Hydroxyapatite Based Material: Natural Resources, Synthesis Methods, 3D Print Filament Fabrication, and Filament Filler

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***Abstract*—Hydroxyapatite is a biomaterial that has been recognized in terms of hard tissue engineering due to its similarity in composition to bioapatite. Moreover, abundant resources and diverse synthesis methods make hydroxyapatite easy to produce. The application in 3D print-based network engineering is also being intensively explored due to the flexibility of the hydroxyapatite scaffold fabrication process. In this review, various hydroxyapatite from natural sources, synthesis methods, hydroxyapatite-based 3D print filament fabrication techniques, and fillers used in the production of filaments are discussed.**

***Keywords*—3D print filament, Filler, Hydroxyapatite, Natural resources, Synthesis**

I. INTRODUCTION

Biomaterials are synthetic or natural materials used to replace or support tissues or structures in the human body [1–2]. Based on their material properties, biomaterials are divided into biopolymers, bioceramics, and biocomposites [3–6]. Biomaterials have diverse chemical, physical, mechanical, and structural properties and allow them to be applied in a variety of biomedical fields depending on their characteristics and biocompatibility [2].

Bioceramics is one of the materials that have been widely used in biomedical applications and have advantages in terms of not causing toxins if applied to the human body [3, 7–10]. In addition, bioceramics are also malleable, have good porosity and compressive strength, and are bioactive [2]. One type of bioceramic that is widely used in biomedical applications is hydroxyapatite (HAp) ($Ca_{10}(PO_4)_6(OH)_2$). HAp is a major inorganic component of bones and teeth, and it has bioactive, inert and nontoxic properties [11]. Because of its advantages, HAp is widely used in applying metal bone implant coating materials, orthopedics, and odontology [12].

HAp can be synthesized using natural sources, especially from animals such as crab shells, fish bones, eggshells, and shell shells. These sources have the potential to be a source of HAp because they are rich in calcium or calcium precursors and enormous numbers as waste. HAp can be synthesized using various methods such as chemical precipitation, hydrothermal, electro spraying, microwave irradiation, self-propagating combustion, emulsion and microemulsion, surfactant-assisted precipitation, chemical vapor, flux cooling, electrospinning, sol-gel method, homogeneous precipitation method, wet precipitation method, solid-state, alkaline hydrothermal hydrolysis, alkaline hydrolysis, and pyrolysis. The different methods used produce distinct characteristics of the resulting HAp.

Nowadays, 3D printed materials based on HAp is intensively carried out. HAp must be fabricated into a filament before printing 3D. Methods used in printing HAp filament 3D print include inkjet-based 3D printing, stereolithography-based 3D printing, and extrusion-based 3D printing. In producing 3D printed materials, HAp can be combined with different fillers to improve the physical, chemical, biocompatibility, and mechanical properties of its filaments. Such fillers employed include polylactic acid, poly-ε-caprolactone nanocomposites, polymethyl methacrylate nanocomposite, polyvinyl alcohol nanocomposite, and β-tricalcium phosphate (BCP). This review provides an in-depth study of the HAp synthesis process from natural sources, synthesis methods, HAp-based 3D printing filament fabrication techniques, and fillers used to produce HAp-based 3D print filaments.

II. DISCUSSION

II.1 HAp from Natural Resources

(1). Crab Shell

Crab shell is one of the natural sources for HAp synthesis with high calcium content and exists in large amounts as waste. Based on research conducted by Cahyaningrum et al.[13] the species Scylla Serrata contains about 53-78% of calcium carbonate ($CaCO_3$) from its crab shells' dry weight. Rizkayanti et al. also reported that the waste of Portunus Pelagicus crab shells contains 66.62% of calcium, a good precursor for synthesizing HAp [14].

Cahyaningrum et al. reported the synthesis of [15] HAp from *Scylla Serrata* crab shells using wise drop and single drop methods of phosphate. The HAp synthesized using the wise drop method has a HAp phase of 87.37% and the single drop method has a phase of 62.3% which is by the ISO-13779: 2008 standards of 50%. Based on surface area analysis, it is found that wise drop HAp has a smaller pore size than single drop HAp which causes the volume of HAp wise drop pore to be greater than the volume of HAp single drop pore.

