchange [31], while pores with a diameter 100–350 μm are suitable for cell colonization and vascularization leading to bone penetration into ceramics structure [50]. Thus, besides conventional single mode porous HA, porous ceramics with bimodal pore-size distribution [25,49] or even a porosity gradient stimulating bimodal structure of natural bone (cortical and cancellous) [39] have been developed. The porosity-graded HA samples could be realized via multiple and differentiated impregnations performed using cellulosic sponges and HA slurries prepared with powders of different crystallinity degree. Fig. 2 presents a SEM micrograph showing the morphology of the porous HA with a porosity gradient [39].

A dependence of bone ingrowth on the pore size has been proved [51]. Some reports, however, stated that the level of pore interconnectivity might be more critical than the pore size [52]. For highly biodegradable porous ceramics, interconnectivity degree is seemly more impor-

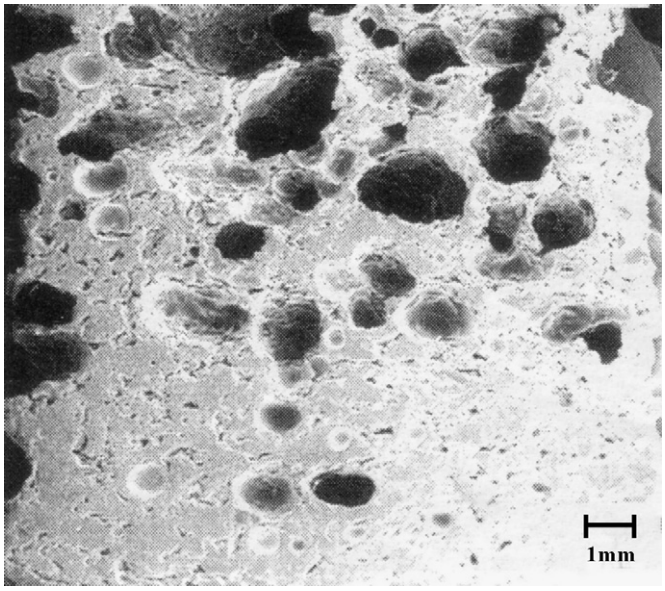

Fig. 2. A SEM micrograph showing the morphology of polymeric sponge method derived-porous hydroxyapatite with the porosity gradient [39].

tant than the pore size, but for non-biodegradable materials interconnectivity and pore size were found to be of equal significance. In vitro human osteoblast cells can pervade pore interconnections if a minimal passage diameter of 20 μm is provided, whereas the most favorable size for cell penetration is above 40 μm. In vivo cell penetration and chondroid tissue formation inside macropores become possible at an interconnection size above 20 μm, and mineralized-bone formation occurs above 50 μm [2].

Apparent density and structural texture affect the mechanical properties of porous ceramics. When pore connectivity is made to be fixed, implants with larger pore size have lower mechanical strength due to the decreased density. Richart [53] proposed that the thickness of inter-pore walls is responsible for the mechanical strength of porous HAs. Flexural strength and Young's modulus of porous ceramics are correlated with the total porosity of the ceramics via an exponential function [51]. Mechanical failure may be initiated in macropore interconnection.

Compressive strengths of porous human bones vary between 2 and 12 MPa for cancellous bone and between 100 and 230 MPa for cortical bone [5]. The as-prepared artificial porous HA have mechanical strength as low as 1.3–16 MPa [8,44,45], but bone ingrowth lead to the enhanced compressive strength of porous implants. Even for low density implants this observation is more obvious due to faster bone growth. The compressive strength of porous HA, for example, was reported to increase from 2 to 20 MPa after 3 months implantation [8]. Porous calcium phosphates with lower density shows superior implants for filling of osseous defects as a result of faster osteointegration rate resulting in in vivo mechanical performance. An optimum balance between porosity and strength must be achieved to assure that the implant can withstand the applied forces in the course of operation and in the initial stage at the implantation site.

4. Preparation methods

Great diversity of clinical reconstructive requirements for the defects of the skeleton has led to development of various methods to prepare porous ceramic implants. This is to allow design and production of porous HA with controlled porosity, good pore interconnectivity, mechanical strength, and surface properties. Some of these methods can be briefly explained as follows:

4.1. Formation of porous structure using pore-creating volatile particles which burn away during sintering

Various kinds of pore making agents including paraffin, naphthalene, carbon, starch, flour, hydrogen peroxide, or synthetic polymers (for example polyvinyl butyral) are admixed to HA powders or slurries. After molding, the organics burn away from the molding body during sintering. This approach allows direct control over the pore characteristics since their fraction, size, morphology, and distribution are controlled by type, amount and properties of the added volatile phase. Removal of pore-creating organics can either be conducted by physical processes like vaporation and sublimation or chemical reactions like combustion and pyrolysis [2]. Obtained porous ceramics usually have closed macropores with a varied pore size of 0.1–5000 μm diameter [15].

