



A comprehensive review of biodegradable synthetic polymer-ceramic composites and their manufacture for biomedical applications

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ABSTRACT

The application of various materials in biomedical procedures has recently experienced rapid growth. One area that is currently receiving significant attention from the scientific community is the treatment of a number of different types of bone-related diseases and disorders by using biodegradable polymer-ceramic composites. Biomaterials, the most common materials used to repair or replace damaged parts of the human body, can be categorized into three major groups: metals, ceramics, and polymers. Composites can be manufactured by combining two or more materials to achieve enhanced biocompatibility and biomechanical properties for specific applications. Biomaterials must display suitable properties for their applications, about strength, durability, and biological influence. Metals and their alloys such as titanium, stainless steel, and cobalt-based alloys have been widely investigated for implant-device applications because of their excellent mechanical properties. However, these materials may also manifest biological issues such as toxicity, poor tissue adhesion and stress shielding effect due to their high elastic modulus. To mitigate these issues, hydroxyapatite (HA) coatings have been used on metals because their chemical composition is similar to that of bone and teeth. Recently, a wide range of synthetic polymers such as poly (L-lactic acid) and poly (L-lactide-co-glycolide) have been studied for different biomedical applications, owing to their promising biocompatibility and biodegradability. This article gives an overview of synthetic polymer-ceramic composites with a particular emphasis on calcium phosphate group and their potential applications in tissue engineering. It is hoped that synthetic polymer-ceramic composites such as PLLA/HA and PCL/HA will provide advantages such as eliminating the stress shielding effect and the consequent need for revision surgery.

1. Introduction

Many clinical applications such as treatments for orthopedic disorders are topics of interest in the field of tissue engineering. Owing to its importance and applications in human life, this area of research has attracted extensive attention from researchers and the field is thus expected to remain active indefinitely.

Bone-related disorders are becoming one of the main worldwide clinical health issues, in particular for the elderly. To repair and treat broken hard tissues, various types of biomaterials and devices have been widely applied in damaged parts of skeletal systems. Biomaterials can be divided into inorganics (metals and ceramics) and organics (polymers). Single-class materials may not be able to satisfy all of the requirements for a given implant application. Therefore, through the combination of two or more classes, composites with multiscale structures and the desired properties for specific applications are achievable.

Metals and alloys such as stainless steels, cobalt-chromium (Co–Cr) alloys, and titanium (Ti) and its alloys play an important role as biomaterials for the fixation or replacement of load-bearing bones that have been damaged. Owing to their favorable properties such as high strength, high ductility, and high fracture toughness, more than 70% of implant devices are made from metallic biomaterials [1]. Although metallic materials possess high mechanical strength, there is still an issue with their biomechanical compatibility due to their higher elastic modulus compared to that of natural bone.

There are many other materials such as polymer-ceramic composites that could also be investigated. In the following sections, each of these classes is discussed, including their advantages and disadvantages.

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Fig. 1. Calcium phosphate-based biomaterials for bone graft applications (Adopted from Ref. [13]).

1.1. Ceramics as biomaterials

As some of the main components of human bone tissue, ceramic-based materials such as calcium phosphate, tricalcium phosphate, tetracalcium phosphate, alumina, silica, and zirconia have been studied for medical applications such as implant devices [2,3]. Because of their biocompatibility and their similar structure to that of natural bone, ceramics are a favorable group of biomaterials.

Ceramic nanobiomaterials, especially, calcium phosphate-based materials have been extensively studied for a broad range of orthopedic and dental applications, including β -tricalcium phosphate (β -TCP) and hydroxyapatite (HAp) [4,5]. Calcium phosphates play an important role in the human body and their degradation and bioactivity depend on the Ca/P ratio. These biomaterials can be used for various biomedical applications in the form of nanoparticles, cement, and coating [6]. The current biomedical applications of calcium phosphate-based materials include bone reconstruction [7], coating of orthopedic implants [8,9], dental applications [10], and drug delivery [11,12]. Fig. 1 shows the various biomedical devices made of calcium orthophosphates bioceramics.

Due to the biological functions and possibility to control the mechanical properties of calcium phosphates, this family of ceramics have attracted much attention for different biomedical applications. Currently, great effort has been made to develop calcium phosphate-polymer composites, in particular, HAp and TCP.

1.1.1. Hydroxyapatite

HA with the chemical formula of $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ as a typical example of calcium phosphates family has been widely used as a bone substitute [14–17]. HAp ceramics with a molar ratio of 1.67 Ca/P are bioactive ceramics that are used as a coating on the surface of various biomaterials [18,19]. However, owing to their brittle nature, they are not suitable to be used in the bulk form or for load-bearing applications [20,21]. To overcome this issue, HAp can be used as thin film coatings on other groups of materials for bone-graft material applications [22,23]. According to previous works, the modification of materials with HAp ceramic coatings can improve the bioactivity, osteoconductivity, osteoinductivity, and resorbability of composite biomaterials [7,24,25]. Meanwhile, HAp can also be used in its fine-powder forms as a filler, for example in tablets and capsules, to make the medicines easier to measure [26]. Fig. 2 illustrates the various sizes and shapes of HA particles.

Extensive attempts have been made to achieve a suitable coating on the surface of different materials such as metals and polymers or to incorporate a new phase in matrix materials by considering their biocompatibility and bioactivity. Polymer matrix composite (PMC) is a material consisting of a polymer (resin) matrix combined with a fibrous

reinforcing dispersed phase. In this regard, HA can be applied as an appropriate choice of coating or filler for the following reasons:

1. It will enhance the biocompatibility of the substrate biomaterials (or matrix biomaterials) owing to its similarity in structure and composition to those of natural bone and teeth [28,29];
2. The incorporation of HA particles into a polymer matrix can improve the degradation rate of the composites, which is attributed to the percentage of HA particles and enhancement of their bioactivity of them [30,31]; and
3. HA can be considered as a promising bone-graft material for creating strong chemical bonding between the implant and host bone tissues.

In conclusion, owing to its similar chemical structure to that of natural bone, along with its bioactivity, osteoconductivity, and osteoinductivity, HA has been successfully applied in biodegradable polymer-based composites and metallic biomaterials [32,33].

1.1.2. Tricalcium phosphate

Tricalcium phosphate (TCP) with three polymorphs including α -TCP, β -TCP, and α' -TCP is another well-known bioceramics for bone repair applications. β -TCP is receiving increasing attention due to its excellent biocompatibility, bioactivity, and bioresorbability [34–37]. Fig. 3 shows porous β -TCP ceramics which polymethylmethacrylate balls are used to obtain various pore sizes.

