



# 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  $\beta$ -tricalcium phosphate ( $\beta$ -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  $\alpha$ -TCP,  $\beta$ -TCP, and  $\alpha'$ -TCP is another well-known bioceramics for bone repair applications.  $\beta$ -TCP is receiving increasing attention due to its excellent biocompatibility, bioactivity, and bioresorbability [34–37]. Fig. 3 shows porous  $\beta$ -TCP ceramics which polymethylmethacrylate balls are used to obtain various pore sizes.

The mechanical strength of HA is higher than  $\beta$ -TCP [10]. However,  $\beta$ -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,

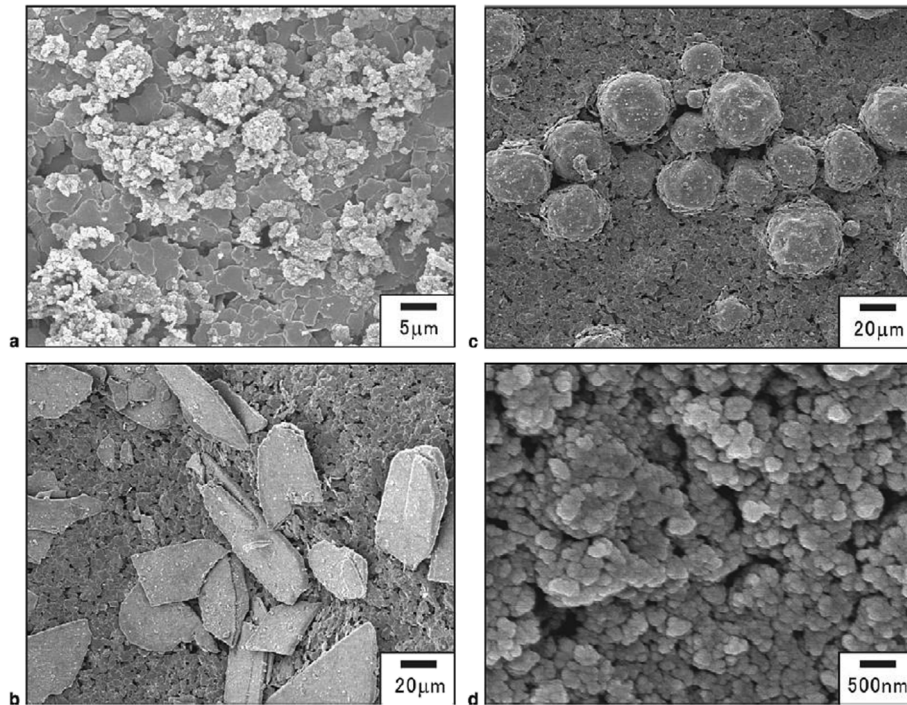


Fig. 2. SEM micrographs of HA particles with different sizes and shapes: a) microscale, b) plate, c) spherical, d) nanoscale (Adapted from Ref. [27]).

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

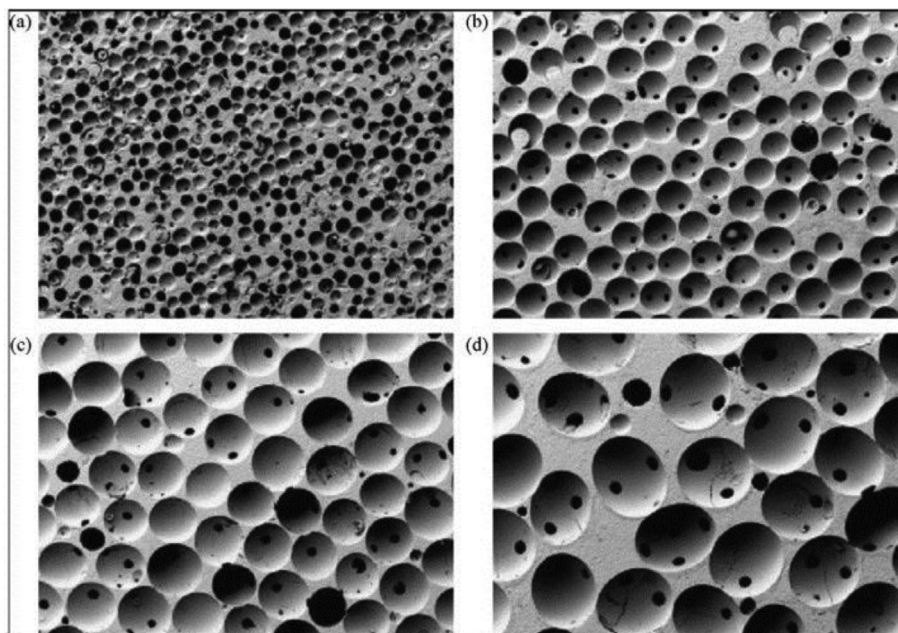


Fig. 3. Porous  $\beta$ -TCP with different pore sizes: (a) 100–200  $\mu\text{m}$ , (b) 300–400  $\mu\text{m}$ , (c) 500–600  $\mu\text{m}$ , and (d) 700–800  $\mu\text{m}$  (Adopted from Ref. [13]).

**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]

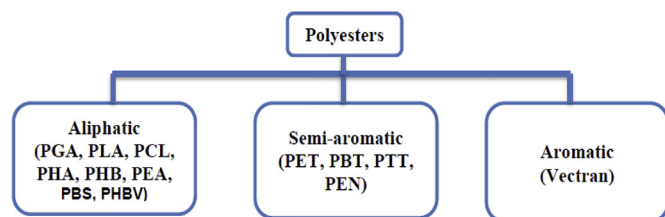


Fig. 4. Three main categories of polyesters (Adapted from Ref. [65]).