4.2. Formation of porous structure via admixture of water-soluble porogens with HA powders without sintering process

This method has been developed by Tadic et al. [54]. It consists of mixing salt crystals and water soluble polymers as pore creating agents with calcium phosphate powders followed by cold-isostatic pressing. Since porogens are easily water soluble they can be removed without any heat treatment. Pores are formed by the salt crystals and channels between these pores are formed by the polymeric fibers. The obtained porous HA showed good pore interconnectivity with the pore diameters in the range of 250–400 μm as shown in Fig. 3.

4.3. Conversion of marine coral skeleton and natural bone

The three-dimensional skeletal structure of certain marine corals mimics human cancellous bone and can be used as a template for making any porous structures. In this method, hydrothermal exchange reaction converts calcium carbonate in the coral skeleton into HA in the presence of phosphate ions. Di-ammonium hydrogen phosphate is normally used as the source of phosphate

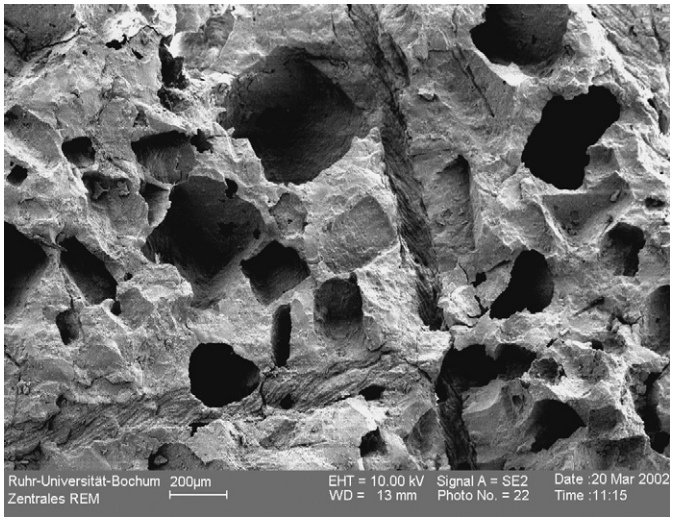

Fig. 3. A SEM picture of porous HA after the removal of NaCl and PVA as pore and pore connectivity-creating agents with water [54].

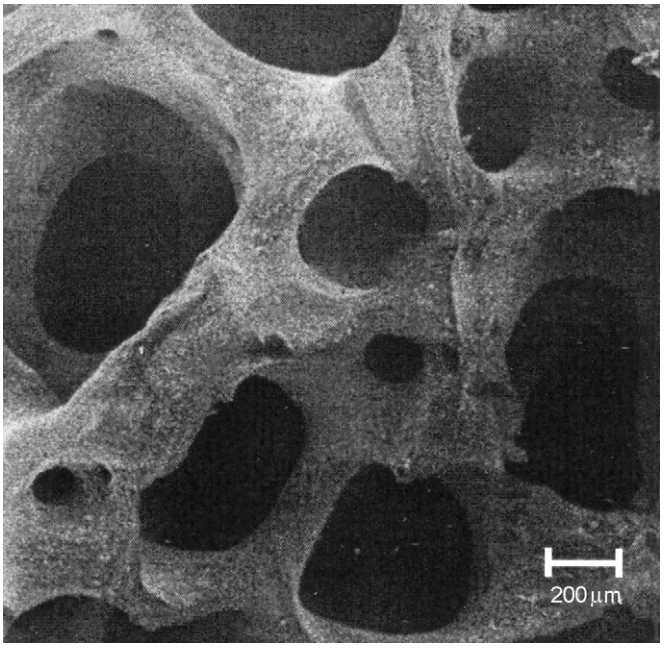

Fig. 4. A SEM micrograph of Endobon® [56].

ions, as shown in the following:

$$10CaCO_3 + 6(NH_4)_2HPO_4 + 2H_2O \rightarrow 2Ca_5\ (PO_4)\ _3OH + 6(NH_4)_2CO_3 + 4H_2CO_3 (1)$$

The resulting porous HA have macropores of around 200–500 μm diameter with good interconnectivity and 50–65% porosity, and these are enough facts for its usefulness in obtaining artificial bone substitutes, however, the limited amount of the marine coral is its obstacle. Another factor should be considered is difficulty in controlling porosity; diverse corraline species have different skeleton porosities. For example, in *Porites* corals pore diameters range from 190 to 230 μm mean in *Goniopora* corals could range from 270 to 550 μm [55]. A commercially available porous HA, Endobon® (Biomet UK Ltd), is manufactured from natural cancellous bones by removal of the organic component while preserving the trabecular structure. With pore size of 100–1500 μm and excellent interconnecting pore system (see Fig. 4), it is highly osteoconductive [56].