The mechanical strength of HA is higher than β -TCP [10]. However, β -TCP is more resorbable compared to HA which leads to faster growth of new bone surrounding the implanted scaffolds [38,39]. Other types of bioactive ceramics and their applications are summarized in Table 1.

1.2. Polymers as biomaterials

In recent years, a wide range of polymers have been extensively investigated for bone-tissue engineering applications [54,55]. Biodegradable polymeric materials can be categorized into natural and synthetic polymers. Naturally derived polymers such as collagen (as a biological protein [56]) and gelatin (derived from collagen [57]) have shown problems such as instability, incompatible characteristics, immunogenicity, and poor biodegradability. However, owing to the modifiable properties of most synthetic polymers [58] such as poly(lactic-co-glycolic acid) (PLGA) and polyurethanes (PURs), they offer excellent applicability [59,60]. These biodegradable polymers can be used for wound management, orthopedic devices, dental applications, cardiovascular applications, drug delivery, and tissue engineering. Both natural and synthetic polymers play essential roles in modern medicine [61–64].

Among synthetic polymers, polyesters have attracted more attention than other types of polymers. This group can be categorized into three important classes, as shown in Fig. 4 and the abbreviations for polyesters are listed in Table 2.

Synthetic polymers such as the polylactic acid (PLA), poly-L-lactic acid (PLLA), PLGA, polyether ether ketone (PEEK), and polymethyl methacrylate (PMMA) are the most frequently employed polymers for medical applications owing to their favorable properties [59,66,67].

PLA can be considered as one of the best options for many biomedical applications, owing to its biocompatibility with host tissue without the need for a second surgery, along with its ease of manufacturing, hydrophobic nature, and biodegradability [68–72]. PLA is a biodegradable thermoplastic polymer that is derived from renewable resources such as corn starch and sugar cane. It is available in various types, including PLLA, poly-D-lactic acid (PDLA), and poly-DL-lactic acid (PDLLA), which can be used for different purposes such as in fabricating screws, pins, rods, and plates. PLA is a semi-crystalline polymer with a slow rate of crystallisation [73,74].

Applications of polymers in soft tissues (e.g., skin, muscle, tendons,

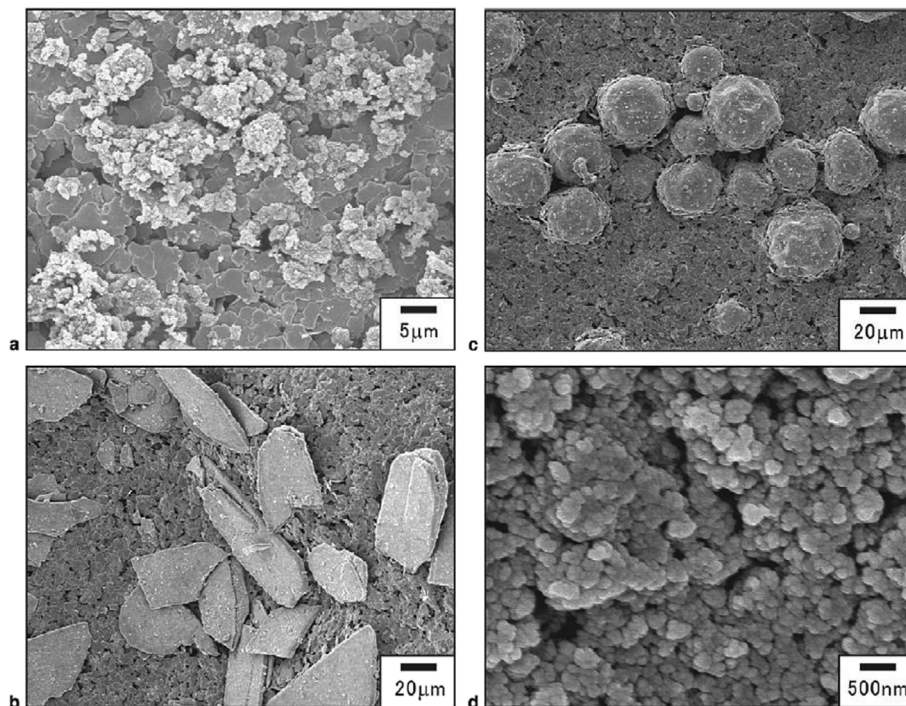


Fig. 2. SEM micrographs of HA particles with different sizes and shapes: a) microscale, b) plate, c) spherical, d) nanoscale (Adapted from Ref. [27]).

and ligaments) and hard tissues (e.g., bone, cartilage, and tendon) depend on the functions of the damaged parts in the human body [75–77].

Table 3 lists the physical and mechanical properties of conventional polymers that have been studied in recent years.

Another synthetic biopolymer which has been the focus of much attention is PLGA. PLGA is a biodegradable polymer that shows great potential to be used for these purposes owing to its safety, desirable mechanical properties, great cell adhesion, and controllable degradation rate [79]. PLGA is known as a random ring-opening copolymerization of PLA and PGA. In this regard, through the variation of the percentage of these two polymers, the degradation rate of PLGA products is controllable. Therefore, PLGA is preferred compared to PGA

and could be used in various biomedical applications such as sutures and cancer drug delivery systems [80,81]. When the implants are made from PLGA, the rate of bone healing and growing has demonstrated a great acceleration [82]. Fig. 5 shows the chemical structure of PLGA and its monomers.

1.3. Polymer/ceramic composite biomaterials

Polymer-ceramic composites such as PLLA/HA can be an appropriate choice for non-load-bearing applications that require a high rate of degradation [8].

