Type of contribution:
Editorial
Research Paper
Case Study
▶ Review Paper
Scientific Data
Report of Tech. Application

mesi
e-issn. 2798-5245

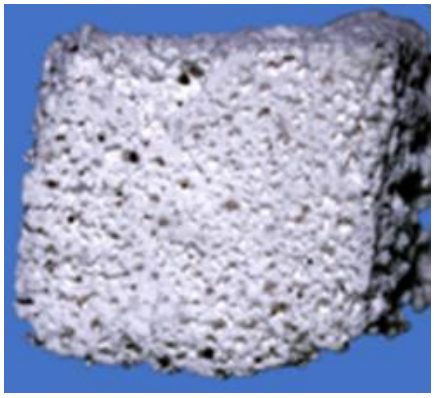
Mechanical Engineering for Society and Industry
Vol. 3, No. 3 (2023) pp 136-151
Special Issue on Technology Update 2023
https://doi.org/10.31603/mesi.10397

Effect of sintering temperature and polyvinyl alcohol composition as binder on the formation of porous hydroxyapatite as bone graft using sponge replication method: A review

Baharudin Priwintoko[1,3], Rifky Ismail[1,3], Deni Fajar Fitriyana[2,3], Yusuf Subagyo[1,3], Anthasius Priharyoto Bayuseno[1]

[1] Department of Mechanical Engineering, Faculty of Engineering, Diponegoro University, Semarang 50275, **Indonesia**
[2] Department of Mechanical Engineering, Universitas Negeri Semarang, Kampus Sekaran, Gunungpati, Semarang 50229, **Indonesia**
[2] Center for Biomechanics, Biomaterial, Biomechatronics, and Biosignal Processing (CBIOM3S), Diponegoro University, Semarang 50275, **Indonesia**
✉ baharudinpriwintoko@students.undip.ac.id

This article contributes to:



Highlights:

- This review highlights the increasing need for Porous Hydroxyapatite (HA) as a bone regeneration material using an innovative approach.
- Waste materials such as egg shells, bones, limestone and sea shells can be used to make Hydroxyapatite (HA).
- Sintering temperature and the use of polyvinyl alcohol (PVA) influence the creation of porous HA.

Abstract

Hydroxyapatite (HA) is one of the inorganic components that has a role as a bone regeneration material. The potential for utilizing waste is one of the opportunities in HA commodities. Several types of waste materials that can be used as raw materials for HA include eggshells, beef bones, fish bones, limestone, and marine biota shells. Nowadays, the use of HA is not only limited to regeneration materials but also as a bone tissue scaffold. Porous HA is a form of HA that is in great demand today because it can be a good scaffold and regeneration material. One method that can be used for the fabrication of porous HA is the sponge replicated method. In its fabrication, the sponge replicated method is influenced by sintering temperature and binder composition. Polyvinyl alcohol (PVA) is one of the widely used binders because it can be evaporated without leaving traces and is biocompatible. This paper will examine the effect of sintering temperature and composition of PVA as the binder in pore HA fabrication. In particular, this paper compares the fabrication process with the characteristics of the resulting porous HA against commercial products and ISO 13379:2015 standards. According to the preliminary study, pore HA that conforms to the standard will have a good impact on the healing process of bone defects. The novelty of this research is to explore in depth related to the fabrication of HA pores using the sponge replicated method with sintering temperature parameters and the composition of PVA as a binder so that it is expected to be a literature for future researchers.

Keywords: Pore hydroxyapatite, Sintering temperature, Polyvinyl alcohol, sponge replicated method

Article info
Submitted: 2023-10-19
Revised: 2023-11-27
Accepted: 2023-11-28

Publisher
Universitas Muhammadiyah Magelang

1. Introduction

Hydroxyapatite (HA) is a naturally occurring mineral that is an important component of bone and teeth [1]. HA is a ceramic material that forms the mineral phase of bone and is mainly

composed of calcium and phosphate in a ratio of 1.67 each [2]. Hydroxyapatite has the chemical formula $Ca_5(PO_4)_3$ (OH), but it is usually written Ca_{10} $(PO_4)_6$ $(OH)_2$ to indicate that the crystal unit cell consists of two entities. Pure HA contains 39.68% by weight calcium and 18% by weight phosphorus. Hydroxyapatite biological implants are influenced by their raw materials and synthesis process which makes the product properties vary [3].

Porous HA is one of the most widely developed products to date. Porous HA has a high porosity, making it useful in various bone tissue engineering [4]. Porous HA is widely used as a filler material for bone defects and augmentation, artificial bone graft material, revision prosthesis, bone graft substitute in metaphyseal and diaphyseal defects, and cranial reconstruction [5]. Porous HA can be used to facilitate bone growth until the entire growth process occurs and antibodies, bone growth factors, and other biological molecules can be delivered to the defect site [6]. Porous HA can be fabricated by several methods such as sintering, foaming, and freeze drying [7]. The properties of HA pores vary, following the manufacturing method. Many factors affect the characteristics of HA pores, generally, the pore size and temperature treatment in fabrication will affect the mechanical strength of HA pores. HA pores with a neat structure, and hole morphology with nanopores can facilitate rapid bone growth and repair [8]. The porosity level of good porous HA is greatly influenced by its constituent materials and fabrication method. Generally, the higher the porosity value will reduce its mechanical strength, on the contrary, the lower it will increase its mechanical strength. However, pore HA is not only about mechanical strength but also how to bridge nutrients for good tissue repair [9].

Porous HA has a wide range of applications in biomedical engineering, including bone tissue regeneration, cell proliferation, and drug delivery. Firstly, porous HA can be used in defect healing and bone augmentation. Porous HA can be used as a filling material for bone defects and augmentation, as well as a substitute for bone grafts in metaphyseal and diaphyseal defects and cranial reconstruction [10]. Porous HA is also widely used as an artificial bone graft material to promote growth and cast repair. Prosthesis cases also require porous HA for prosthesis surgery to promote bone growth and maintain prosthesis stability. Porous HA is also widely used in dentistry such as dental implants and toothpaste to promote the regeneration and repair of tooth enamel [3]. Drug delivery systems also require the role of HA pores to deliver various types of drugs, including antibiotics and anticancer drugs [11].

Porous structures of HA can be generated using various methods, including solution casting, freeze drying, Electrospinning, In situ mineralization of HA in polymers, and Electrodeposition. The process of solvent casting for biocomposites entails dissolving the polymer in an organic solvent, combining it with grain ceramics, and pouring the solution into a pre-defined 3-D mold, followed by allowing the solvent to evaporate. This fabrication technique stands out for its simplicity, enabling easy preparation and operation without the necessity for specialized equipment. Numerous tissue engineering (TE) approaches, both in vivo and in vitro, spanning from cells to films/scaffolds, offer the potential for the restoration of damaged articular cartilage. Polymer/bioceramic composite scaffolds have gained increasing attention in the realm of bone and cartilage regeneration due to their mechanical stability and biocompatibility. Noteworthy is the work of Aboudzadeh et al., who utilized a combination of freeze-drying and solvent casting to create poly(lactic-co-glycolic acid) (PLGA)/NHA composite scaffolds. These scaffolds exhibited sizes ranging from 50 to 200 µm, a well-interconnected porous network, and an average porosity of 70%. In their study, N-methyl pyrrolidone served as an approved solvent, particularly suitable for parenteral pharmaceutical products, including implants with acceptable toxicology. The investigation of biodegradable poly (D, L-lactide-co-glycolide) scaffolds with varying percentages of nHA (25, 35, and 45 wt.%) involved a comprehensive assessment of porosity, pore distribution, bioactivity, and biocompatibility. A notable finding was the enhanced bioactivity observed with an increase in the nHA content of the nanocomposite scaffold [12].

The thermally induced phase separation (TIPS), also known as the freeze-drying method, originated in the early 1980s and has garnered significant attention for producing nanofibers comparable to natural extracellular matrix (ECM) collagen. This method is valued for its capability to design structures with specific pore size and porosity, exhibiting lower variability. The TIPS process relies on the principle that solvent effectiveness diminishes with decreasing temperature. In this process, a homogeneous solution at high temperature undergoes phase separation as it cools, becoming thermodynamically unstable and separating into a multi-phase system to minimize free energy. This results in the formation of a polymer-rich phase (with a higher polymer concentration) and a polymer-lean phase (with a lower polymer concentration). After solvent removal, the polymer-rich phase solidifies, forming a microstructure. During TIPS, the solvent

initially solidifies, pushing the polymer-ceramic mixture into interstitial spaces. Subsequently, the frozen mixture undergoes lyophilization using a freeze-dryer, causing the ice solvent to evaporate. The ultimate membrane structure depends on the competition between liquid-liquid phase separation and the solidification process. This competition can be controlled by understanding the relationship between liquid-liquid phase separation and other phase transitions. Generally, micro and macro structures are manipulated by adjusting parameters such as polymer material, polymer concentration, cooling temperature, and solvent. Foams produced through this process typically exhibit oriented tubular pores with diameters exceeding several hundred microns (>100 µm) and isotropic pore networks featuring smaller pore sizes (10 µm) that connect the larger tubular pores [13].