4.4. Ceramic foaming technique

This technique involves foaming of ceramic suspensions or swelling of ceramic green bodies via gas evaporating chemical reactions from organic and inorganic sources. Some foaming agents tested were hydrogen peroxide, carbonate salt, and baking powder. They were added to the HA slurries while stirring to let it foam, and then subjected to polymerization followed by sintering [57]. Porous HA obtained has pore sizes of 30–600 μm [15]. Tamai et al developed a modified version of ceramics foaming method they called "foam–gel" technique [58]. This technique involves a crosslinking polymerization step that gelatinizes the foam-like HA slurry in a rapid manner, thus promoting the formation of an interconnected porous structure. The wall surface of the device obtained is very smooth and HA particles are aligned closely to one another and bound tightly. With average pore size 150 μm and average interpore connections 40 μm, this device is favorable for interpore cell migration or tissue ingrowth. Gel casting of foams can be applied to produce ceramic scaffolds with high mechanical strength. The disadvantage of this technique is that it typically results in a structure of poorly interconnected pores and non-uniform pore size distribution.

4.5. Polymeric sponge method

Another approach for fabricating porous ceramics is via the replication of a polymeric sponge substrate to produce reticulated open-celled porous ceramics. Porous ceramics obtained from reticulated polymer substrates have a number of distinct properties such as controllable pore size and complex ceramic shapes suitable for different applications [57,59]. The polymeric sponge method, as this method named, is performed by impregnating porous polymeric substrates (sponges) with HA slurry. Porous HA prepared via the polymeric sponge method have shown well- interconnected pores but poor mechanical strength for load bearing applications. It was shown that the polymeric sponge method results in a proper pore size distribution, as osteoconduction requires. This is characterized by the existence of micro/meso/macropores with adequate degree of interconnection [39].

This method allows control on rheological properties of the ceramics powder suspension by varying the characteristics of starting powders. It has been shown that by

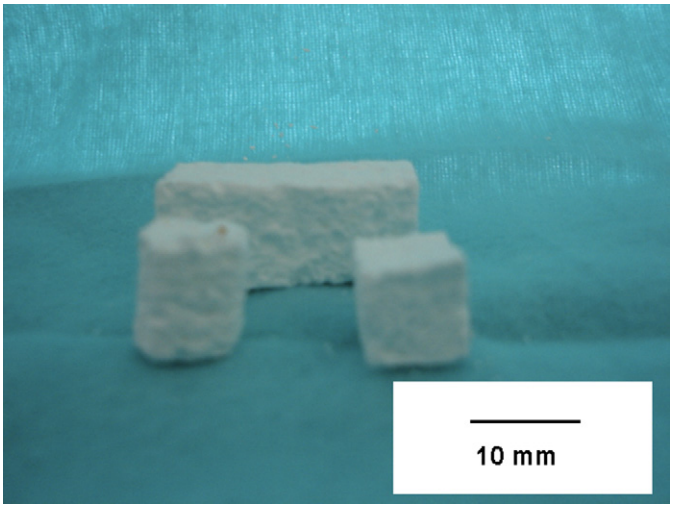

Fig. 5. Porous hydroxyapatite bodies of various shapes produced via polymeric sponge method using sol–gel derived HA powders.

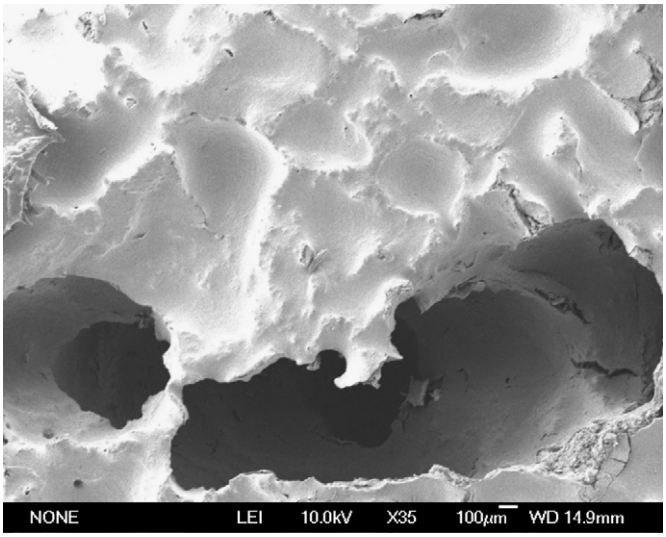

Fig. 6. SEM images showing the morphology of macroporosity of porous hydroxyapatite with 400–600 μm pore diameters and excellent pore interconnectivity [45].