According to previous work [83], the addition of HA particles to

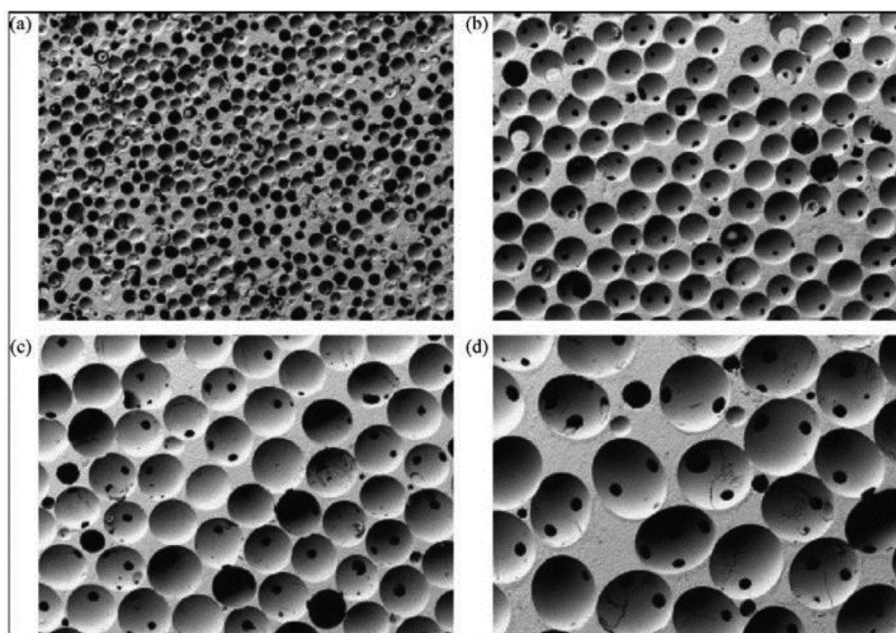


Fig. 3. Porous β -TCP with different pore sizes: (a) 100–200 μm , (b) 300–400 μm , (c) 500–600 μm , and (d) 700–800 μm (Adopted from Ref. [13]).

Table 1
Biomedical applications of various ceramics.

Ceramics	Applications	Ref.
Calcium sulphate and carbonate	Bone defects filler, orthopedics and dentistry	[40,41]
Alumina ceramics	Dentistry, arthroplasty, antimicrobial activities	[42–44]
Zirconia ceramics	Dentistry, HA stabilizer, metallic implants coating	[45]
Bioactive glass ceramics	Replacing a vertebral body, material coatings, orthopedic applications	[46]
Silicate bioactive glasses	Bone repairing devices, drug delivery, modifier for synthetic and natural polymers	[47–53]

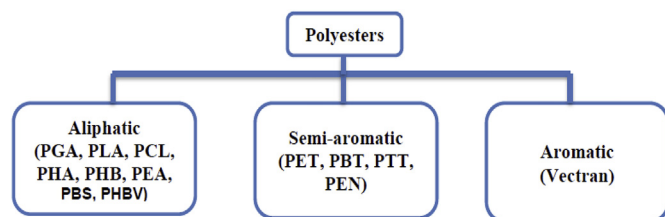


Fig. 4. Three main categories of polyesters (Adapted from Ref. [65]).

Table 2
Abbreviations for polyesters.

Polyester	Abbreviation
Polyglycolide or Polyglycolic acid	PGA
Polylactic acid	PLA
Polycaprolactone	PCL
Polyhydroxyalkanoate	PHA
Polyhydroxybutyrate	PHB
Polyethylene adipate	PEA
Polybutylene succinate	PBS
Poly (3-hydroxybutyrate-co-3-hydroxy valerate)	PHBV
Polyethylene terephthalate	PET
Polybutylene terephthalate	PBT
Polytrimethylene terephthalate	PTT
Polyethylene naphthalate	PEN

polymeric composites increases the glass transition temperature of the polymers without any changes in the crystallinity and melting temperature.

PLA is one of the most well-researched and commonly used polymers for biodegradable medical applications [84–86]. It was granted approval by the United States Food and Drug Administration (FDA) for medical applications in 1996 [87,88]. Monomers of this polymer such as PLLA, PDLA, and PDLA are non-toxic [85]. PLA exhibits high mechanical strength but is brittle with a glass transition temperature of approximately 55 °C [89,90]. Various attempts have been made to improve the processability and flexibility of these polymers. For example, the use of plasticisers and polymer blending are the most frequently used methods for enhancing the flexibility of polymers [91,92].

Owing to the favorable features of PLA such as its biodegradability, biocompatibility, and ease of processing, this polymer offers a wide range of applications for medical science [93–95]. Fig. 6 shows the result of using PLA plates to fix a jaw fracture without the need for further support. According to this research, by improving the mechanical properties of PLA through the control of the copolymer's ratio (L/D), PLA plates could be used to fix the damaged parts without the

Table 3
Physical and mechanical properties of commonly used polymers (Adapted from Ref. [78]).

Polymers	Density, g/cm ³	Tensile strength, MPa	Tensile modulus, GPa	Glass transition temperature, °C	Melting temperature, °C
PLA	1.21–1.25	21–60	0.35–3.5	45–60	150–162
PLLA	1.24–1.30	15.5–150	2.7–4.14	55–65	170–200
PGA	1.50–1.71	60–99.7	6.0–7.0	35–45	220–233
PCL	1.11–1.14	20.7–42	0.21–0.44	(–60)–(–65)	58–65

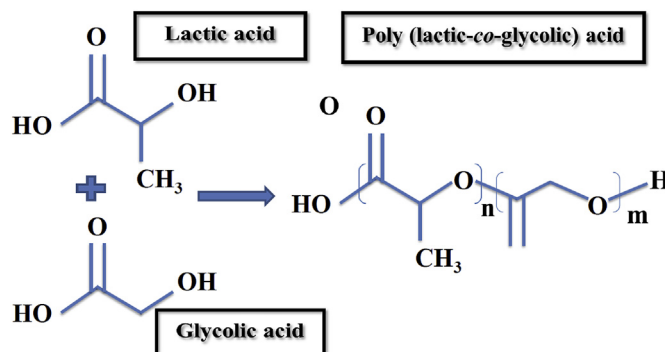


Fig. 5. Chemical structure of PLGA and its monomers (n and m demonstrate the number of repetition of each unit).

need for additional surgery or supports (in this study the D/L ratio was 85/15).

In general, the degradation products of PLA in the human body can cause inflammatory reactions; thus, ceramics have been investigated about incorporation into PLA-based composites to improve their biocompatibility.

PLLA-based composites have been extensively studied as biodegradable materials for biomedical applications such as in bone-fracture fixations; sutures, interference screws, and meniscus repair [98,99]. On the one hand, HA-PLLA composites can solve some problems that have been posed by metallic implants such as stress-shielding and the need for a second surgery [100,101]. On the other hand, further investigation is required to improve the weak bonding between HA and the PLLA surface [32].

PLGA is another favorable synthetic polymer which has a good biodegradability and biocompatibility [102,103]; however, this polymer suffers from poor mechanical properties and bioactivity and may not provide strong osseointegration [103]. To address these issues, using ceramics, in particular, HA as a coating on PLGA is recommended [104,105]. PLGA-based composites have also been frequently studied for biomedical purposes [106]. Porous PLGA-HA composites have been manufactured through different methods as listed in Table 8. Fig. 7 shows the porous scaffolds of neat PLGA and PLGA/nano-HAP scaffolds after removing the excess powder of HA particles which are prepared through selective laser sintering (SLS) [107]. Table 4 lists the mechanical properties of pure PLGA and PLGA/nano-HAP scaffolds with 0–20 wt % HAP particles.