Rizkayanti et al. [14] investigated the synthesis of HAp using crab shells by wet chemical precipitation method with various temperatures obtained that HAp synthesized at 80^{o}C has the nearest lattice parameters with Ca/P parameter of 1.66.

(2). Fish Bone

Research conducted by Mustafa et al. [16] on the synthesis of HAp using tilapia fish bones and spines with various calcination temperatures from 800-1000 ^{o}C. They

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obtained the optimum Ca/P ratio of 1.699 calcined at 900 ^{o}C which is very close to the theoretical Ca/P value of 1.67. Anggresani et al. [17] reported the synthesis of HAp using mackerel bones using the dry precipitation method and phosphate precursor. The result obtained the best Ca/P ratio of 1.67 at 900 ^{o}C calcined temperature and pH 12.

Pal et al. [18], reported HAp synthesis using *Latest calcarifer* fish bones by calcination in various temperatures of 200-1200 ^{o}C. The degree of crystallinity and HAp crystals size increased with increasing calcination temperature, and the Ca/P ratio is also close to the stoichiometric HAp ratio. In vitro testing also confirmed that the resulting HAp was non-cytotoxic. Hasan et al. [19] also conducted another study on the synthesis of nano HAp using *Ambygaster sirm* fish bones by calcination at 600-1000 ^{o}C. The yield of HAp product is in the range of 50-53% and a spherical morphological shape with an agglomerate structure was obtained. HAp forms are the crucial factors that influenced the final properties, performance, and compatibility of the resulting HAp.

(3). Egg Shell

Based on research conducted by Faridi et al. [20], eggshell waste is one of the biggest sources of HAp due to its abundant amount. As many as 250,000 tons of eggshell waste are generated annually worldwide. Moreover, the eggshell shell contains 94% calcium carbonate (CaCO3), representing-11% of the egg mass [21]. Before used, the egshell waste must be washed with distilled water and boiled or soaked with boiling water. After the washing process, the eggshells are dried using atmospheric air or an oven at a certain temperature [21–24].

In research conducted by Gergely et al. [22] eggshells were calcined at 900 ℃ to synthesize calcium phosphate powder, reduced its size using ball mill then reacted with phosphoric acid isothermally. The HAP product showed nano-sizes and homogeneity of HAp increased. Another study conducted by Mohd Pu'ad et al [24] on the synthesis of HAp from eggshells using a combination chemical precipitation method showed that at 700 ^{o}C the Ca/P ratio of HAp reach 1.67. Goh et al. [21] investigated the influence of pH on the properties of HAp using wet chemical methods by microwave irradiation. HAp width of 10-15 nm and length of 60-80 nm is obtained at pH 10. A rounded particle shape and Ca/P ratio of 1.67 are also reported.

(4). Clam Shell

Khiri et al. [25] have reported the synthesized HAp from *Ark Clam Shell*, which contains calcium and calcium precursors of 98-99%. The synthesis of HAp based on Ark Clam Shell was conducted using the wet chemical precipitation method with various sintering temperatures of 200-1200 ^{o}C. The result showed that the optimum Ca/P ratio was obtained at 1200 ^{o}C. An increase in sintering temperature decreases the density resulting from reducing HAp porosity. Another study was conducted by Syafaat et al. [26], on the synthesis of HAp from *Amusium Peuronectes shell* extract using a precipitation temperature of 1050 ^{o}C. The lattice parameters and density results are close to the theoretical values. In addition, HAp crystal sizes range from 79,750 ± 0.066 to 90.932 ± 0.071 nm and a Ca/P ratio of 1.67. Sari et al. [27], also investigated the synthesis and characterization of HAp from Perna Viridis shells using precipitation methods at various calcination temperatures of 650, 750, 850, and 950 ^{o}C. Based on the study, HAp synthesized from Perna Viridis shells showed a crystal size of (82.5±5.3) nm, microstrain 0.0061, lattice parameters 8.66Å and x-ray density of 10.27 g/cm^{3}. In addition, HAp with a ratio of Ca / P of 1.67 was obtained at 60 minutes of stirring time. The comparison of the natural resources used against the hydroxyapatite produced can be seen in Table 1. Based on Table 1 the use of natural resources as raw material for HAp depends on the amounts of natural resources in an area. In addition, the characteristics of the HAp produced vary according to the type of method used.