Electrospinning represents a straightforward and adaptable technique for producing polymer-based nanofibers that exhibit notable porosity, holding the potential to bring about a transformative impact on the field of structural materials. Its versatility stems from the ability to spin a wide array of materials, encompassing both inorganic and organic substances. Electrospun nanofibers possess distinctive and intriguing qualities, allowing for their utilization in the hierarchical assembly of nanofibers within well-defined functional nanostructures. The electrospinning method has found extensive use in fabricating ceramic nanofibers, capable of achieving diameters in the sub-micron or nanometer range, surpassing the capabilities of alternative textile technologies like spin melting. Furthermore, electrospinning offers advantages over other fabrication methods, showcasing simplicity in generating diverse fiber patterns with enhanced porosity and presenting a distinctive and cost-effective approach for synthesizing metal oxide nanowires. Notably, electrospun nanofibers, characterized by their smaller diameter, large surface area to volume ratio, and unique attributes, find applications in various fields, such as the filtration of submicron or nanomaterials and the deposition of ultra-thin films composed of inorganic, organic, and biological materials. The pronounced porous structure of these nanofibers holds particular significance, creating favorable conditions for potential applications in drug delivery, dispersion distribution, and the delivery of nanomaterials [14].

In situ mineralization represents a biomimetic phenomenon in which mineralization occurs near the polymer, similar to the natural mineralization of hydroxyapatite (HA) along with collagen and other proteins in bone. This concept has received significant attention for the development of ceramic/polymer composite materials since its introduction by Kokubo et al. in 1990 [15]. More recently, it has emerged as a distinct research domain in biomimetic mineralization (biomineralization), a multifaceted process involving the controlled nucleation and growth of HA carbonates (bone-like minerals) onto polymer scaffolds in simulated body fluids (SBF). Once carbonated HA cores form on the surface, they grow by assimilating calcium and phosphate ions from the surrounding solution. In general, the deposition process shows similarities to other bioactive surfaces: calcium ions are attracted due to the negative surface potential, which causes the deposition of calcium-rich amorphous calcium phosphate until the surface potential is reversed. Next, phosphate-rich amorphous calcium phosphate is deposited, and this amorphous inorganic layer eventually crystallizes into apatite. Given that this process somewhat mimics natural biological bone mineral growth, which occurs in biocompatible aqueous solutions under mild reaction conditions, the resulting carbonated HA shows similarities to bone apatite, including low crystallinity and nanoscale size. These characteristics are essential for effective resorption and remodeling of the bone structure [16]. Based on several methods that have been carried out in various previous studies, it is necessary to examine the advantages and disadvantages of existing methods. **Table 1** provides information regarding the advantages and disadvantages of this method.

Sponge replicated is a method that uses sponge polymer as a 3D mold of HA pores. A method that can be combined with sponge replicated is solvent casting. The method can use the sponge as a 3D mold. Furthermore, in the fabrication process of sponge spliced with solvent casting, the removal of the sponge polymer as a 3D mold is done by sintering [17]. According to Wang et al, sponge replicated methods can create highly porous hydroxyapatite structures with a uniform pore size distribution, making them highly reproducible. Furthermore, sponge replicated methods allow precise control over the pore size and porosity of hydroxyapatite scaffolds. The use of the sponge replicated method can also be cost-effective compared to other methods for preparing porous hydroxyapatite scaffolds. Sponge replicated methods can be used to prepare hydroxyapatite scaffolds for various biomedical applications, including bone tissue engineering and drug delivery systems [18]. Sponge replicated methods have the ability of precise structure replication, high porosity control, flexibility in porous structure design, controllable scale, and high biocompatibility [19].

Table 1. Comparative analysis of fabrication methods for porous materials incorporating hydroxyapatite

No	Methods	Advantage	Disadvantage	Refs.
1.	Solution casting/solvent casting	Ability to produce well-defined pore structures, pore size control, and ability to produce porous materials with a variety of pore shapes and sizes	Difficulty in controlling the distribution of pores, the potential for cracks to occur, and the difficulty of controlling the mechanical strength of the resulting material	[20]
2.	Freeze drying	Involves maintenance of controlled porous structure, defense of HA chemical properties, and gentle water removal	Involves long processing times, high production costs, risk of air contamination, and limitations on the type of suitable materials	[21]
3.	Electrospinning	Involves nanometer-scale fiber formation, control of porosity and structure, diversified applications, and the forming capabilities of composite materials	Difficulties in controlling fiber dimensions, process complexity, limitations in mass production, challenges in controlling fiber orientation, and critical solvent selection	[22]
4.	In situ mineralization of HA in polymers	Natural integration of materials, control of porosity and distribution of HA, improvement of mechanical properties, and the ability to form multiphase structures	Complicated control, difficulty in controlling the HA particle size distribution, slow processing, and influence on the polymer material manufacturing process	[23]
5.	Electrodeposition	Layer thickness control, pure and adherent growth, microstructure control, and application on various substrates	Non-uniformity of grain distribution, process complexity and parameter optimization, limitations in substrate shape, and the influence of electrolyte pollution	[24]

In addition, the composition has an important role in the formation of pore HA. The use of binders as adhesives in pore-forming HA compositions can improve various properties required as porous scaffolds. Various binders have been widely used in the past two decades, such as alginate, palm stearin, carboxymethyl cellulose, poly(acrylic acid), sago starch, and polyvinyl alcohol (PVA) [25]–[30]. The use of PVA as a binary is one of the most widely studied materials. That is because the biopolymer can evaporate at a certain temperature, leaving a clean material free from binder contamination [31]. Apart from that, PVA also has water-soluble properties, is biodegradable, has good thermal stability, good film-forming ability, and high biocompatibility. These properties make PVA effective in facilitating binder removal after HA material formation is complete, leaving no residue and with a good level of biocompatibility [32].

Therefore, this study aims to review new findings on the fabrication of pore HA using sponge replicated methods and PVA composition as binder. This review also examines the criteria of HA pores that must be met according to the ISO 13379: 2015 standard that must be met. Furthermore, this study is expected to facilitate authors, researchers, and manufacturers in the development of HA pore fabrication. This is very important because of the high need for porous scaffolds to treat bone defects in the health world [33]. Therefore, understanding the selection and use of appropriate fabrication methods can help significantly in meeting the supply needs of porous scaffolds.

The technique of sponge replication can be integrated with solvent casting. In this approach, the scaffold acts as a framework supporting the growth of tissues, fostering the restoration, proliferation, and regeneration of native tissues. Consequently, composite materials derived from engineered tissues predominantly consist of cells and biomaterials. For applications in bone tissue engineering, the materials used as scaffolds must exhibit biocompatibility, osteoconductivity, and possess macroporous structures [34]–[37]. High porosity and pore connectivity are essential to ensure sufficient nutrient diffusion through the scaffold [38]. Hydroxyapatite, the primary constituent of the mineral phase found in human bone, has been extensively employed in the field of tissue engineering. This is attributed to its outstanding biological characteristics, which encompass biocompatibility, osteoconduction, and osteoinduction [39]. A technique for creating porous ceramics involves using a polymer sponge replica. This process includes saturating a polymer sponge with a mixture containing ceramic particles and a compatible binder. The

saturated sponge is compressed to eliminate excess mixture, followed by drying and heating to eliminate the sponge components. Subsequently, the resultant structure is fired at elevated temperatures [40]. The ceramic foam generated through this approach exhibits a clearly defined open-cell arrangement, and its porosity is uniform when the sponge precursor is chosen to possess a consistent cell structure [41].

Sponge replicated methods have some disadvantages and advantages. The following are the disadvantages and advantages of the sponge replicated method.

The disadvantages [42]:

- Limited pore size, may be limited to the achievable pore size, which may impact the effectiveness of the scaffold for certain applications.
- Limited scalability, difficult for large-scale production, which may limit its use in industrial applications.
- Contamination, prone to contamination, which may affect the quality and effectiveness of hydroxyapatite scaffolds.

The advantages [18][43]:

- Reproducibility, can be used to prepare highly porous structures with uniform pore size distribution, making them easy to produce.
- Control, allowing precise control over the pore size and porosity of the hydroxyapatite scaffold.
- Selectivity, can be selective in the type of materials used to create the scaffold, allowing the incorporation of other materials to improve the properties of the scaffold.