The results of previous investigations have shown that the size and shape of HA particles (micro- or nanoscale; spherical or plate-shaped) have effects on the fracture behaviour of the composites [108–113]. For

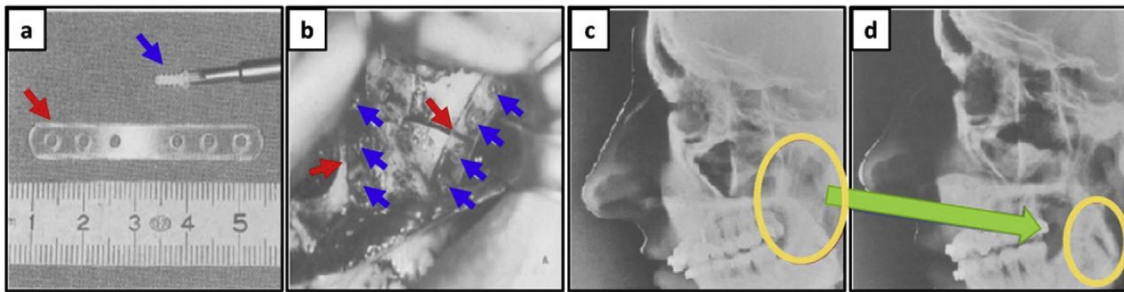


Fig. 6. (a) Screws and plate made of PLA, (b) upper jaw with the plates and screws in situ, (c) and (d) lateral cephalogram, with the screws and plate, taken immediately postoperatively and six weeks postoperatively, respectively. (Adapted from Refs. [96,97]).

instance, the highest critical energy release rate with the most extensive surface roughness is related to the micro-HA-PLLA, whereas these nano-HA-PLLA composites have a brittle fracture surface owing to the nanoscale interactions between PLLA fibrils and primary HA particles [113]. Table 5 lists the physical properties of PLLA and gHA-PLLA composite. Fig. 8 shows the effects of HA on the stress-strain behaviour of the composite. In this study, pure PLLA presented a maximum stress of around 2.8 ± 1.2 MPa and a strain at break of $38 \pm 7\%$. However, the microcomposite samples showed a five-fold decrease in maximum stress down to 0.57 ± 0.2 MPa and an increase in the strain at break up to $41 \pm 8\%$.

2. Manufacturing techniques for polymer-ceramic composite biomaterials

The choice of proper fabrication methods to manufacture composites is one of the most challenging issues in medical science to achieve the desired implants. Traditional fabrication techniques including electrospinning, gas foaming, solvent casting and particulate leaching,

Table 4

Mechanical properties of pure PLGA and PLGA/nano-HAP scaffolds (Adopted from Ref. [107]).

Scaffold	Compressive strength, MPa	Modulus, MPa
PLGA	1.82	22.75
PLGA/nano-HAP	3.28	32.81

Table 5

Physical properties of PLLA and gHA-PLLA (Adapted from Ref. [114]).

Sample	Average fiber diameter, nm	Porosity, %
PLLA	510 ± 150	79 ± 3
gHA-PLLA	440 ± 170	88 ± 5

phase separation, and melt mixing have been widely used to fabricate scaffolds [83,115–119]. Apart from the advantages of all these manufacturing methods, one of their major drawbacks in the manufacturing

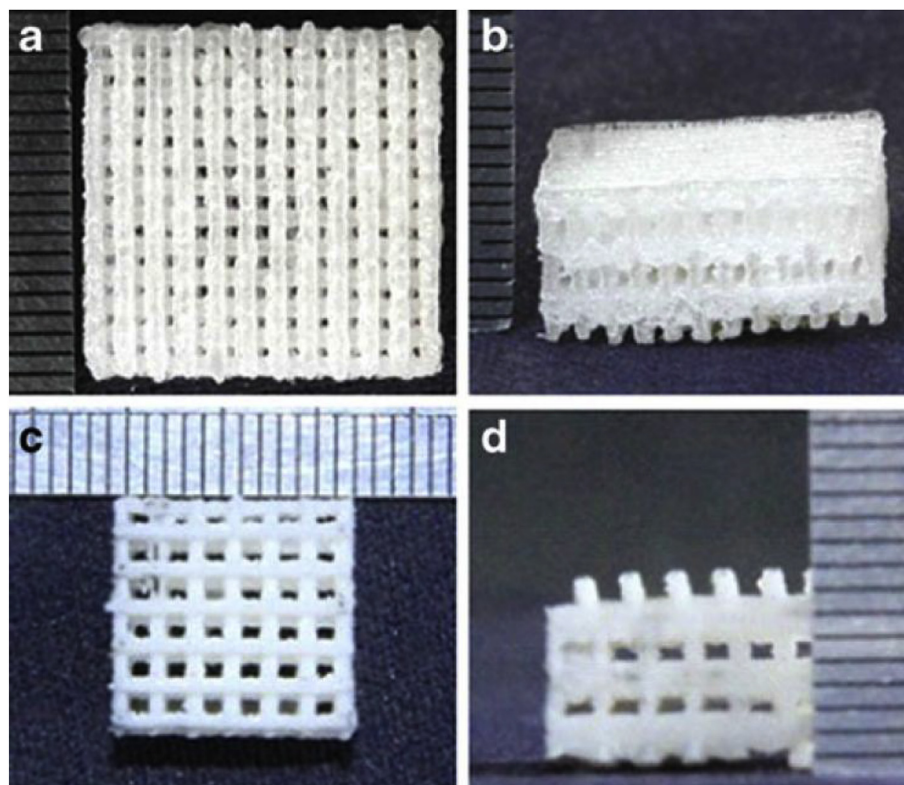


Fig. 7. SEM images of: (a) neat PLGA (top view), (b) neat PLGA (front view), (c) PLGA/HA composites (top view), and (d) PLGA/HA composites (front view) manufactured by SLS (Adapted from Ref. [107]).