varying the characteristics of starting powders, that powders of 20% and 80% crystallinity degree, rheological properties of the ceramics powder suspension can be controlled [60]. This allowed the possibility of preparing HA ceramics with crystallinity and porosity gradients mimicking the physicochemical features of cortical and spongy bones. Use of well controlled HA suspension enable to make HA ceramics with crystallinity and porosity gradients mimicking the physicochemical features of cortical and spongy bones as well as to fabricate porous HA grafts for controlled drug delivery [39].

We have reported the preparation of HA porous bodies (see Fig. 5) via polymeric sponge method; the samples which were prepared using sol–gel method—derived HA powders and commercial HA powders showed a considerable compressive strength ranging from 1.3 to 10.5 MPa [44,45] for the increased apparent density from 1.27 to 2.01 g/cm^3. This is higher than the 0.55–5 MPa compressive strength obtained for the apparent densities of 0.0397–0.783 g/cm^3, as reported by Ramay et al. [61]. The porous HA showed macropores of 400–600 μm diameters with good pore interconnecting channels, as Fig. 6 shows. It was also shown that homogeneity of slurry and heating rate affected porosity and density of porous bodies, in turn influencing the compressive strength [45]. More homogeneous slurries and faster heating rate gave porous bodies with the increased compressive strength due to higher apparent density and crystallinity [44,45]. Fig. 7 shows SEM images showing the difference in microporosity of two porous HA samples obtained at different stirring times. The sample of longer stirring time shows higher density with larger grains. Our porous HA samples have been tested for their biomedical performance as microcarriers for animal cell loading. Fig. 8 shows an initial stage of attachment of Vero (African Green Monkey kidney) cell on the surface of the porous HA. The Vero cell lines can be regarded as a representative for attached mammalian cell lines and have been utilized both in laboratorial and in industrial scales for vaccine production, virus transfections, and screening of Vero toxins. Possible attachment and

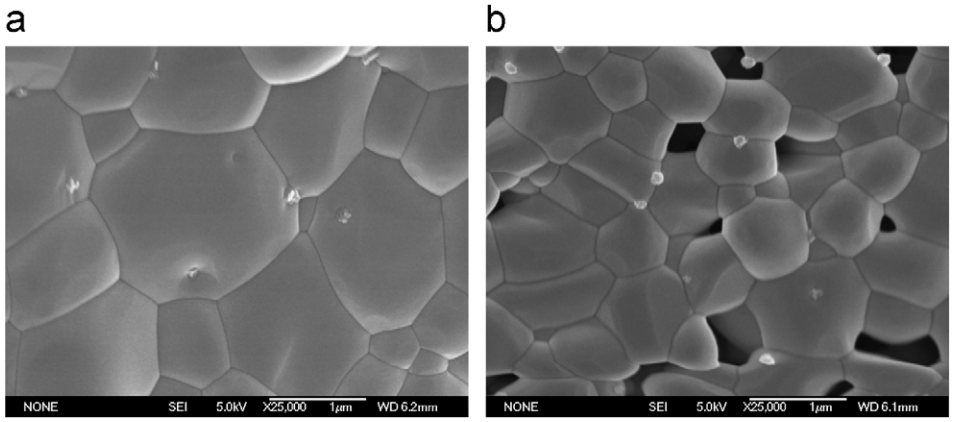

Fig. 7. SEM images showing the difference in microporosity of two porous hydroxyapatite samples obtained at different stirring times. The sample of longer stirring time (a) shows higher density with larger grains than the counterpart (b) [45].

subsequent growth of the Vero cell lines on the porous HA microcarrier will be of clear indicative for its applicability to anchorage-dependent mammalian cell culture. After four days Vero cells have covered the whole surface of porous HA microcarrier as shown in Fig. 9 [16].