Sponge replicated methods are generally considered to be a cost-effective method for preparing ceramic foams, as they use relatively inexpensive polyurethane foam molds. In addition, the ease of use and reproducibility of the PU replica technique may further contribute to its cost-effectiveness compared to other methods. It should be noted that the cost of making ceramic foam using any method may vary depending on several factors, including the materials used, the complexity of the process, and the desired application of the foam. Therefore, the choice of ceramic foam manufacturing method will depend on the specific needs and requirements of the application, as well as the available resources and budget.

The sponge replicated method is part of solvent casting, where the solvent casting method has a sintering indicator. Some factors that affect the results of sintering include heat rate, preheat temperature, main heat temperature, holding time, and other factors from the type of furnace used [44]. Heat rate plays a major role in the sintering process, especially in many new sintering techniques. High heat rates can lead to rapid sintering and densification, but can also cause thermal shock and cracks in the material [45]. Preheat can affect the temperature gradient between sintered and unsintered areas, which can affect the quality of the final product. Low preheat can cause large temperature gradients, curling, warping, and fuzziness at the edges of the material [46]. Main heat is the temperature at which the sintering process is carried out and can affect the microstructure and properties of the final product. The main heat needs to be carefully controlled to ensure the material is sintered properly without causing thermal shock or other defects [47]. Meanwhile, holding time can affect densification, microstructure, open porosity, energy consumption, and the sintering time required to achieve the desired final product properties [48]. The selection of sintering conditions will depend on the specific needs and requirements of the application, as well as the available resources and budget.

Furthermore, the fabrication of pore HA by sponge replicated methods is also influenced by the binder. Binder has an important role in forming HA pore bonds from powder fabrication. Binders can provide bonds between powder particles so that a green body is formed [49], [50]. Binders should meet criteria such as being soluble (in cold conditions), so that the solvent used is minimal (specifically wet granulation), not hygroscopic, the smallest possible viscosity, and easy to wet the mixture of ingredients. The function of binders in tablet formulations is to provide strength and reduce the friability of granules and tablets [51]–[53]. Some factors that affect the effectiveness of binders are related to the active substance and other additives in the formulation, and some are related to the binder and solvent [54]. Some classifications that are often used as binders are natural polymers, synthetic polymers, and sugars. Synthesized polymers have also been used as binders in the manufacture of hydroxyapatite scaffolds, but the biocompatibility of these binders must be carefully considered [55]. Natural polymers such as chitosan and silk have been used as binders in the preparation of pore HA. Sugars such as guar gum have also been used as binders in the preparation of pore HA [56].

2. Previous Research with Sponge Replicated Methods

Ismail et al. [57] conducted a research investigation in 2021 to examine the influence of hydrothermal holding time on the characterization of hydroxyapatite derived from green mussel shells. Hydroxyapatite nanoparticles were successfully synthesized through the hydrothermal method using green mussel shells as a source of calcium carbonate. The process involved calcination, hydration, and carbonation of the green mussel shells to produce Precipitated Calcium Carbonate (PCC). The obtained clamshell PCC was then combined with $(NH)_4$ $2HPO_4$, maintaining a Ca/P mole ratio of 1.67. The hydrothermal reaction was conducted at 160℃, with varying holding times (14, 16, and 18 hours). Characterization of hydroxyapatite formation was performed using XRD and SEM-EDX. XRD analysis indicated the presence of hydroxyapatite crystals in the product. SEM images revealed the uniformity of hydroxyapatite crystals. The optimal results were achieved at a hydrothermal holding time of 18 hours, demonstrating the highest purity of the produced hydroxyapatite without any impurity phases.

Afriani et al. [58] conducted a study wherein hydroxyapatite (HA) pores were formed from clamshell waste using the sponge replication method. The researchers synthesized porous scaffolds for bone therapy by incorporating waste clam shells into the process through the polyurethane sponge replication method. This synthesis involved adding polyvinyl alcohol (PVA) to hydroxyapatite slurry, followed by heating at 900 °C to decompose polyurethane and PVA. This decomposition left behind macropores in the scaffold. The optimal slurry ratio for producing these porous scaffolds was determined to be 80:20 hydroxyapatite: PVA. The confirmation of polymer decomposition was achieved through thermogravimetric analysis, X-ray diffraction, and FTIR spectrophotometer. The porous scaffolds developed in this study were confirmed to meet the requirements for bone therapy applications.

Ferracini et al. [59] conducted a study encompassing mechanical, clinical, and histological examinations of hydroxyapatite (HA) pores. The focus was on assessing the efficacy of HA porous scaffolds created through the sponge replica method in addressing maxillary bone defects in human subjects. The research involved 13 patients with a total of 16 defects treated using cylindrical HA Blocks. Evaluation of the experimental sites was carried out through 3D Cone Beam Computer Tomography scans (CBCT), and histological analysis was conducted three months post-healing. The outcomes demonstrated a notable level of HA biological osteoconduction, accompanied by microscopic evidence indicating the emergence of new bone at the core of the graft block. The sampled tissues exhibited a composition of 39 ± 1% new bone, 42 ± 3% marrow space, 17 ± 3% residual HA Block, and 4.02 ± 2% osteoid tissue. Specifically, new bone formation within the block was determined to be 8 ± 3%. These research findings provide substantial support for the effectiveness of HA porous scaffolds produced through sponge replicas in treating maxillary bone defects in human patients.

The exploration of in vivo regeneration studies concerning mineralized bone tissue in biomimetic sponges with anisotropic characteristics has been conducted. The investigation revealed that employing alginate sponges featuring anisotropic microporous domains (MAS) holds promise for applications in bone tissue engineering. The formation of the sponge occurs through ionic crosslinking in the presence of various fractions of HA. This research indicates that the inclusion of HA imparts distinctive physical and biological attributes to the sponge, enabling it to support the bio-mimetic regeneration of newly formed bone. The findings suggest that MAS stands out as a potential scaffold for promoting hard tissue regeneration in various anatomical compartments [60].

Additionally, the examination of porous scaffolds modified with gum ghatti for applications in bone tissue engineering has been explored. This investigation delves into the utilization of gum ghatti (GG), a plant extract, as a natural binding agent for the modification of porous hydroxyapatite (HA) scaffolds intended for bone tissue engineering applications. The scaffolds were crafted using a template-assisted polymer sponge replication technique and subjected to comprehensive characterization, including assessments of their structural, functional, morphological, and mechanical attributes. The scaffolds' degradation stability and bioactivity were evaluated through exposure to simulated body fluid (SBF). Preliminary studies involving cytotoxicity, biocompatibility, and cell proliferation assays were conducted using Madin-Darby Canine Kidney (MDCK) cell lines. The findings suggest that the resulting porous HA scaffold exhibits favorable properties for bone tissue engineering applications. It demonstrates the capacity to form a mechanically stable spongy bone architecture and features highly interconnected micro and macroporous characteristics with a pore size ranging from 200 to 500 micrometers. The unique

formulation developed in this study holds promise as a suitable porous scaffold material for applications in bone tissue engineering [61].

The investigation focused on the fabrication of hydroxyapatite (HA) scaffolds utilizing gambas sponge (Luffa cylindrica) as an innovative template. The research delved into the impact of HA solid loading on various scaffold characteristics, including shrinkage, porosity, and compressive strength. Findings indicated that elevated HA loading in the slurry resulted in diminished shrinkage and porosity, coupled with heightened compressive strength. The resulting HA scaffolds exhibited a porous structure featuring pore sizes ranging from 50 to 400 µm, rendering them suitable for use as cancellous bone implants. The study's conclusion emphasized the substantial influence of material wall strength and surface defects on the compressive strength of HA scaffolds, with the former being contingent on the solid loading of ceramics. This research contributes valuable insights into the fabrication of HA scaffolds using innovative templates, holding potential applications in the realm of tissue engineering [19].

An innovative adaptation of the polymer sponge technique for constructing highly porous composite bone scaffolds, characterized by a substantial aspect ratio suitable for addressing critical-sized bone defects, was explored. This modification involved employing the polymer sponge method to create composite bone scaffolds comprised of hydroxyapatite (HA) and alumina. Comparative analysis revealed that the adjusted approach yielded scaffolds exhibiting superior physical and mechanical attributes in contrast to the conventional foam replica technique. The resultant scaffold, developed through the proposed method, demonstrated total and open porosity values of 75.22 ± 2.97% and 68.19 ± 1.61%, respectively, along with a compressive strength of 4.25 ± 0.73 MPa. These characteristics render the scaffold well-suited for applications in bone tissue engineering. The innovative methodology presented in this study enables the production of samples with a substantial aspect ratio, making them apt for the repair of critical-sized bone defects [62].