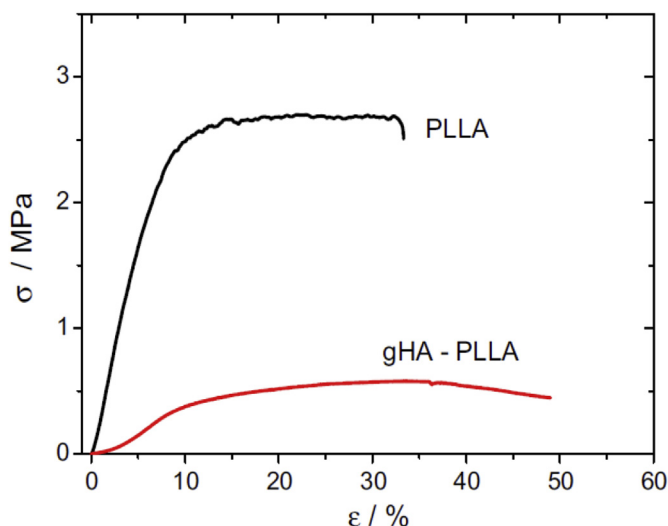


Fig. 8. The stress-strain behaviour for pure PLLA and gHA-PLLA composite (Adapted from Ref. [114]).

of porous structures is the inability of conventional methods to completely control the architecture of scaffolds, such as pore size and interconnections [120]. Further and even more importantly, the use of solvents in some of these methods can affect the biocompatibility of scaffolds [121].

2.1. Additive manufacturing

Additive manufacturing is a new and modern technique that shows great potential to offer complete control of architectural details such as pore size, which significantly affects the properties of scaffolds. This technique is receiving much attention, in particular for 3D-printed biopolymers because of the possibility of designing specific and complex structures [122–126]. Owing to the 3D architecture and geometry of native tissue environments, it is necessary to design and manufacture scaffolds to mimic the structure of natural bone. There are different variations of 3D printing, including stereolithography (SLA) [127], fused deposition modelling (FDM) [128], selective laser sintering (SLS) [129], and bioprinting [130]. Fig. 11 shows diagrams for these variations as they are applied in manufacturing different materials.

2.1.1. Stereolithography (SLA)

SLA is a manufacturing procedure which takes a short time to complete and allows the creation of functional products within a day. In this method, by applying an electron beam or UV light, a chain reaction will start. Monomers are UV-active and will convert this to polymer chains. A 3D model is built layer by layer on a mobile platform. A laser then touches the container, solidifying the parts required to achieve the creation of the SLA prototype (Fig. 11(a)).

2.1.2. Fused deposition modelling (FDM)

FDM as an additive manufacturing technique is frequently applied to different materials, particularly polymers. As seen in Fig. 11(b), built and support materials are extruded, and the parts form layer by layer. Fig. 9 shows the structure of 3D printed PLA scaffolds via FDM.

One of the challengeable issues in this method is its difficulty in the direct production of polymer-ceramic composites. Other complementary manufacturing techniques such as melt extrusion are needed to obtain a suitable filament for FDM [131]. Fig. 10 shows manufacturing of PLA/HA filament through melt extrusion.

2.1.3. Selective laser sintering (SLS)

The basic concept of SLS is similar to that of SLA. It uses a moving

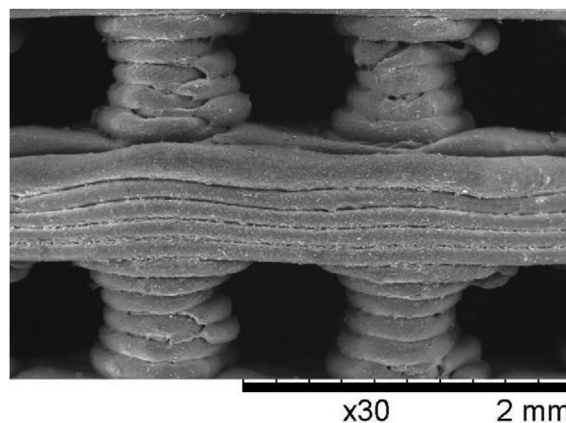


Fig. 9. PLA scaffolds manufactured by FDM (Adapted from Ref. [123]).

laser beam to trace and selectively sinter powdered polymer and/or metal composite materials into successive cross-sections of a 3D part. As in all rapid-prototyping processes, the parts are built upon a platform that adjusts in height equal to the thickness of the layer being created. The additional powder is deposited on top of each solidified layer and sintered. This powder is rolled onto the platform from a bin before forming the layer. The powder is maintained at an elevated temperature so that it fuses easily on exposure to the laser (Fig. 11(c)).

2.1.4. Bioprinting

In bioprinting, thermal inkjet bioprinters electrically heat the print head to produce air-pressure pulses that force droplets from the nozzle, whereas acoustic bioprinters use pulses formed by piezoelectric or ultrasound pressure (Fig. 11(d)).

Depending on the materials and applications, any of these methods can be employed. Table 6 summarizes the most commonly used materials with the advantages and disadvantages of each approach.

Of all the 3D printing techniques, FDM is used more frequently, owing to its lack of need for solvents. One of the most significant drawbacks of FDM is that the type of material employed with this method must be in filament form. The exclusive availability of this technique for thermoplastics is another disadvantage. However, owing to the high speed and low cost of FDM, it is the most commonly used printing technique to fabricate polymer composites.

Another concern regarding 3D printing is how to remove undesirable particles or powders that can be formed in unprinted volumes [151].

In recent studies, researchers applied 3D printing to the fabrication of PLA composites to achieve a uniform structure [126,152–154]. Because the chemical formulae and properties of synthetic HA are similar to those of the main inorganic constituent of bones and teeth, it can be considered the best surface coating. HA has a porous structure with excellent biocompatibility, and bioactivity, and so is used as a coating on the surface of PLA [155,156].

2.2. Surface coating of polymers

There is a wide range of methods, as summarized in Table 7, to produce a thin film on the surface of polymer materials, including plasma spraying [157–159], magnetron sputtering [29,160–168], biomimetic crystallisation techniques [169,170], electrophoretic deposition [171,172], and sol-gel techniques [173,174].