TABLE 1.
COMPARISON OF NATURAL RESOURCES AND PRODUCED HYDROXYAPATITE

Resource	Method	Size	Mophology	Ca/P Ratio	Ref.
Green Mussel Sheells (*Perna viridis*)	Precipitation	82.5±5.3 nm	Plate/ Irreguler	1.67	[27]
Asian Moon Scallop *(Amusium pleuronectes*)	Precipitation	87.198 ± 0.091 nm	Round/Elongated	1.67	[26]
Crabs shells (*Scylla serrata*)	Wise and single drop	-	Circular	1.67	[15]
Rajungan shells	Precipitation	53.43-71.27 nm	-	1.66	[14]
Ark Clam Shell (*Anadara granosa*)	Precipitation	35-69 nm	Granular	1.67	[25]
Eggshells	Mechano-chemical	100 nm	Grain Sticked	1.67	[21]
Sardinella (*Amblygaster sirm*)	Calcination	<100 μm	Spherical	1.64	[19]
Lates calcarifer	Calcination	55 μm	Irregular	1.62	[18]
Tenggiri Fish Bones	Calcination	0.1-0.3 μm	Granular	1.67	[17]

II. 2 HAp Synthesis Method Using Natural Source

(1). Dry Method

The dry method is a synthesis method of HAp without using solvents. In its application, the dry method does not require precise control of process parameters because it does not greatly affect the characteristics of the resulting powder. In this process, the diffusion coefficient of HAp obtained is low and relatively cheap [28–29].

(a). Solid State Method

A solid-state reaction is a reaction of decomposing solid mixed reactants to produce solids and gases by heating [30]. In the method solid-state, chemical precursors with calcium and phosphate content are calcined and ground to

obtain HAp [31]. Products with Stoichiometric and crystalized can be obtained by synthesis of solid states, but elevated temperatures and long heat treatment times are required [32].

This method is simple and cheap for mass scale HAp production [33]. Pramanik et al. [34] reported that the precursor's calcium (CaO) and phosphate (P_2O_5) combined chemically to form the hexagonal structure of HAp [34]. A recent study reported that producing nano-sized HAp can be controlled by applying heating or cooling and surfactants in pretreatment processes [32].

(b). Mechanochemical Method

Mechanochemical is a method that uses a ball mill or planetary mill to exert pressure, shear, or friction to increase temperature and pressure, thereby increasing diffusion during the process. Mechanochemical methods are usually carried out in sealed containers made of stainless steel materials, agate, zirconia etc, to control the air because this process is moisture sensitive [31]. Fathi and Zahrani [35–36] have synthesized fluoridated HAp using mechanochemical methods in a high-energy planetary mill with zirconia balls in mixing calcium hydroxide ($Ca(OH)_2$), phosphorus pentoxide (P_2O_5) and calcium fluoride (CaF2) in various milling times at a constant ball-powder weight ratio (35:1) of 300 rpm. This study produced fluorapatite with high purity and nano size. Shu et al. [37] investigated the synthesis of HAp using a planetary ball mill containing 150 g zirconia balls to grind urea, dicalcium phosphate dihydrate ($CaHPO_4).{}_2H_2O$), and calcium carbonate. They reported that after 24 hours of grinding the size of HAp was 50–150 nm in length and 8 nm in width. Moreover, the crystallinity of HAp decreased due to the formation of carbonated HAp [37].

(2). Wet Method

The wet method is a method of synthesis of HAp by using a water solution during the synthesis process. Some wet methods include chemical precipitation, hydrothermal, and hydrolysis. Wet methods have advantages in easy control of the average size of powder and morphology. However, lack of its low crystallinity due to the low-temperature process [32]. The wet method uses various temperatures, precursors, and types of solvents. Wet methods were employed to obtain regular morphological and nanometric structures biomineralisation processes in vivo [38–39]. The simple process of the wet method makes it possible to set the right parameters to control the growth of crystals so that the resulting product is more homogeneous and different CaP phases are obtained [28].