Research has been conducted on hydroxyapatite scaffolds with ion substitution for bone regeneration, employing the sponge replication technique. This investigation delves into the synthesis and characterization of biodegradable scaffolds designed for bone regeneration, incorporating nano-hydroxyapatite particles with zinc and fluorine ion substitution. The scaffolds, with a porosity ranging from 65-75%, were crafted using the sponge replication technique. Noteworthy features of the scaffolds include both macroporosity and microporosity, along with apatite formation ability. They exhibit key attributes of intelligent scaffolds such as biomimicry, osteoinductive/osteopromotive properties, bioactivity, and osteoconductivity. The resulting scaffolds find applications in diverse areas such as tissue engineering, filtration, and catalyst support. The utilization of ion-substituted hydroxyapatite also introduces novel possibilities in the realm of bone regeneration, capitalizing on its adaptable levels of bioactivity and biodegradation [63].

Research has been carried out on scaffolds made from biphasic calcium phosphate derived from powders synthesized through hydrothermal methods. This investigation focuses on the manufacturing process of biphasic calcium phosphate (BCP) scaffolds utilizing powders synthesized hydrothermally. These scaffolds, created via robocasting, exhibit varied pore dimensions. Results indicate favorable biomineralization capabilities in the obtained scaffolds, showcasing promising attributes for applications in bone regeneration and tissue engineering. The compressive strength of the sintered scaffolds falls within the reported mechanical properties range of cancellous bone, a characteristic intricately linked to the particle size distribution [26].

Investigations have been carried out to explore the incorporation of hydroxyapatite into crosslinked gelatin/chitosan/poly(vinyl alcohol) hybrids, utilizing reinforced composite sponges and assessing their water absorption capabilities. This research delves into the creation of robust composite sponges using cross-linked gelatin, chitosan, poly(vinyl alcohol), and hydroxyapatite particles. These sponges exhibit favorable mechanical properties and water absorption capacity, making them well-suited for applications in biomedical and tissue engineering. The introduction of hydroxyapatite particles enhances the mechanical characteristics of the sponge, and its porosity and pore size facilitate cell migration. Various analyses have confirmed the presence of effective bonding between the particles and the polymer matrix. Overall, crosslinked GCPH sponges emerge as promising candidates for use in biomedical and tissue engineering applications [64].

The process of creating and examining bioceramic scaffolds through the polymer sponge replication technique has been executed. This research outlines the synthesis of hydroxyapatite powder (HAP) through the wet precipitation method and the subsequent generation of scaffolds utilizing the polymer replication technique. An analysis of the scaffolds was conducted to assess their microstructure, chemical bonding, and bioactivity. The findings revealed that the scaffolds

exhibited porous structures characterized by openness and interconnectivity, yielding a porosity range of 72-75%. Additionally, the scaffolds demonstrated notable bioactivity, as evidenced by the development of an apatite layer on their surface following immersion in a simulated body fluid medium [65].

The study details the development and characterization of a porous hydroxyapatite scaffold using the polymeric sponge method. It focuses on creating porous hydroxyapatite (HA) scaffolds through this method for potential use in artificial bone applications. Porous HA is valued for its excellent osteoconductivity and resorbability, which contribute to accelerated bone growth. The process involves saturating a porous polyurethane foam structure with a slurry containing HA powder, water, and additives, and this approach has proven to be successful. The assessment of the hydroxyapatite porous scaffolds includes techniques such as scanning electron microscopy (SEM), X-ray diffraction (XRD), and Fourier transform infrared (FTIR) spectroscopy [66].

Research has been conducted on the fabrication of sponge-like hydroxyapatite (HA) induced by a modified articular cartilage membrane template. This investigation focuses on synthesizing scaffold materials with a sponge-like structure using a modified porcine bone articular cartilage membrane as a template. The crystallographic structure and composition of the synthesized samples were analyzed through SEM, XRD, FTIR, and TEM. The results indicated that the samples consisted of carbonated HA crystals, and the sponge-like structure comprised extensive nano-hydroxyapatite plates. Physicochemical properties of the samples, including density, porosity, and specific surface, were examined, revealing that the sponge-like HA exhibited high values for these parameters. Furthermore, experimental cell culture results demonstrated a significant enhancement in the bioactivity, osteoconductivity, and differentiation of human osteosarcoma MG-63 cells when exposed to the sponge-like HA [67].

The production of scaffolds composed of biocompatible hydroxyapatite/nano-carbonated polymer has been executed. This investigation focuses on creating sponge scaffolds that incorporate nano-carbonated hydroxyapatite (nCHA) along with different polymers like natural gelatin (GE), chitosan (CS), and polyvinyl alcohol (PVA), aiming for applications in tissue engineering and biomedicine. The scaffolds were characterized using XRD, SEM, and FTIR techniques, revealing a porosity exceeding 70%. The morphology of the scaffolds underwent significant changes depending on the NCHA/polymer combination employed. Biocompatibility assessments with rat bone marrow-derived mesenchymal stem cells (RMSCs) showed no notable cytotoxicity. This study indicates the potential utility of these sponge scaffolds in tissue engineering and biomedical applications [68].

The synthesis and characterization of porous hydroxyapatite, incorporating a gelatin coating for potential use in bone scaffolds, were undertaken in this study. This paper explores the process of creating and examining porous hydroxyapatite with a gelatin coating specifically tailored for applications in bone scaffolds. The primary goal was to assess the effects of different gelatin concentrations on scaffold properties, aiming to optimize mechanical and physical features for effective use in bone scaffold applications. Employing the polymer sponge method, researchers produced gelatin-coated porous hydroxyapatite scaffolds (HA-gelatin), adjusting gelatin concentrations to 13 wt%, 15 wt%, 17 wt%, and 19 wt%. Thorough testing of the scaffolds' mechanical and physical characteristics indicated compliance with established criteria for human bone regeneration. The most favorable outcomes were achieved with a 19% gelatin concentration, resulting in pore sizes between 100 and 300 µm, a compressive strength of 6.7 MPa, and a porosity of 67.12%. FTIR tests revealed the presence of carbonate ion groups from hydroxyapatite, phosphate groups, and NH groups from gelatin in the HA-gelatin scaffold [69].

The sponge replication technique is employed not only in the fabrication of porous hyaluronic acid (HA) but also in certain metal fabrication processes intended for implant applications. Investigations into the microstructure, mechanical characteristics, degradation patterns, and biocompatibility of sponge-impregnated and sintered porous Fe-Mn alloys have been carried out. This study is centered on the production and analysis of porous iron-manganese (Fe-Mn) alloys utilizing sponge impregnation and sintering methods. The alloy's composition varies with sintering temperature, resulting in manganese (Mn) content ranging from 12 to 44 wt.%. The porous Fe-Mn alloy displays a well-connected porous structure characterized by high porosity (approximately 85%) and an average pore size ranging from 375 to 500 µm. Mechanical properties, such as yield strength and elastic modulus, closely resemble those of cancellous bone. Over time in simulated body fluid (SBF), the degradation rate of the alloy diminishes, indicating its potential as a biodegradable implant material. Additionally, the porous Fe-Mn alloy demonstrates favorable biocompatibility, as evidenced by increased cell proliferation upon direct culture of osteoblastic MC3T3-E1 cells [70].

J. Liu et al. [71] conducted a research study on scaffolds made of a porous Nb-Ti-Ta alloy intended for application in bone tissue engineering. The investigation delves into the manufacturing process, mechanical characteristics, and compatibility with the living tissues of these scaffolds. The alloy was created utilizing a combination of sponge impregnation and sintering techniques, resulting in a three-dimensional (3D) network structure that is well-connected, featuring a pore size ranging from 100 to 600 µm and a porosity level between 50% and 80%. The mechanical properties of the alloy were determined to closely resemble those of human bone and can be tailored to meet specific requirements. Additionally, the porous structure of the alloys contributes to their favorable biocompatibility, rendering them potentially valuable for applications in hard tissue implants. **Table 2** describes the variation of the sponge replicated method, composition variation, and the resulting characterization of porous scaffolds.