2.2.1. Plasma spraying

The plasma coating process as one of the surface coating methods is an established technology to produce coating films. This method is applied to different polymeric materials as a coating in bone tissue engineering [175,176]. In this technique, the processing temperature

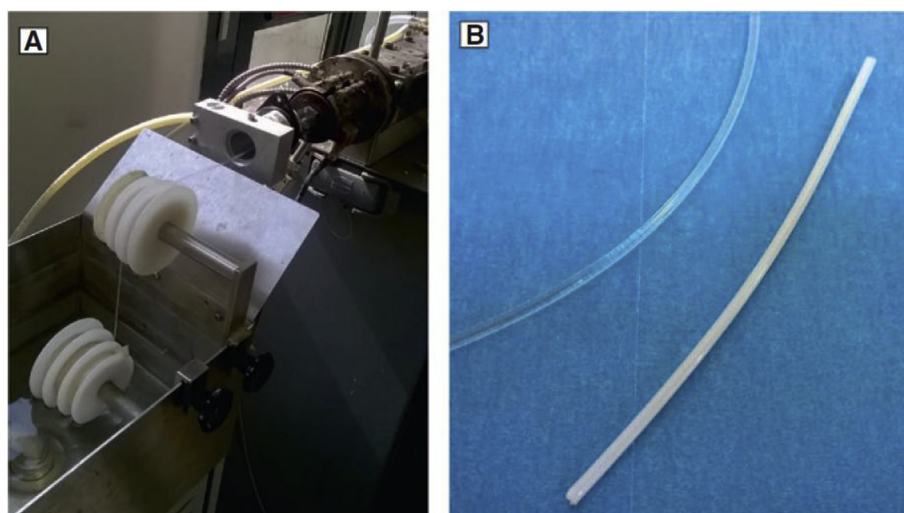


Fig. 10. a) Extrusion process of PLA/HA composites, and b) PLA and PLA/HA filament (white one) (Adopted from Ref. [131]).

can reach 16,000 K. The gas flowing such as He, H₂, N₂, or mixtures of them is ionised. Particles in powder form are injected by impact into the plasma plume to melt and sprayed onto the substrate to produce a coating. The composition of the used gas and the percentage of it, energy input, and the distance between the substrate and coating can be considered as important factors in this process [177].

2.2.2. Magnetron sputtering

Compared to other methods of physical vapour deposition, magnetron sputtering is widely used in many industries to produce high quality, dense, uniform, and thin films which can be applied for a wide range of materials. Moreover, a high rate of deposition is achievable. Compared to other deposition techniques, magnetron sputtering has the low level of damage to soft substrates, in particular for polymers.

There are different variations of magnetron sputtering, such as pulsed direct current (DC) and radio frequency (RF). The highly flexible method of RF magnetron sputtering is widely used owing to its modifiable conditions such as controllable crystallinity [165]. In this regard, the effects of different processing parameters such as power, the pressure of the used gas (usually argon), and the target substrate and its morphology should be given consideration. The type of gas used, pressure, power, the distance between target and substrate, substrate bias potential and the properties of the target have been investigated as sputtering parameters. These factors affect the morphology, uniformity, and the features of the coating [178–184]. In recent studies to control the uniformity of film coatings, the substrate rotation, movement, and sample position have been experimentally investigated [185]. Inert gases such as argon or helium are used to bombard a target. The ejected atoms from the target will deposit on all surfaces and make a thin film. To cool the target water can be applied. Fig. 12 shows the schematic of the magnetron sputtering method.

2.2.3. Sol-gel techniques

Due to the low synthetic temperature of this method, it is known as the most straightforward technique to produce sub-micron dimensions of HA. The sol-gel process can be considered as aqueous (if water is applied as the reaction medium) and nonaqueous (if organic solvents are used as the reaction medium). This chemical procedure has several steps. First, a sol which is a stable colloidal solution is formed by hydrolysis and partial condensation of precursors such as an inorganic salt or a metal alkoxide. Then it will go towards the formation of a gel-like phase. A new phase has both a liquid and solid phase which their morphologies can be placed between discrete particles and continuous polymer networks. The drying process is accompanied by a significant

amount of shrinkage and densification due to the removal of the remaining liquid or solvent. Solid products are known as xerogel and aerogel, respectively. To enhance mechanical properties and structural stability thermal treatment is typically applied. Fig. 13 shows the schematic of a sol-gel method.

The different manufacturing methods of the most common synthetic polymer-hydroxyapatite composites that have been studied in recent years are summarized in Table 8.

As a new generation of materials, biodegradable polymers offer excellent biomedical applications ranging from wound management to drug delivery [230]. Table 9 summarized the biomedical applications of synthetic polymer-ceramic composites with the greatest history of usage.

3. Summary and future research directions

According to previous studies, various parameters should be considered as requirements for the achievement of successful implants and scaffolds.

1. The first and foremost requirement is the choice of appropriate materials with good mechanical properties. Biomaterials should have good biocompatibility, bioresorbability, a controllable rate of biodegradation, excellent mechanical strength, and bioactivity.
2. The next requirement is to design scaffolds with suitable structures. Bone-tissue engineering has used various types of structures and architectures to construct medical implants and devices. The appropriate design of scaffold structures has a significant impact on their mechanical properties. Based on previous studies, it is worth emphasising that successful scaffold structures are highly dependent on the porosity, pore size, and shape. 3D porous scaffolds allow fast cell growth and attachments, and high transportation rates of nutrients and waste.
3. Furthermore, these structures provide a large surface area for bone growth. Therefore, highly porous scaffolds in 3D forms play a vital role in meeting these aims. The recommended porosity for scaffolds is approximately 90%.
4. Another essential requirement that should be studied in more detail concerns the adhesion between coatings and substrates. Various efforts have been made to enhance adhesive strength. For example, hydrogel groups of HA can improve the adhesive strength by creating strong chemical bonds between HAp nanoparticles and the PLLA and PLGA matrix. Even more importantly, composites that contain HA demonstrate high mechanical strength compared to pure