(a). Chemical Precipitation

The chemical precipitation method is a widely used technique in the synthesis process of HAp because of its low cost. In the process of synthesis of HAp using the chemical precipitation method aqueous solution is used and a chemical reaction occurred between calcium and phosphorus ions at controlled temperature and pH. In addition, the neutralization reaction is the most widely used to remove water as a by-product. The HAp powder is calcined at 400-600 °C, to obtain a stoichiometric apatite structure [40–43]. Temperature, the reagent addition rate, calcination, pH, and purity of reagents affect morphological properties (shape and size), stoichiometry, specific surface area and degree of crystallinity of the HAp synthesized through chemical precipitation. The slow addition of phosphate ions provides a lower nucleation rate and a higher rate of crystal growth, leading to larger particles [31]. Yelten and Yilmaz et al. [44], employed this chemical precipitation method to synthesise HAp by varying three process parameters, such as reaction temperature (30, 50 and 85), acid addition rate (slow and fast acid addition rate) and heat treatment temperature (950 and 1250). The results showed that in all parameters the spherical morphology of HAp had been successfully obtained. XRD results showed that heat treatment at 1250 produced peak-forming that showed more crystal structure compared to heat treatment at 950. Next, Afshar et al. also use calcium hydroxide and phosphoric acid to synthesize HAp using chemical deposition methods. SEM micrographs show that a rod-like HAp with a lateral size of about 200 nm and a diameter of 50 nm is produced [45].

(b). Hydrothermal

In the hydrothermal method, aqueous media is placed under conditions above the environment pressure and temperature [46] for stimulating reactions of solutions containing calcium and phosphate precursors. High temperature and pressure increase the reactivity of chemical reactions and condensation effect to promote nucleus formation of HAp with high crystallinity [47]. Hoai et al. [48] and Ortiz et al. [49] investigated the HAp synthesis with various hexamethylenetetramine (HMTA) and cetyltrimethylammonium bromide (CTAB) concentrations, and cooling rates. It was reported that rapid cooling produces a smaller average particle size of HAp. Moreover, a higher concentration of additives increases the average size of HAp particles. In addition, Hoai et al. [48] North and Klinkaewnarong synthesize nanometric HAp through a sonochemical process (20 kHz) at 25 and various irradiation times, followed by calcination at 600 °C [50]. A smaller diameter is obtained for 20 minutes of ultrasonic irradiation with Ca/P ratio of 1.5. The synthesis of HAp by emulsions allows for control of particle size and morphology due to the agglomeration is limited [51–53]. This synthesis can be done in water emulsions in oil, oil in water, and double emulsions of water-oil-water by various surfactants. Amin et al. [51–53] successfully synthesize HAp nanocrystalline with a reverse microemulsion technique. Morphology and size of HAp can be controlled, and minimize HAp transformation [53] could be minimized. Ma et al. also [51] successfully synthesized nano spherical HAp in water-in-oil microemulsion at room temperature in a short period with a round and uniform size.

(c). Hydrolysis

Hydrolysis is a diffusion of hydrogen and hydroxide ions by water ionization to form a non-stoichiometric HAp [54]. Mechay et al. [55], have investigated the HAp synthesized using polyol media (propanediol and ethylene glycol) in the hydrolysis of calcium nitrate and diammonium phosphate. HAp formed needles and plates structured with 140-180 nm length and 60-80 nm widths with a similar thickness (15-20 nm) in both solvents. Wang et al. [56] used different concentrations of alcohol solvents from 0 to 90% to hydrolyze the calcium hydrogen phosphate dihydrate (DCPD) into HAp at a temperature of 75 for 1 hour. It was found that the size of HAp crystals was influenced by alcohol concentration. For the concentration range of 0 to 70%, the higher the alcohol

concentration, the lower crystallinity. Moreover, for concentrations of 70 to 90%, crystallinity tends to increase with increased concentration.