Table 2. Review of the influence of pore HA characterization

Composition	Methods	Sintering	Results	Refs.
• HA:PVA 60:40 70:30 80:20 • PU foam	Sponge replicated	900 °C for 5 hours	• PVA 40 worst result • PVA 20 best results • 72%-73% • macropores with an average size of 460 µm	[58]
• 70% HA • 2% PVA • 28% other (dolapix CE-64) • PU Foam	Sponge replicated	• Preheat 500 °C • Mainheat 1300 °C for 3 hours	• Compressive streght 0.8 MPa • Porosity averange 85%	[60]
• 10,11,12 grams HA • 10 grams of starch • 3% Darvan	Sponge replicated from gambas	• preheat 600 °C, for 1 hour • main heat 1250 °C for 1 hour	• Compressive streght 3.31-6.45 MPa • Pore size 50-400 µm • Porosity 56.51%-53.26%	[19]
• HA • gum ghatti (5% and 10%)	Sponge replicated	• 1100 °C • 1150 °C • 1200 °C	• Pore size 200-500 µm. • Best 10% GG and 1200°C • Highest porosity 79.3%	[61]
• HA 41.2 grams • Sigma-Aldrich (CMC) 5 grams Alumina powder 3.6 grams	Sponge replicated	Sintered 400 to 800, then 800 to 1200, then cooling 1200 to 800	• Compressive 4.25±0.73 MPa • Pore size 200-500 µm • total porosity 75.22±2.97% • Open porosity 68.19± 1.61%	[62]
• HA:PVA • ZnHA:PVA FHA:PVA	Sponge repicated	• 800 °C for 3 hours • 1250 °C for 3 hours	• Pore size 100-200µm • Porosity 65-75%	[63]
Biphasic calcium phosphate	robocasting	400 °C for 1 hour, sintered at 1100 °C for 2 hour	Compressive 300x300= 6.58 MPa, 250x500=5.1 MPa, 300x600=3.46 MPa, 500x500=3.64 MPa	[26]
CTS (DD = ~95%), methanal (or named as formaldehyde), PVA, HA, aqueous lactic acid and sodium chloride solution	freeze drying-reinforced sponges composites	-	• Pore size 50-100 µm • 80% porosity	[64]
HA slurry containing 70 wt% of HAP powder and 3% of polyethylene glycol	Sponge replicated	1300 °C for 2 hours	Porosity 72-75%	[72]
10 grams of hydroxyapatite (eggshell) powder was mixed with 0.5 grams of methylcellulose, 2.5 grams of dicalcium phosphate (DCP) and 40 ml of distilled water.	Sponge replicated	1200 °C for 2 hours	• Pore size 80 to 400 µm • Porosity 62.67%	[65]
ACM (Articular Cartilage Membrane), NaCl, $NaHCO_3$, KCl, Na_2HPO_4, $12H_2O$, $CaCl_2$, Na_2SO_4, $MgCl_2$, $6H_2O$, $(CH_2OH)_3CNH_2$, HCl, NaOH, H_2O_2, ethanol glutaraldehyde, HA Powder	Freeze drying	-	• Density of approximately 1.3 gr/cm^3 • Average porosity 64%	[66]

Table 2 (cont.) Review of the influence of pore HA characterization

Composition	Methods	Sintering	Results	Refs.
$Ca(NO_3)_2.4H_2O$, , Urea, Di-ammonium hydrogen phosphate, $(NH_4)2HPO_4$, (NH4OH, ≥30% w/w). Gelatin (GE) powder, PVA, (Mw=88kDa) was extracted from shrimp shells.	Lyophilization-Freeze drying	-	Pore size 2-400 µm	[67]
Fe47-Mn53 powder, 6% polyvinyl alcohol (PVA), 0.5% sodium alginate, 1% carboxy methyl cellulose (CMC), and 92.5% deionized water	Sponge replicated	1100, 1150, and 1200 °C	a. Pore size • Fe-12Mn-1200=375 µm • Fe-30Mn-1150=424 µm • Fe-44Mn-1100=500 µm b. porosity • Fe-12Mn-1200=85.5% • Fe-30Mn-1150=84.6% • Fe-44Mn-1100=84.1%	[69]
Hydroxyapatite (HA), gelatin, poly-(vinyl alcohol) (pva), ethansol pa-45, hydrogen peroxide (h_2o_2), polymeric sponge, distilled water, and 96% ethanol	Sponge replicated	1250 °C for 8 hours	a. Pore size • Gelatin 13% 131.62 - 303.87 • Gelatin 19% 106.91 - 231.12 b. Compressive • Gelatin 13=0.6 MPa • Gelatin 15 = 1.8 MPa • Gelatin 17=3.79 MPa • Gelatin 19=6.7 MPa c. Porosity • Gelatin 13=88% • Gelatin 15=81% • Gelatin 17=68% d. Gelatin 19=67%	[68]
Nb, Ta, Ti, PU Sponge, PVA	Sponge replicated	• 400 °C for 2 hours • 1700 °C for 2 hours	• Pore size 100-600 µm • Porosity of 50%-80%	[70]

3. Effect of Sintering Temperature on Characterization of HA Pores

Figure 1 shows the effect of sintering temperature on the hardness and strength value of HA porous. The sintering temperature is one of the important factors in HA pore fabrication. Some of the above studies have examined the effect of sintering temperature on the characterization of pore HA. Research on the effect of sintering temperature on the characterization of HA pores from goat bone has been investigated. The sintering temperatures investigated were 700, 900, 1100 and 1300 °C. It was found that the sintering temperature affected the hardness and compressive strength morphology of pore HA. It was found that the highest hardness value was at 1100 temperature and the highest compressive strength was at 1100 temperature. Furthermore, for the morphology of the material, the pore size is obtained with a diameter of ±100-500 µm with the phenomenon of high calcination temperature resulting in the HA wall in the HA pore material becoming thinner and the diameter of the porous interconnection becomes larger, thus reducing the mechanical properties of the HA pore material [73].

Furthermore, the effect of gum ghatti addition on HA pores concerning sintering temperature was investigated. This study used compositions of 5 wt% and 10 wt% of gum ghatti and sintering temperatures of 1000, 1100 and 1200 wt%. It was found that some phenomena on compressive strength and porosity were maximum at sintering temperature 1200 ℃ with 5 wt% compressive at 0.57 MPa and porosity 79.3% and 10 wt% compressive at 2.42 MPa and porosity 66.5%. This study also investigated the effect of sintering temperature on the degradation of SBF solution. It was found that the smaller the sintering temperature, the smaller the crystal breakage and amorphization, resulting in smaller HA pore degradation, and vice versa [61].

Other research states that the sintering temperature used is the best temperature for HA based on each type of base material. Based on the review that has been done, the temperatures used range from 700 to 1300 ℃. Then before the mainheat is reached at sintering, several studies

use preheat to lift the agent shaft [62]. In addition, preheating can reduce the temperature difference between the heater and the material to be sintered. This will help avoid distortion and excessive residual stresses that can occur due to significant temperature differences [74]. In addition, preheat is also able to reduce the risk of cracking in the material and improve dimensional stability [75].

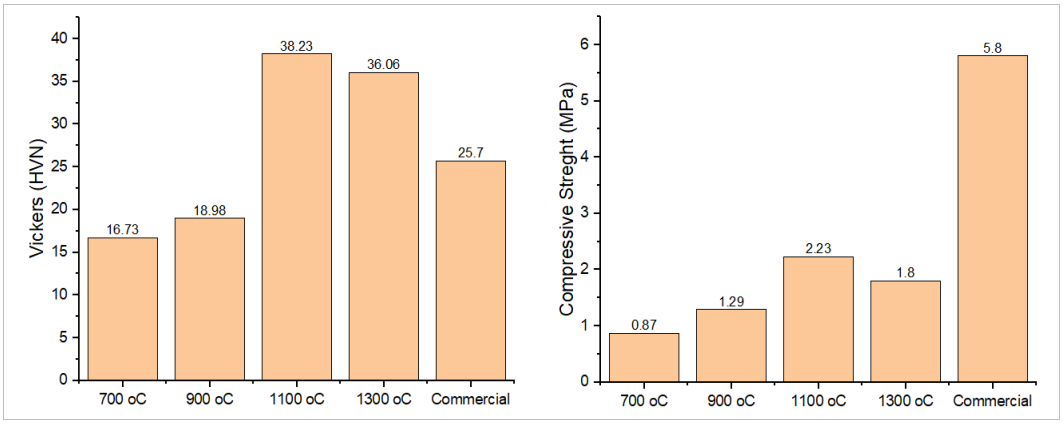


Figure 1. Effect of sintering temperature on the hardness value (left) and compressive strength value (right) of HA porous [73]

4. Effect of Binder on Pore HA Characterization

Binder has a function as an adhesive between HA powder particles. The type and composition of the binder is a factor that influences the composition of HA pore formation from powder fabrication. Polyvinyl alcohol is one type of binder that is often used. PVA is widely used because it is a type of biopolymer that can evaporate at certain temperatures, leaving the material clean and free of binder contamination. Several studies to investigate the effect of PVA composition have been conducted. Afriani et al. [58] examined the effect of PVA composition on the fabrication of HA pores from sponge replicated methods. The composition of PVA used was 40 wt%, 30 wt% and 20 wt%. It was found that the more PVA content, the lower the characteristics of the resulting pore HA, on the other hand, the higher the PVA content, the higher the characteristics of the resulting pore HA [58]. Other studies also use PVA as a binder composition such as Serrano-Bello et al. [60] used PVA with a composition of 2%, Batra & Kapoor [63] used PVA with a composition of 3%-10%, Vo et al. [64] used PVA with a composition of 2.5%, Siddiqi et al. [67] used PVA at a certain composition, Pristiono & Rudyardjo [68] used PVA with a composition of 4%, P. Liu et al [69] used PVA with a composition of 6%, and J. Liu et al. [71] who used PVA composition from 3%-6%. It was found that the binder will be maximized at the best composition. It is said that the best composition is the appropriate composition not less and not more. So there is a possibility that the composition of the binder has an optimal point to form a bond in the fabrication of powders into solids [58], [60], [63], [64], [67], [68], [71], [76].