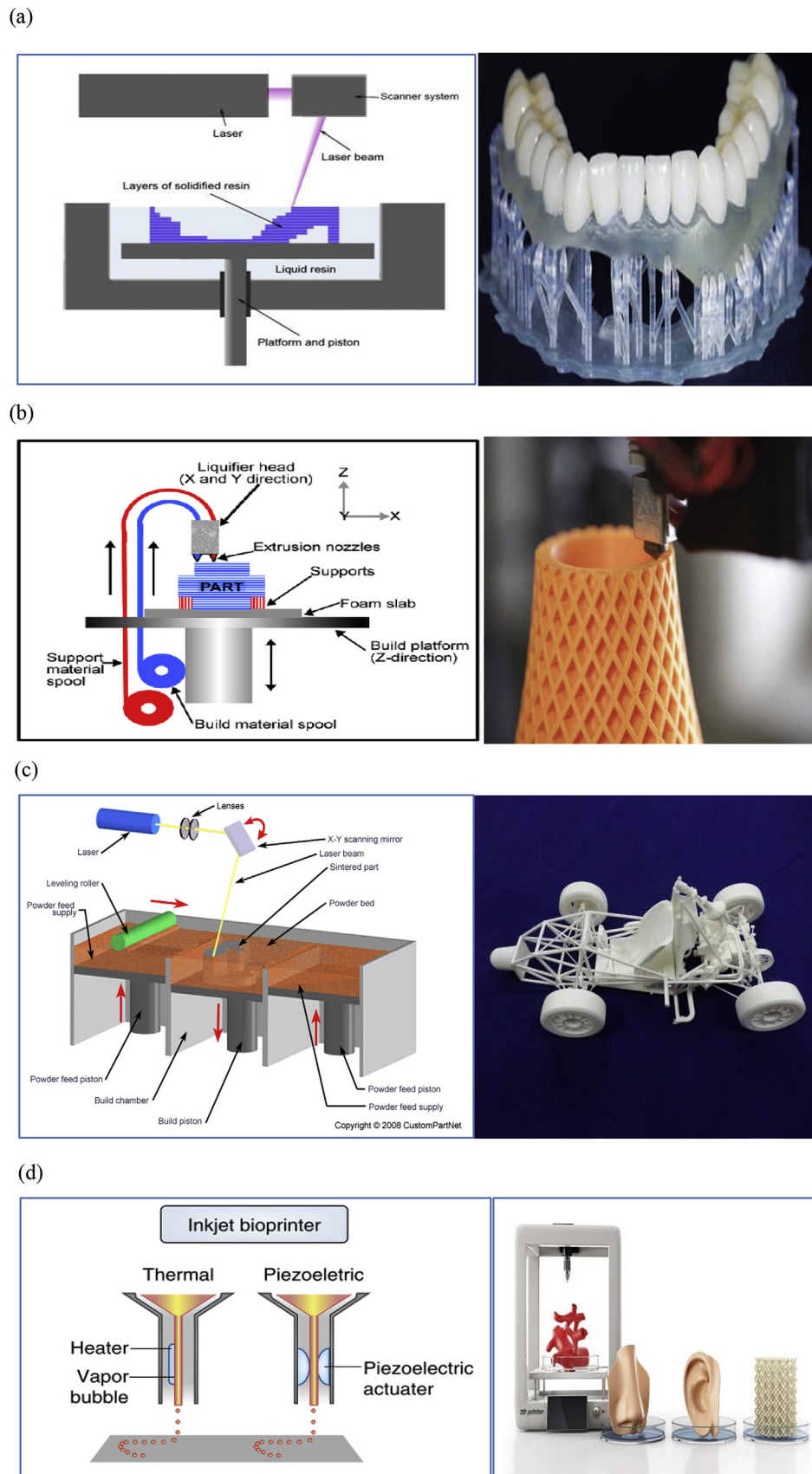


Fig. 11. Diagrams of: (a) SLA, (b) FDM, (c) SLS, (d) inkjet bioprinting and their models (Adapted from Refs. [132–139]).

Table 6
Advantages and disadvantages of various types of 3D printing.

Common materials	Technique	Advantages	Disadvantages	Ref.
PCL, PPF, PDLA	SLA	High printing resolution	Material limitation, cytotoxicity, high cost	[127,140–144]
PCL, TCP, ABS	FDM	Low cost, good strength, multi-material capability	Anisotropy, nozzle clogging	[128,144,145]
PCL, PEEK, PLGA	SLS	Good strength, easy removal of support powder	High cost, powdery Surface	[129,144,146,147]
Low-viscosity materials (< 10 cP)	Inkjet bioprinting	Low cost, multimaterial capability, easy removal of support powder	Clogging of binder jet, binder contamination	[130,144,148]
PCL, HA, Hydrogels	Extrusion bioprinting	High printing resolution, soft materials capability	Low mechanical strength, slow	[130,144,148–150]

Table 7
Advantages and disadvantages of various coating techniques.

Method	Advantages	Disadvantages
Plasma spraying	Strength bonding, preferable dissolution behaviour	The complex process due to the number of interacting parameters, difficulty in the internal coating of bores, high-cost
Magnetron sputtering	Thin, uniform, and dense films, easy to scale up, low damage to soft tissues, high rate of adhesion, high rate of deposition, suitable for a wide range of materials	Nonhomogeneous ion current distribution across the target surface, high-cost
Sol-gel	Excellent control of product purity and composition, ability to deposit films and coatings on different surfaces, low temperatures	Easy to crack in the drying process, the high cost of raw materials

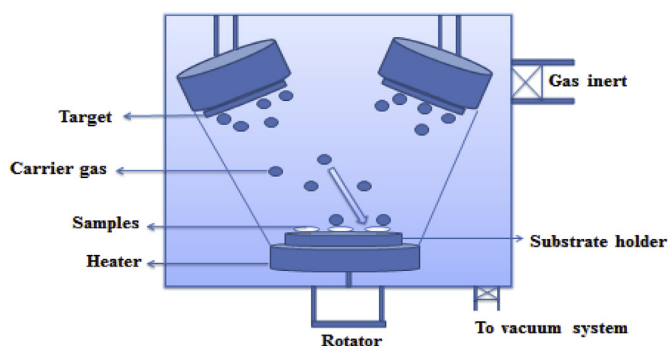


Fig. 12. Schematic of a sputtering technique.

ones.

- An appropriate degradation behaviour is another critical requirement for biodegradable materials. The addition of nanofillers could decelerate the degradation rate of a biodegradable composite.

As pointed out above, owing to their unique and beneficial properties, polymeric materials are being used as a new generation of materials for medical applications. Although various types of biomaterials have been extensively studied for biomedical purposes, many other materials could be investigated. In this regard, the physiochemical properties of this new generation of biomaterials, their surface morphology, and their potential applications in tissue engineering should be studied in detail. It is expected that, by employing polymers, the observed problems could at least be reduced.