(d). Sol-Gel

The sol-gel process produces HAp of various sizes ranging from nanoscale to microscale and has a high degree of flexibility. In the gel sole technique, monomers are converted into soles (solid particle colloidal suspensions) that act as precursors of the solid phase of the 3D network. Several precursors can be employed in this process such as calcium dioxide or calcium nitrate reacted with triethyl phosphite or triethyl phosphate in aqueous or organic solutions [55–57]. It was reported that low temperature and pH produced a high degree of homogeneity and purity HAp [58]. However, this method has a drawback in terms of its high cost and inconsistent productivity [59].

In the sol-gel method, removal of organic waste and the excess solvent is required for the development of crystal structures, moreover, the crystallinity of the product can be adjusted by varying Ca/P ratio [60]. The comparison of the methods used against the hydroxyapatite produced can be seen in Table 2. Based on Table 2. precipitation is a frequently used method and the best method than the other method because producing high crystallinity of HAp, short processing time and low cost.

TABLE 2.
COMPARISON OF SYNTHESIS METHODS AND PRODUCED HYDROXYAPATITE

	Method	Degree of Crystallinity	Size	Morphology	Processing Time	Temp (℃)	Ref.
Dry	Solid State	High	5-70 nm	Spherical	< 24 h	100-1100	[34]
	Mechanochemical	Low	Length 50-150 nm and width ~8 nm	Nanofibers	24 h	50-1460	[37]
Wet	Chemical Precipitation	High	59.06 nm	Hexagonal-dipyramidal	< 24 h	1200	[45]
	Hydrothermal	Low	8-50 nm	Nanoplate	< 24 h	25-70	[50]
	Hydrolisis	High	21-24 nm	Needle to very thin platelet	> 24 h	950	[56]
	Sol Gel	High	-	Plate like grain	< 24 h	500-700	[57]

II.3 HAP-Based 3D Printing Technology

The 3D printing process is a printing process using deposition layers of biomaterials that occur with or without encapsulation cells. There are several series of processes in 3D printing including the preparation phase, printing phase, and post-handling phase. Among them, several methods are often used such as inkjet-based 3D printing processes [61], stereolithography-based 3D printing (SLA), extrusion-based 3D printing techniques [62−63], and 3D printing techniques used in HAP-based composite fabrication.

(1). Inkjet-Based 3D Printing

Inkjet-based 3D printing is commonly known for continuous inkjet printing and drop-on-demand inkjet printing. There are two different mechanisms in the inkjet-based 3D printing process [61]: continuous inkjet printing and drop-on-demand inkjet printing [64]. The drop-on-demand inkjet printing process is divided into two methods, i.e., thermal and piezoelectric drop-on-demand inkjet printing methods which are used to create pressure pulses and encourage the formation and release of droplets [65]

The study of inkjet-based 3D printing techniques has been widely reported by several researchers. For example. Zhu et al. [66] use inkjet-based 3D printing techniques to synthesize $CaSO_4$/HAP/β-TCP (β-tricalcium phosphate) nanocomposites as scaffold bone tissue engineering. Other studies have shown that an increased CaP/CaSO4 ratio significantly influences compressive strength. Moreover, the physicochemical properties of HAP/CaSO4 ink powder are shown better than those of β-TCP/CaSO4 powder [67]. Studies conducted Strobel et al. [68] on indirect 3D printing of the powder with 35 wt.% HA, 35 wt.% β-TCP, and 30 wt.% of the modified potato starch powder produce porous biphasic calcium phosphate (BCP).

(2). Stereolithography (SLA)-Based 3D Printing

In the context of the SLA-based 3D printing technique, ultraviolet (UV) ray is used to harden the photopolymer resin selectively. When this is carried out, it further can facilitate the 3D model's construction in layers. SLA-based 3D printing has many advantages compared to inkjet-based printing including high printing speed, high resolution, and reproducibility [69]. In this technique, the light pattern will be controlled using a digital mirror array, thus facilitating the selective cross-linking process in the one-layer pre-polymer solution. SLA-based printing can further ensure high cell viability because there is no application of external force to the cells during the printing process [70]. In this case, either UV or near-UV blue light (405 nm) rays are used in SLA-based 3D printing systems [71].