Next, it is necessary to pay attention to the results of research that has been carried out previously with the current porous HA standards. The standard currently used is ISO 13379:2015 where there are several characteristics that must be met. Characteristics that must be met include a calcium phosphate (Ca/P) ratio of $1.6 \leq Ca/P \leq 1.8$, the composition of the HA crystalline phase must have a mass fraction above 50%, and mechanical properties of compressive strength ≥ 1.5 MPa. Several research reviews that have met compressive strength standards include Prawira et al [73] at sintering temperatures of 1100℃ and 1300 ℃, by Pristiono et al [68] with gelatin binder compositions of 15%, 17% and 19%, by Neto et al [26] at all compositions, by Fadli et al [9] on all compositions, and by Afriani et al [58] on the composition HA/PVA 80/20.

5. Conclusion

In the last two decades, pore HA has become a widely developed study. The fabrication process is an important factor in determining the quality of pore HA. Sintering and binder become the important factors that must be considered in sponge replicated methods. It was found that the sintering temperature used varied with a range of 700℃ to 1300℃. Furthermore, PVA is one of the binders that is currently still widely used, because PVA is a biopolymer that can evaporate at certain temperatures, leaving the material clean and free from binder contamination. The composition of PVA that has been studied also varies from 2.5% to 40%. Several research reviews have been able to meet several ISO 13379:2015 standards. The calcium Ca/P ratio, crystalline phase composition,

and compressive strength values are the main focus of ISO 13379:2015. Temperature 900℃ to 1300℃ being the sintering conditions, HA/PVA composition 80/20, and addition of gelatin at 15% to 19% being the best parameters in this review which depend on the conditions and materials used. Next, choosing the right sintering temperature and PVA composition will produce HA pores with good characterization under scaffold standards in biomedical applications. Further studies are needed regarding the selection of sintering temperature and HA/PVA composition on the formation of porous HA. Different HA base materials can provide optimal compositions and different sintering temperatures to produce optimal porous HA according to ISO 13379:2015 standards.

Authors' Declaration

Authors' contributions and responsibilities - The authors made substantial contributions to the conception and design of the study.

Funding – No information about funding from the authors.

Availability of data and materials - All data are available from the authors.

Competing interests - The authors declare no competing interest.

Additional information – No additional information from the authors.

References

[1] A. Atala, R. Lanza, and R. Nerem, *Principles of Regenerative Medicine*. Elsevier, 2019.

[2] Y. Zhang and L. Rehmmann, "Extraction of high-value compounds from marine biomass via ionic liquid-based techniques," in *Innovative and Emerging Technologies in the Bio-marine Food Sector*, Elsevier, 2022, pp. 417–439.

[3] T. U. Habibah and H. G. Salisbury, *Hydroxyapatite Dental Material*. Treasure Island (FL): StatPearls Publishing, 2019.

[4] M. Sari, Aminatun, T. Suciati, Y. W. Sari, and Y. Yusuf, "Porous Carbonated Hydroxyapatite-Based Paraffin Wax Nanocomposite Scaffold for Bone Tissue Engineering: A Physicochemical Properties and Cell Viability Assay Analysis," *Coatings*, vol. 11, no. 10, p. 1189, Sep. 2021, doi: 10.3390/coatings11101189.

[5] W. Wang and K. W. K. Yeung, "Bone grafts and biomaterials substitutes for bone defect repair: A review," *Bioactive Materials*, vol. 2, no. 4, pp. 224–247, Dec. 2017, doi: 10.1016/j.bioactmat.2017.05.007.

[6] S. Bhat, U. T. Uthappa, T. Altalhi, H.-Y. Jung, and M. D. Kurkuri, "Functionalized Porous Hydroxyapatite Scaffolds for Tissue Engineering Applications: A Focused Review," *ACS Biomaterials Science & Engineering*, vol. 8, no. 10, pp. 4039–4076, Oct. 2022, doi: 10.1021/acsbiomaterials.1c00438.

[7] Z. Wu, Z. Zhou, and Y. Hong, "Isotropic freeze casting of through-porous hydroxyapatite ceramics," *Journal of Advanced Ceramics*, vol. 8, no. 2, pp. 256–264, Jun. 2019, doi: 10.1007/s40145-018-0312-2.

[8] K. Zhou *et al.*, "Hierarchically Porous Hydroxyapatite Hybrid Scaffold Incorporated with Reduced Graphene Oxide for Rapid Bone Ingrowth and Repair," *ACS Nano*, vol. 13, no. 8, pp. 9595–9606, Aug. 2019, doi: 10.1021/acsnano.9b04723.

[9] A. Fadli, P. Widiyanti, D. Noviana, A. Prabowo, and H. Ismawati, "Preparation of Hydroxyapatite Scaffold using Luffa Cylindrica Sponge as Template," *Jurnal Rekayasa Kimia & Lingkungan*, vol. 15, no. 2, pp. 62–70, 2020, doi: 10.23955/rkl.v15i2.15957.

[10] X. Wang, G. Wang, A. Marchetti, L. Wu, L. Wu, and Y. Guan, "Preparation of porous hydroxyapatite and its application in Pb ions effective removal," *AIP Advances*, vol. 9, no. 2, p. 025123, Feb. 2019, doi: 10.1063/1.5086705.

[11] S.-M. Huang, S.-M. Liu, C.-L. Ko, and W.-C. Chen, "Advances of Hydroxyapatite Hybrid Organic Composite Used as Drug or Protein Carriers for Biomedical Applications: A Review," *Polymers*, vol. 14, no. 5, p. 976, Feb. 2022, doi: 10.3390/polym14050976.

[12] A. Prasad, M. R. Sankar, and V. Katiyar, "State of Art on Solvent Casting Particulate Leaching Method for Orthopedic ScaffoldsFabrication," *Materials Today: Proceedings*, vol. 4, no. 2, pp.

898–907, 2017, doi: 10.1016/j.matpr.2017.01.101.

[13] M. Friuli, P. Nitti, M. Madaghiele, and C. Demitri, “A possible method to avoid skin effect in polymeric scaffold produced through thermally induced phase separation,” *Results in Engineering*, vol. 12, p. 100282, Dec. 2021, doi: 10.1016/j.rineng.2021.100282.

[14] J. Xue, T. Wu, Y. Dai, and Y. Xia, “Electrospinning and Electrospun Nanofibers: Methods, Materials, and Applications,” *Chemical Reviews*, vol. 119, no. 8, pp. 5298–5415, Apr. 2019, doi: 10.1021/acs.chemrev.8b00593.

[15] F. Baino and S. Yamaguchi, “The use of simulated body fluid (SBF) for assessing materials bioactivity in the context of tissue engineering: Review and challenges,” *Biomimetics*, vol. 5, no. 4, pp. 1–19, 2020, doi: 10.3390/biomimetics5040057.

[16] T. Nonoyama, “Bioceramics x soft material as a simple model to mimic functions in bones,” *Journal of the Ceramic Society of Japan*, vol. 130, no. 10, pp. 817–824, 2022, doi: 10.2109/jcersj2.22089.

[17] Sutygina, Betke, and Scheffler, “Open-Cell Aluminum Foams by the Sponge Replication Technique,” *Materials*, vol. 12, no. 23, p. 3840, Nov. 2019, doi: 10.3390/ma12233840.

[18] C. Wang, H. Chen, X. Zhu, Z. Xiao, K. Zhang, and X. Zhang, “An improved polymeric sponge replication method for biomedical porous titanium scaffolds,” *Materials Science and Engineering: C*, vol. 70, pp. 1192–1199, Jan. 2017, doi: 10.1016/j.msec.2016.03.037.

[19] A. Fadli, A. Lubis, F. Huda, and K. Komalasari, “Hydroxyapatite Scaffolds Fabrication using Gambas Sponge (Luffa cylindrica) as Novel Template,” in *Proceeding of the First International Conference on Technology, Innovation and Society*, Jul. 2016, pp. 53–56, doi: 10.21063/ICTIS.2016.1009.

[20] M. Yazdimamaghani, M. Razavi, D. Vashaee, K. Moharamzadeh, and A. R. Boccaccini, “Porous Magnesium-Based Scaffolds for Tissue Engineering,” *Materials Science and Engineering: C*, vol. 71, no. February, pp. 1253–1266, 2017, doi: 10.1016/j.msec.2016.11.027.

[21] J. T. Y. Lee and K. L. Chow, “SEM sample preparation for cells on 3D scaffolds by freeze-drying and HMDS,” *Scanning*, vol. 34, no. 1, pp. 12–25, Feb. 2012, doi: 10.1002/sca.20271.