Some of the above-mentioned methods have been combined to produce porous HA with improved properties. Ramay and Zhang prepared HA porous scaffolds by combining the gel-casting technique with polymer sponge method. This novel technique resulted in porous HA with improved mechanical strength and controllable pore structure. The scaffolds prepared were found to have a homogeneous microstructure, and an open, uniform and interconnected porous structure with a pore size of 200–400 μm [60]. Sepulveda et al. [62,63] combined the foaming and polymerization process, and this was followed by sintering at 1250/1350 °C.

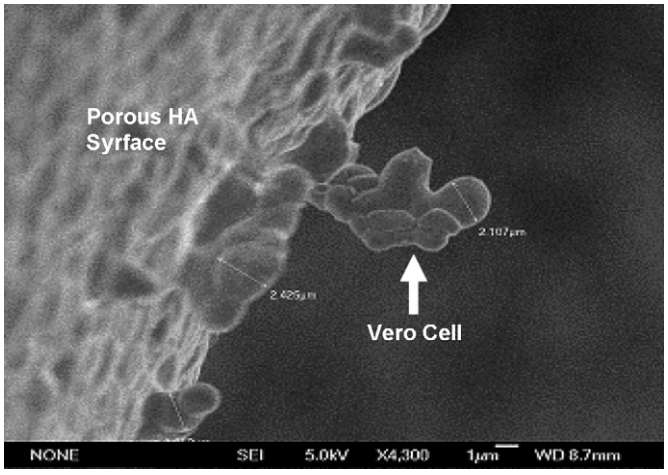

Fig. 8. A SEM image showing an initial stage of attachment of Vero (African Green Monkey kidney) cell on the surface of the porous HA [16].

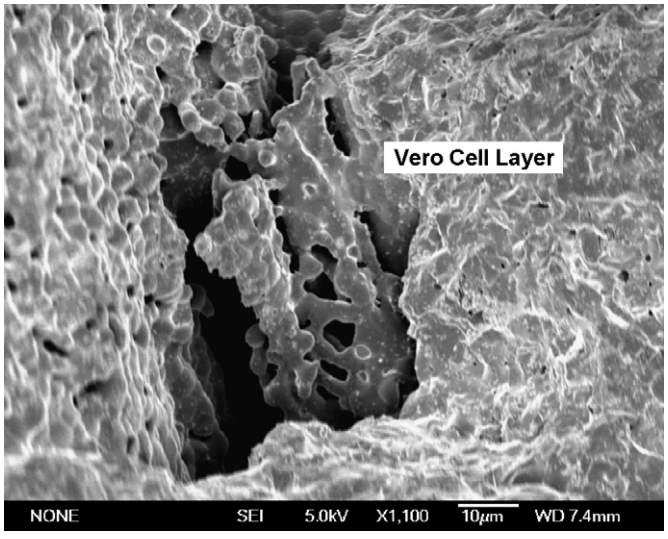

Fig. 9. A SEM image showing after a massive formation of cell layer after fourth day: Vero cells have covered the whole surface of porous HA microcarrier [16].

Porous HA can also be produced by a number of miscellaneous methods including starch consolidation [64], microwave processing [65], cold isostatic pressing [66] and electrophoretic deposition technique [67]. The differences in the methods used to produce porous HA can directly affect the pore characteristics.

The starch consolidation method is based on the swelling ability of starch when it is heated to 80 °C in the presence of water. This method can result in flexural strengths of as low as 2 MPa for pore volume fractions of 70% and as high as 15 MPa for pore volume fractions of 45%. The microwave processing technique has produced porous HA with a porosity of up to 73%. The porosity of the ceramic can be controlled by varying the morphology of the starting materials, adjusting green density, as well as altering the sintering time and temperature. Cold isostatic pressing and sintering of HA powder produces spherical, interconnected pores of 100–200 μm in size. Eletrophoretic deposition (EPD) of submicron HA powders produces uniform and crack-free bulk porous HA scaffolds with good mechanical strength and interconnected porosity with a wide range of pore sizes.

5. Conclusions

The applications of porous HA in the biomedical field are enormous; they have been used for hard tissue scaffolds, cell loading, and drug releasing agents. In bone tissue engineering, porous HA are used as filling material for bone defects and augmentation, artificial bone graft material, prosthesis revision surgery. Its high surface area leads to excellent osteoconductivity and resorbability favorable for fast bone ingrowth. A number of main methods which have been used to prepare porous HA are admixture of pore-creating organics which burn away during sintering, ceramic foaming technique, conversion of marine coral skeleton and natural bone, and polymeric sponge method. Variation in preparation methods allowed design and production of porous HA with controlled porosity, good pore interconnectivity, mechanical strength, and surface properties as demanded by clinical reconstructive requirements.

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