Several previous studies have extensively explored SLA-based 3D printing techniques. One of the studies is the research conducted by Barry et al. [72], HAP-based oligocarbonate dimethacrylate (OCM-2) composite scaffold which was produced using UV rays [72]. In the research, visible light can reduce the potential risk of carcinogenesis compared to UV or near-UV light, so that the printed tissue scaffold has higher cell viability. Furthermore, Woesz et al. [73] demonstrated the use of a printing system using visible light. The process of fabricating a micropore HAP scaffold using the SLA approach with visible light, resulted in a strut size scaffold of 450 m, with designed and fully interconnected macroporosity [73]. In addition, Le Guéhennec et al. [74] have also applied the SLA technique in 3D printing. In this case, the process of HAP composites 3D printing using the SLA technique is limited by several factors including the

trapping of monomers and unreacted residues as well as the use of photoinitiators and radicals that can compromise the integrity of bone matrix synthesis and increase the cytotoxicity risk [74].

(3). Extrusion-Based 3D Printing

The principle of extrusion-based 3D printing depends on the extrusion of the material using an extruder through mechanical or electromagnetic actuators to create 3D objects [69, 75]. In this case, Derakhshanfar et al. [76] stated that extrusion-based 3D printing techniques are characterized by different extrusion systems and can be grouped into three including pneumatic, piston, and screw pressure systems. Extrusion-based 3D printing owns many advantages, such as high cell seeding density, high printing speed, and scalability. Such printing techniques can also be applied in continuous cylindrical filament printing using various types of inks [77]. The extrusion-based process itself includes direct ink writing (DIW, also called robocasting) and fused deposition modelling (FDM) in which the raw material will be released through a nozzle [78]. The FDM process relies on the heating of the material (polymer and ceramic-polymer composite) before being released from the nozzle, and by moving the nozzle, the material is deposited on the substrate, layer by layer [79]. The moulded construction produced is further heated to remove the binder and solidify the ceramic [80]. Related to this, Michna et al. [81] have used an extrusion-based 3D printing technique in the fabrication of HAp scaffolds by applying DIW. In the study, the desired characteristics of the moulded HAp scaffold were achieved by adjusting the scaffold architecture and sintering conditions [81]. In addition, Sun et al. [82] also utilized the DIW technique in applying silk fibroin ink impregnated with HAp nanoparticles, to 3D print a scaffold characterized by gradient pore spacing, ranging from 200 to 750 m via the DIW technique [82]. On the other hand, Khodaei et al. [83] carried out an FDM-based approach to making porous poly-lactic acid sacs. The study shows that the modulus of elasticity and strength of the porous polymer scaffold can be similar to the surrounding tissue. The polymers containing 29%, 49%, and 69% porosity in this study had elastic coefficients of 502.7, 537.7, and 483.3 MPa, respectively [83].

II. 4 Filler in 3D Printing Filament Synthesis

(1). Poly (Lactic Acid)

Poly (lactic acid) (PLA) is a non-toxic thermoplastic polymer produced by ring-opening polymerization of lactide and can be collected from fermented sugar feedstocks [84]. PLA has a linear aliphatic structure, causing it to have interesting biodegradability, good biocompatibility, and excellent mechanical properties [85]. In addition, changes conducted on the ratio of D- to L-isomers can be utilized to modify the properties of PLA. Therefore, PLA is widely used as a matrix for building biodegradable composites for bone repair [86–87], and bone fixation devices that are applied in orthopedics and oral surgery [88]. However, the unpredictable hydrolysis process and poor hydrophilicity further limit the range of PLA applications [89]. Such a problem can be overcome by binding bioactive ceramics such as HAp with PLA [90–91]. HAp/PLA composites are considered potential biomaterials for bone repair and replacement since the degradation rate of PLA can be slowed by the dispersion of HAp nanoparticles. Meanwhile, its mechanical properties can also be improved by expanding the distribution of HAp nanoparticles [92]. Furthermore, the porous HAp /PLA scaffold can be printed using extrusion 3D printing for load-bearing bone tissue applications with the compression strength of the printed construction can be adjusted using element model and simulation. According to Mondal et al. [93], in vitro results showed that the HAp/PLA scaffold cells had better adhesion and proliferation than the PLA scaffold [93]. In addition, another research carried out by Esposito Corcione et al. [94] fabricating HAp/scaffold PLA microspheres through FDM. This research revealed that the HAp/PPLA scaffold had higher porosity and a rougher surface than the PLA-based scaffold. However, the mechanical performance of the HAp/PLA scaffold tends to decrease [94]. Different from PLA, poly-L-lactic acid (PLLA) has slower degradation, which is believed to result in a lower rate of inflammatory tissue reaction [95].