[22] C. Zhang, H. Li, Z. Guo, B. Xue, and C. Zhou, “Fabrication of Hydroxyapatite Nanofiber via Electrospinning as a Carrier for Protein,” *Journal of Nanoscience and Nanotechnology*, vol. 17, no. 2, pp. 1018–1024, Feb. 2017, doi: 10.1166/jnn.2017.12620.

[23] J. Liu *et al.*, “Polycaprolactone/Gelatin/Hydroxyapatite Electrospun Nanomembrane Materials Incorporated with Different Proportions of Attapulgite Synergistically Promote Bone Formation,” *International Journal of Nanomedicine*, vol. Volume 17, pp. 4087–4103, Sep. 2022, doi: 10.2147/IJN.S372247.

[24] S. N. Aulia, R. H. Mulyani, and D. H. Prajitno, “Electrodeposition of Composite Hydroxyapatite-Chitosan from Local Materials on Stainless Steel 304,” *Jurnal Kartika Kimia*, vol. 2, no. 2, Nov. 2019, doi: 10.26874/jkk.v2i2.37.

[25] N. Kanasan, S. Adzila, N. AzimahMustaffa, and P. Gurubaran, “The Effect of Sodium Alginate on the Properties of Hydroxyapatite,” *Procedia Engineering*, vol. 184, pp. 442–448, 2017, doi: 10.1016/j.proeng.2017.04.115.

[26] A. S. Neto and J. M. F. Ferreira, “Biphasic calcium phosphate scaffolds derived from hydrothermally synthesized powders,” *Lekar a Technika*, vol. 48, no. 3, pp. 77–83, 2018.

[27] K. Okuda, R. Shigemasa, K. Hirota, and T. Mizutani, “In Situ Crystallization of Hydroxyapatite on Carboxymethyl Cellulose as a Biomimetic Approach to Biomass-Derived Composite Materials,” *ACS Omega*, vol. 7, no. 14, pp. 12127–12137, Apr. 2022, doi: 10.1021/acsomega.2c00423.

[28] S. Sözügeçer and N. P. Bayramgil, “Preparation and characterization of polyacrylic acid-hydroxyapatite nanocomposite by microwave-assisted synthesis method,” *Heliyon*, vol. 7, no. 6, p. e07226, Jun. 2021, doi: 10.1016/j.heliyon.2021.e07226.

[29] M. R. Mohd Roslan *et al.*, “The State of Starch/Hydroxyapatite Composite Scaffold in Bone Tissue Engineering with Consideration for Dielectric Measurement as an Alternative Characterization Technique,” *Materials*, vol. 14, no. 8, p. 1960, Apr. 2021, doi: 10.3390/ma14081960.

[30] M. B. Jalageri and G. C. Mohan Kumar, “Hydroxyapatite Reinforced Polyvinyl Alcohol/Polyvinyl Pyrrolidone Based Hydrogel for Cartilage Replacement,” *Gels*, vol. 8, no. 9,

p. 555, Sep. 2022, doi: 10.3390/gels8090555.

[31] J. Brady, T. Dürig, P. I. Lee, and J.-X. Li, "Polymer Properties and Characterization," in *Developing Solid Oral Dosage Forms*, Elsevier, 2017, pp. 181–223.

[32] I. Novella, B. Rupaedah, D. R. Eddy, Suryana, F. S. Irwansyah, and A. R. Noviyanti, "The Influence of Polyvinyl Alcohol Porogen Addition on the Nanostructural Characteristics of Hydroxyapatite," *Materials*, vol. 16, no. 18, p. 6313, Sep. 2023, doi: 10.3390/ma16186313.

[33] P. Ghelich, M. Kazemzadeh-Narbat, A. Hassani Najafabadi, M. Samandari, A. Memić, and A. Tamayol, "(Bio)manufactured Solutions for Treatment of Bone Defects with an Emphasis on US-FDA Regulatory Science Perspective," *Advanced NanoBiomed Research*, vol. 2, no. 4, p. 2100073, Apr. 2022, doi: 10.1002/anbr.202100073.

[34] T. Ghassemi, A. Shahroodi, M. H. Ebrahimzadeh, A. Mousavian, J. Movaffagh, and A. Moradi, "Current concepts in scaffolding for bone tissue engineering," *Archives of Bone and Joint Surgery*, vol. 6, no. 2, pp. 90–99, 2018, doi: 10.22038/abjs.2018.26340.1713.

[35] M. Filippi, G. Born, M. Chaaban, and A. Scherberich, "Natural Polymeric Scaffolds in Bone Regeneration," *Frontiers in Bioengineering and Biotechnology*, vol. 8, May 2020, doi: 10.3389/fbioe.2020.00474.

[36] M. Shariful Islam, M. Abdulla-Al-Mamun, A. Khan, and M. Todo, "Excellency of Hydroxyapatite Composite Scaffolds for Bone Tissue Engineering," in *Biomaterials*, IntechOpen, 2020.

[37] M. Bahraminasab, "Challenges on optimization of 3D-printed bone scaffolds," *BioMedical Engineering Online*, vol. 19, no. 1, pp. 1–33, 2020, doi: 10.1186/s12938-020-00810-2.

[38] C. O'Connor, I. Woods, A. Hibbitts, A. Dervan, and F. J. O'Brien, "The Manufacture and Characterization of Biomimetic, Biomaterial-Based Scaffolds for Studying Physicochemical Interactions of Neural Cells in 3D Environments," *Current Protocols*, vol. 3, no. 2, Feb. 2023, doi: 10.1002/cpz1.688.

[39] H. Siddiqui, K. Pickering, and M. Mucalo, "A Review on the Use of Hydroxyapatite-Carbonaceous Structure Composites in Bone Replacement Materials for Strengthening Purposes," *Materials*, vol. 11, no. 10, p. 1813, Sep. 2018, doi: 10.3390/ma11101813.

[40] Y. Chen, N. Wang, O. Ola, Y. Xia, and Y. Zhu, "Porous ceramics: Light in weight but heavy in energy and environment technologies," *Materials Science and Engineering: R: Reports*, vol. 143, p. 100589, Jan. 2021, doi: 10.1016/j.mser.2020.100589.

[41] A. Scarano, F. Lorusso, P. Santos de Oliveira, S. Kunjalukkal Padmanabhan, and A. Licciulli, "Hydroxyapatite Block Produced by Sponge Replica Method: Mechanical, Clinical and Histologic Observations," *Materials*, vol. 12, no. 19, p. 3079, Sep. 2019, doi: 10.3390/ma12193079.

[42] T. G. Chatzimitakos and C. D. Stalikas, "Sponges and Sponge-Like Materials in Sample Preparation: A Journey from Past to Present and into the Future," *Molecules*, vol. 25, no. 16, p. 3673, Aug. 2020, doi: 10.3390/molecules25163673.

[43] J. S. Meschke, "Validation of a Sponge Processing Method for Characterizing Microbes in the Bullitt Center," 2015.

[44] E. Al-Qadhi, G. Li, and Y. Ni, "Influence of a Two-Stage Sintering Process on Characteristics of Porous Ceramics Produced with Sewage Sludge and Coal Ash as Low-Cost Raw Materials," *Advances in Materials Science and Engineering*, vol. 2019, pp. 1–12, Nov. 2019, doi: 10.1155/2019/3710692.

[45] L. K. Singh, A. Bhadauria, S. Jana, and T. Laha, "Effect of Sintering Temperature and Heating Rate on Crystallite Size, Densification Behaviour and Mechanical Properties of Al-MWCNT Nanocomposite Consolidated via Spark Plasma Sintering," *Acta Metallurgica Sinica (English Letters)*, vol. 31, no. 10, pp. 1019–1030, Oct. 2018, doi: 10.1007/s40195-018-0795-4.

[46] Y. Shi *et al.*, "Polymer materials for additive manufacturing—powder materials," in *Materials for Additive Manufacturing*, Elsevier, 2021, pp. 9–189.

[47] M. A. Mazo, I. Padilla, A. Tamayo, J. I. Robla, A. López-Delgado, and J. Rubio, "Evaluation of thermal shock resistance of silicon oxycarbide materials for high-temperature receiver applications," *Solar Energy*, vol. 173, pp. 256–267, Oct. 2018, doi: 10.1016/j.solener.2018.07.080.

[48] N. J. Lóh, L. Simão, J. Jiusti, A. De Noni Jr., and O. R. K. Montedo, "Effect of temperature and holding time on the densification of alumina obtained by two-step sintering," *Ceramics*

International, vol. 43, no. 11, pp. 8269–8275, Aug. 2017, doi: 10.1016/j.ceramint.2017.03.159.