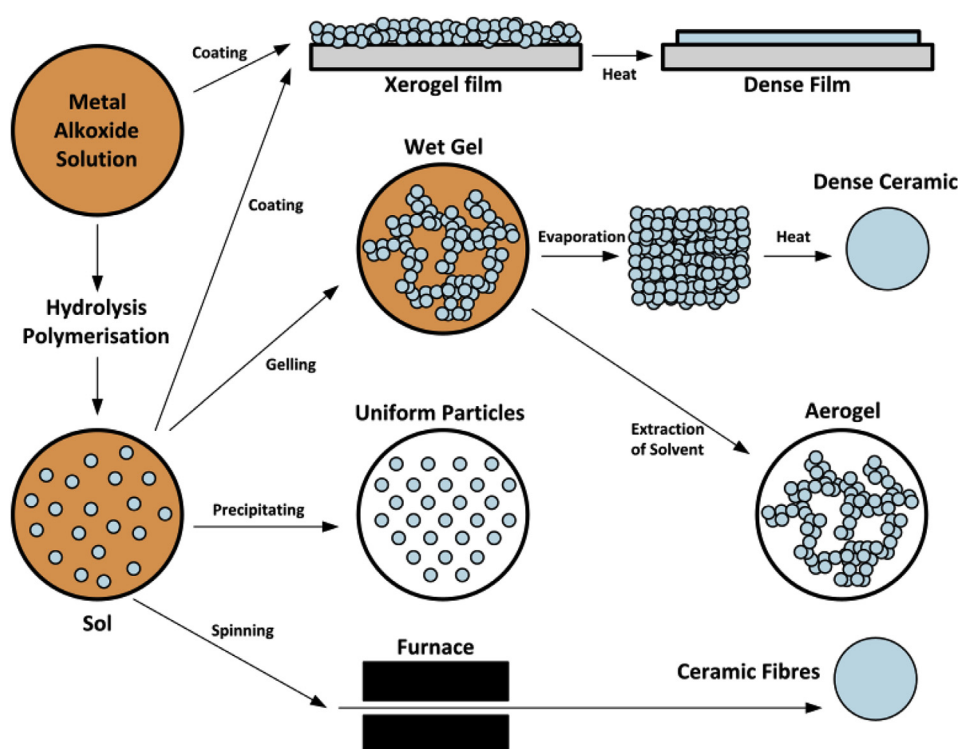


Fig. 13. Schematic of the sol-gel technology (Adapted from Ref. [166]).

Table 8
Different manufacturing methods of conventional synthetic polymer-hydroxyapatite composites.

Polymer-HA composites	Manufacturing techniques of polymer-ceramic composites	Year
PLA/HA	Extrusion and injection molding	2018 [186]
Chitosan/HA	Chemical co-precipitation	2018 [187]
PEEK/HA	Electrophoretic deposition (EPD) and suspension	2018 [188]
PEEK/Ti/HA _p	Sputtering	2017 [189]
PLGA/HA	Solvent casting and injection molding	2017 [190]
PLA/HA	Fused deposition melting (FDM)	2017 [131]
PCL/HA	Co-extrusion	2017 [191]
PLA/HA	Extrusion and injection molding	2017 [192]
PLLA/nHA _p & PLLA/g-HA _p	Precipitation	2016 [193]
PLA/HA	3D printing	2016 [194]
PEEK/HA _p	Post-deposition heat treatment	2016 [195]
PLA/HA	Fused deposition melting (FDM)	2016 [123]
PLLA/HA	Thermally induced phase separation (TIPS)	2016 [196]
PLLA/HA	Thermally induced phase separation (TIPS)	2015 [197]
PLGA/HA	Injection molding	2015 [198]
PLA/HA	Extrusion process	2014 [199]
Chitosan-PLGA/HA	Freeze drying	2014 [200]
PLGA/HA	Solution mixing	2013 [201]
PLGA/HA	Selective laser sintering (SLS)	2013 [107]
PCL/HA	Freezing of emulsions	2013 [202]
PLA/HA	Electrospinning	2013 [203]
PLA/nHA	Air jet spinning	2013 [204]
PLLA/HA & PLGA/HA	Solvent casting	2013 [205]
PLA/HA	Stereolithography (SLA)	2013 [206]
PLGA/HA	Co-solution	2012 [207]
PLLA/nHA	Laser melt electrospinning	2012 [208]
PLGA/HA/collagen	Supercritical fluid extractor	2011 [209]
PLGA/HA	Electrospinning	2011 [210]
PMMA/HA	Pulsed laser deposition and magnetron sputtering	2010 [211]
PLLA/HA _p	Melt extrusion	2010 [212]
PLLA/HA	Phase inversion	2010 [213]
PLLA/HA	Freeze extraction	2010 [214]
PCL/PLA/HA	Electrospinning	2010 [215]
PCL/HA	Selective laser sintering (SLS)	2010 [216]
Carbonated hydroxyapatite/PLLA	Selective laser sintering (SLS)	2010 [217]
PLLA/nHA	Hot pressing	2009 [218]
PLLA/HA & PLLA/collagen/HA	Electrospinning	2009 [219]
PLLA/HA	A two-step immersing replication method	2008 [220]
PCL/HA	Polymer impregnating	2008 [221]
PLA/HA	Electrospinning	2008 [222]
PCL/HA	Fused deposition melting (FDM)	2007 [223]
PLGA/HA	Gas foaming and particulate leaching (GF/PL)	2006 [224]
PLA/HA	Hot pressing	2006 [225]
PLA/HA	Solvent casting	2005 [226]
PCL/HA	Selective laser sintering (SLS)	2005 [227]
PLLA/HA & PCL/HA	Selective laser sintering (SLS)	2005 [228]
PLLA/HA	Solvent casting	2004 [229]

Table 9
Biomedical applications of common polymer-ceramic composites.

Polymer-ceramic composites	Applications	Techniques	Ref.
PCL/ceramic	Bone tissue engineering, hard tissue engineering, bone graft substitutes, neural tissue engineering, tissue generation, wound healing, bone fracture fixation devices, hard tissue repair	Solvent casting particulate leaching, solvent casting, melt-electrospinning, 3D printing, melt extrusion, sol-gel	[47,231–237]
PLA/ceramic	Sutures, repair of fractures of the orbital floor, implants, drug-eluting stents, drug delivery	3D printing, extrusion and injection molding, electrospinning, solvent casting	[123,225,230,238–240]
PLLA/ceramic	Bone tissue engineering, various medical applications, interference screws, suture anchors	freeze-extraction, melt extrusion, particulate leaching	[241–244]
PLGA/ceramic	Bone tissue engineering, hard & soft tissue engineering, meniscus repair, liver disease	Solvent casting particulate leaching, solvent casting, gas foaming, bone neoplasia and tumours, 3D printing	[52,102,245–250]
PDLLA/ceramic	Hard & soft tissue engineering, regeneration of hard-soft tissue defects	Solvent casting particulate leaching, solvent casting	[248,251–253]

On the one hand, according to the studies cited above, traditional manufacturing methods may not be able to produce biomaterials that mimic the natural structure of bone. On the other hand, modern techniques face certain limitations regarding raw materials and outcomes. For instance, currently only a limited range of materials such as

thermoplastics can be used in 3D-printing devices, and these materials cannot meet all the requirements. Furthermore, owing to the various shapes of scaffolds, as mentioned above, creating strong interfacial bonding is difficult.

To achieve long-lasting implant devices with acceptable

biocompatibility, biodegradability, and bioactivity, a variety of materials and manufacturing techniques have been studied in medical science. However, there is still a vital need to develop a range of improved biomaterials and manufacturing approaches.

Conflicts of interest

None.

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