(2). Poly-ε-Caprolactone Nanocomposites

Poly-ε-caprolactone (PCL) is generally used as a synthetic biomaterial for bone tissue and periodontal applications because of its biocompatibility, suitability for various scaffold fabrication techniques, and mechanical stability. However, due to the slow rate of PCL degradation, PCL scaffolds can affect bone regeneration [96]. In this case, these deficiencies can be solved through an effort of modifying the addition of HAp material, so that the resulting bone volume and bone contour can be maintained from time to time after implantation. PCL-based scaffolds can be easily fabricated via 3D printing due to their good printability and fast solidification after extrusion [96]. Hu et al. [97] further reported that fabricated HAp/PCL scaffolds can be adjusted through 3D printing to obtain a hierarchical porous structure and multi-functional performance. On the other hand, Xu et al. [98] fabricated HAp/PCL scaffolds using the SLS technique. The moulded scaffold has a porosity ranging from 78.54% to 70.31%, and the suitable compressive strength ranges from 1.38 to 3.17 MPa.

(3). Polymethyl Methacrylate

Polymethyl methacrylate (PMMA) is a synthetic polymer extensively applied in ophthalmic, orthopaedics, and dental applications [99]. PMMA is also applied as bone cement in various shapes or sizes, so it can be used in the treatment of bone tumors and birth defects of the skeletal system [99]. Petersmann et al. [100] printed a honeycomb structured-PMMA Scaffold using fusion filament fabrication (FFF, one of the extrusion-based 3D printing techniques) for skull implants. In this case, the Scaffold properties can be improved by topological optimization. However, PMMA has some disadvantages, such as brittleness and heat release during the polymerization process, which can cause necrosis at the bone cement interface. Therefore, further modification of PMMA is needed to improve its formation and voltage shielding [101]. Another research carried out by Tontowi et al. [101], further revealed that PMMA powder was mixed with liquid methyl methacrylate (MMA) to first obtain PMMA paste, thus the PMMA paste composited with HAP nano powder can be applied for 3D printing.

Increasing the PMMA content can increase the solidification time, yet it can also decrease the tensile strength of the HAP/PMMA composite due to the addition of HAP [101]. In addition, Lal et al. [102] fabricated the HAP/PMMA scaffold using FDM technology for cranioplasty applications, especially for large skull defects. The result obtained is that the scaffold used tends to be more economical, compared to traditional titanium and polyether ether ketone (PEEK) cranioplasty [102].

(4). Polyvinyl Alcohol Nanocomposite

Polyvinyl alcohol (PVA) is a water-soluble thermoplastic usually used as a backing material for 3D printing. It has good biocompatibility, high water solubility, and chemical resistance, causing the PVA often used in medical devices [103]. PVA is widely used in tissue engineering cartilage because of its tensile strength similar to that of human articular cartilage [104–106]. However, PVA is non-degradable, causing its limited application as implantation sacs in the body [107]. The composition of PVA with calcium phosphate nanoparticles, such as HAP and BCP, shows promising applications for the manufacture of scaffolds in bone tissue engineering [108]. Several studies have ensured that an osteoconductive HAP/PVA scaffold can be achieved for bone replacement [109]. In addition, Chai et al. [110] fabricated a HAP/PVA scaffold through powder-based 3D printing, obtaining that the scaffold printed with PVA 1.0 wt.% had the best compressive strength. Furthermore, the printed HAP/PVA processes excellent cytocompatibility; the comprehensive performance of the HAP/PVA scaffold was better and much more suitable as a bone scaffold than the HAP/polyvinyl pyrrolidone (PVP) and HAP/polyacrylamide (PAM) scaffolds produced with the same approach [111]. Another study [112] further revealed that the porous structure of the HAP/PVA scaffold, such as the pore size, can be adjusted by adjusting the HAP content in the HAP/PVA bio-ink before the printing. The results revealed that the HAP/PVA bio-ink [108] with the weight of 15% HAP shows significantly superior features for extrusion printing, with the modulus of elasticity of the imprinted scaffold similar to that of natural bone.