[49] V. Momeni *et al.*, "Research Progress on Low-Pressure Powder Injection Molding," *Materials*, vol. 16, no. 1, p. 379, Dec. 2022, doi: 10.3390/ma16010379.

[50] H. Miyanaji, K. M. Rahman, M. Da, and C. B. Williams, "Effect of fine powder particles on quality of binder jetting parts," *Additive Manufacturing*, vol. 36, p. 101587, Dec. 2020, doi: 10.1016/j.addma.2020.101587.

[51] T. Dürig and K. Karan, *Binders in Pharmaceutical Granulation*. 2021.

[52] S. P. Forster, E. Dippold, and T. Chiang, "Twin-Screw Melt Granulation for Oral Solid Pharmaceutical Products," *Pharmaceutics*, vol. 13, no. 5, p. 665, May 2021, doi: 10.3390/pharmaceutics13050665.

[53] O. O. Kunle, "Starch Source and Its Impact on Pharmaceutical Applications," in *Chemical Properties of Starch*, IntechOpen, 2020.

[54] A. Cholewinski, P. Si, M. Uceda, M. Pope, and B. Zhao, "Polymer Binders: Characterization and Development toward Aqueous Electrode Fabrication for Sustainability," *Polymers*, vol. 13, no. 4, p. 631, Feb. 2021, doi: 10.3390/polym13040631.

[55] G. Paltanea *et al.*, "A Review of Biomimetic and Biodegradable Magnetic Scaffolds for Bone Tissue Engineering and Oncology," *International Journal of Molecular Sciences*, vol. 24, no. 5, p. 4312, Feb. 2023, doi: 10.3390/ijms24054312.

[56] J. A. Lett, S. M, R. K, and B. M, "Physical characterization of porous hydroxyapatite scaffolds," *Rheumatology and Orthopedic Medicine*, vol. 3, no. 3, 2018, doi: 10.15761/ROM.1000153.

[57] R. Ismail *et al.*, "The Effect of Hydrothermal Holding Time on The Characterization of Hydroxyapatite Synthesized from Green Mussel Shells," *Journal of Advanced Research in Fluid Mechanics and Thermal Sciences*, vol. 80, no. 1, pp. 84–93, 2021, doi: 10.37934/ARFMTS.80.1.8493.

[58] F. Afriani, A. Indriawati, W. B. Kurniawan, Y. Widyaningrum, R. A. Rafsanjani, and Y. Tiandho, "Synthesis of porous hydroxyapatite scaffolds from waste cockle shells by polyurethane sponge replication method," *Gravity : Jurnal Ilmiah Penelitian dan Pembelajaran Fisika*, vol. 6, no. 1, Feb. 2020, doi: 10.30870/gravity.v6i1.6741.

[59] R. Ferracini, I. Martínez Herreros, A. Russo, T. Casalini, F. Rossi, and G. Perale, "Scaffolds as Structural Tools for Bone-Targeted Drug Delivery," *Pharmaceutics*, vol. 10, no. 3, p. 122, Aug. 2018, doi: 10.3390/pharmaceutics10030122.

[60] J. Serrano-Bello *et al.*, "In vivo Regeneration of Mineralized Bone Tissue in Anisotropic Biomimetic Sponges," *Frontiers in Bioengineering and Biotechnology*, vol. 8, Jul. 2020, doi: 10.3389/fbioe.2020.00587.

[61] J. A. Lett *et al.*, "Exploration of gum ghatti-modified porous scaffolds for bone tissue engineering applications," *New Journal of Chemistry*, vol. 44, no. 6, pp. 2389–2401, 2020, doi: 10.1039/C9NJ05575D.

[62] S. M. Imani, S. M. Rabiee, A. M. Goudarzi, and M. Dardel, "A novel modification for polymer sponge method to fabricate the highly porous composite bone scaffolds with large aspect ratio suitable for repairing critical-sized bone defects," *Vacuum*, vol. 176, p. 109316, Jun. 2020, doi: 10.1016/j.vacuum.2020.109316.

[63] U. Batra and S. Kapoor, "Ionic Substituted Hydroxyapatite Scaffolds Prepared by Sponge Replication Technique for Bone Regeneration," *Nanoscience and Nanotechnology*, vol. 6, no. 1A, pp. 18–24, 2016, doi: 10.5923/c.nn.201601.03.

[64] T. S. Vo, T. T. B. C. Vo, T. S. Nguyen, and N. D. Pham, "Incorporation of hydroxyapatite in crosslinked gelatin/chitosan/poly(vinyl alcohol) hybrids utilizing as reinforced composite sponges, and their water absorption ability," *Progress in Natural Science: Materials International*, vol. 31, no. 5, pp. 664–671, Oct. 2021, doi: 10.1016/j.pnsc.2021.09.003.

[65] F. Habib, S. Alam, M. Irfan, and S. Nosheen, "Development and Characterization of Porous Hydroxyapatite Scaffold by Using Polymeric Sponge Method," *International Journal of Sciences: Basic and Applied Research*, vol. 38, no. 2, pp. 1–7, 2018.

[66] X. Liu, Y. Zheng, Y. Ma, T. Huo, and C. Pei, "Self-assembled sponge-like hydroxyapatite induced by modified articular cartilage membrane template," *Ceramics International*, vol. 44, no. 14, pp. 16400–16406, Oct. 2018, doi: 10.1016/j.ceramint.2018.06.050.

[67] S. A. Siddiqi *et al.*, "Fabrication of biocompatible nano-carbonated hydroxyapatite/polymer spongy scaffolds," *Digest Journal of Nanomaterials and Biostructures*, vol. 13, no. 2, pp. 439–450, 2018.

[68] D. Pristiono and D. I. Rudyardjo, "The synthesis and characterization of porous hydroxyapatite using gelatin coating for bone scaffold application," in *AIP Conference Proceedings*, 2020, p. 050007, doi: 10.1063/5.0034658.

[69] P. Liu, D. Zhang, Y. Dai, J. Lin, Y. Li, and C. Wen, "Microstructure, mechanical properties, degradation behavior, and biocompatibility of porous Fe-Mn alloys fabricated by sponge impregnation and sintering techniques," *Acta Biomaterialia*, vol. 114, pp. 485–496, Sep. 2020, doi: 10.1016/j.actbio.2020.07.048.

[70] J. Liu, J. Ruan, L. Chang, H. Yang, and W. Ruan, "Porous Nb-Ti-Ta alloy scaffolds for bone tissue engineering : Fabrication , mechanical properties and in vitro / vivo biocompatibility," *Materials Science & Engineering C*, vol. 78, pp. 503–512, 2017, doi: 10.1016/j.msec.2017.04.088.

[71] J. Liu, J. Ruan, L. Chang, H. Yang, and W. Ruan, "Porous Nb-Ti-Ta alloy scaffolds for bone tissue engineering: Fabrication, mechanical properties and in vitro/vivo biocompatibility," *Materials Science and Engineering: C*, vol. 78, pp. 503–512, Sep. 2017, doi: 10.1016/j.msec.2017.04.088.

[72] A. A. Mehatlaf, S. B. H. Farid, and A. A. Atiyah, "Fabrication and Investigation of Bioceramic Scaffolds by a Polymer Sponge Replication Technique," *IOP Conference Series: Materials Science and Engineering*, vol. 1076, no. 1, p. 012080, Feb. 2021, doi: 10.1088/1757-899X/1076/1/012080.

[73] S. Eka Prawira, J. Triyono, and T. Triyono, "Pengaruh Temperatur Kalsinasi Terhadap Sifat Mekanik Material Scaffold Hidroksiapatit Dari Tulang Kambing," *Mekanika: Majalah Ilmiah Mekanika*, vol. 18, no. 1, pp. 22–27, 2019, doi: 10.20961/mekanika.v18i1.35042.

[74] C. L. A. Leung, R. Tosi, E. Muzangaza, S. Nonni, P. J. Withers, and P. D. Lee, "Effect of preheating on the thermal, microstructural and mechanical properties of selective electron beam melted Ti-6Al-4V components," *Materials & Design*, vol. 174, p. 107792, Jul. 2019, doi: 10.1016/j.matdes.2019.107792.

[75] N. Madadi Shishavan, R. Eslami-Farsani, H. Ebrahimnezhad-Khaljiri, and H. Aghamohammadi, "The effects of pre-heating and sintering temperature on the sol-gel synthesis of mullite nanoparticles," *Materials Research Express*, vol. 6, no. 10, p. 105045, Aug. 2019, doi: 10.1088/2053-1591/ab3929.

[76] N. A. Salleh, S. Kheawhom, N. Ashrina A Hamid, W. Rahiman, and A. A. Mohamad, "Electrode polymer binders for supercapacitor applications: A review," *Journal of Materials Research and Technology*, vol. 23, pp. 3470–3491, Mar. 2023, doi: 10.1016/j.jmrt.2023.02.013.