(5). β-Tricalsium Phosphate (BCP)

β-tricalsium phosphate (β-TCP) has low mechanical strength and degrades too rapidly in physiological environments. However, such property can be changed/improved through its combination with HAP [68, 74]. BCP has been used to make bone graft material for 30 years; BCP-based ceramics have proven efficacy in clinical indications [113]. Although there are many 3D printing approaches can be used to fabricate complex BCP-based ceramics, including inkjet printing, SLA, selective laser sintering, and DLP, the performance of BCP and BCP-based ceramics and their printing properties need to be further improved [114]. In the previous research done by Huang et al. [115] porous BCP ceramics were fabricated using extrusion-based 3D printing with a motor-assisted micro-injection (MAM) system; The morphology, pore size, and porosity of the printed BCP scaffolds can be properly controlled to optimize its mechanical properties. Furthermore, in the research carried out by Wang et al. BCP scaffolds were printed using inkjet 3D printing; in this case, PVA solutions of 0.6 and 0.25 of Tween 80 were used as binders to make BCP bio-ink. In this case, BCP scaffold printed with a mass ratio of HA/β-TCP at 60:40 showed the best biocompatibility [116]. The comparison of the type of composite filler used against the hydroxyapatite particle size, modulus young, and surface can be seen in Table 3.

TABLE 3.
COMPARISON FILLER IN 3D PRINTING FILAMENT

Type of Composite Filler	Application of Composite Filler	Parameter				Ref
		Particle Size	Modulus Young	Surface Area	Strength	
Carbon fiber-SiC nanowire hydroxyapatite pyrolytic carbon composites (CHS)	Bone implant	-	7.2 Gpa	-	127 Mpa (flexural strength), 90 Mpa (shear strength)	[117]
Biodegradable poly(L lactide)/hydroxyapatite	Bone Tissue Engineering	-	90 Mpa	-	140 MPa (Flexural Strength)	[118]
Hydroxyapatite (HA)/collagen composite	Bone Tissue Engineering	-	19-360 Mpa	47.4 m^2/m^3	3-22 Mpa	[119]
g-HAp/PLLA	Bone Fracture Fixation	-	-	-	24.40-58.14 MPa	[120]
Biopolymeric aerogel matrices and inorganic nano-hydroxyapatite (n-HA)	Bone Tissue Engineering	-	-	-	7.72 MPa (Tensile strength) 26.92 MPa (bending strengths)	[121]
Spray-dried hydroxyapatite (HA)-reinforced polyethylene (PE)	Bone Augmentation	3.80 mm	3.87 ± 0.21 Gpa	13.536 $m^2 g^{-1}$	23.16 ± 0.40 MPa (Tensile Strength)	[122]
Hydroxyapatite (HAp), and/or barium titanate (BaTiO3—BT)	Bioscaffold	<2 µm	1.2 ± 0.2 2.2± 0.1 Gpa	had length of 138.1 ± 16.4 nm and a width of 14.8 ± 2.2 nm	41.7 ± 3.7-57.2 ± 6.2 MPa (Tensile Strength)	[123]

Hydroxyapatite/agarose powders (HAp)/SAS	Bone Filler and Drug Delivery	300 nm	-	47.8±0.2 m^2/g	-	[124]
PLA/HA-g-PLA	Spinal implants	6-25 nm	3.4-4.3 GPa	13 - 204 nm^2	43-78 MPa (Tensile Strength) 69-108 MPa (Flexural Strength)	[125]

III. CONCLUSION

Based on the review that has been done, it is known that the differences in natural resources and the methods used will result in different specifications of Hydroxyapatite in terms of physical and chemical properties. This occurs due to differences in operating process conditions of Hydroxyapatite synthesis. In addition, details were also carried out on different Hydroxyapatite-based 3D printing for the fabrication process. A review related to 3D printing techniques and Hydroxyapatite-based materials is expected to improve strategies for producing functional tissue and improvements in the medical field.

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