**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 <sup>3</sup>	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

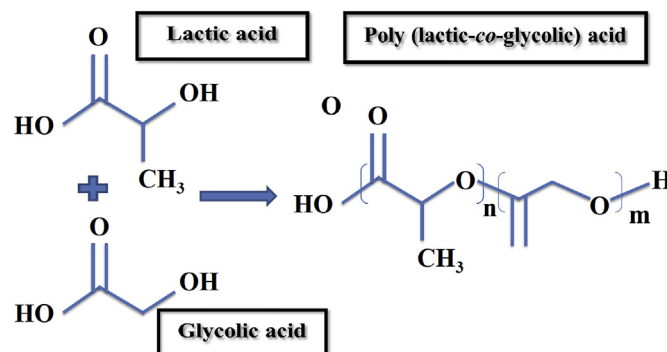


Fig. 5. Chemical structure of PLGA and its monomers (n and m demonstrate the number of repetition of each unit).

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

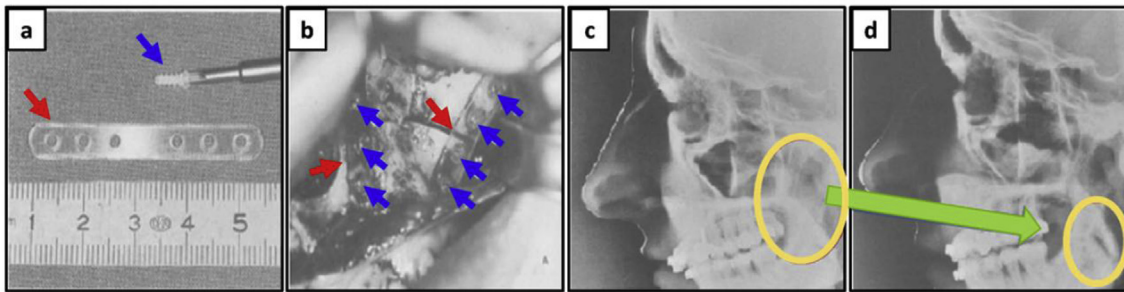


Fig. 6. (a) Screws and plate made of PLA, (b) upper jaw with the plates and screws in situ, (c) and (d) lateral cephalogram, with the screws and plate, taken immediately postoperatively and six weeks postoperatively, respectively. (Adapted from Refs. [96,97]).

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  $2.8 \pm 1.2$  MPa and a strain at break of  $38 \pm 7\%$ . However, the microcomposite samples showed a five-fold decrease in maximum stress down to  $0.57 \pm 0.2$  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	$510 \pm 150$	$79 \pm 3$
gHA-PLLA	$440 \pm 170$	$88 \pm 5$

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

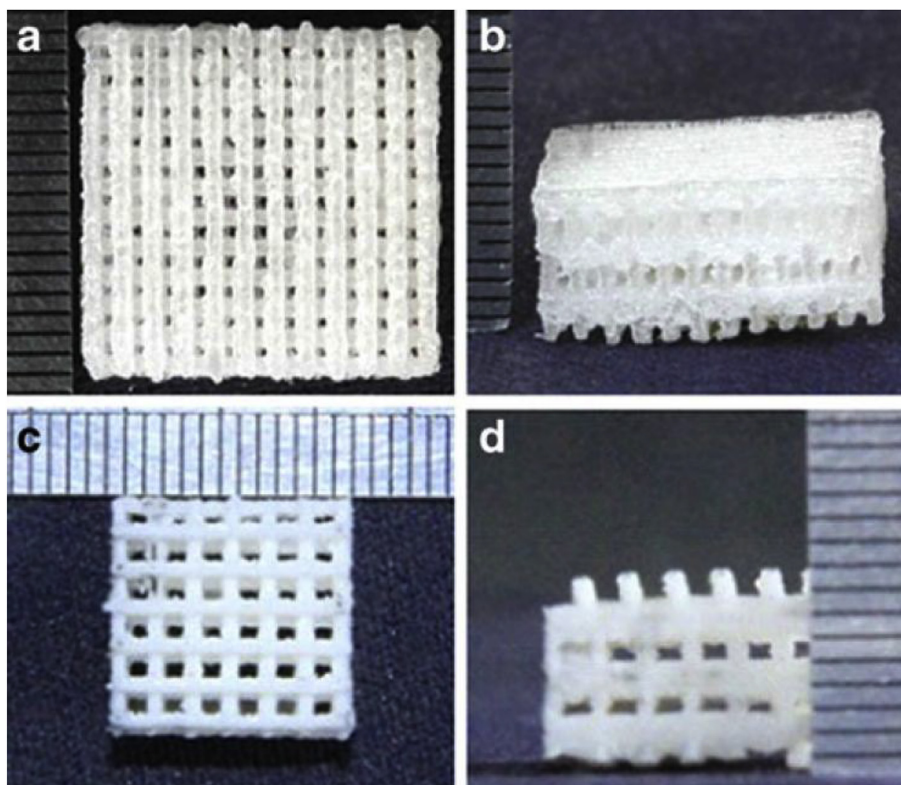


Fig. 7. SEM images of: (a) neat PLGA (top view), (b) neat PLGA (front view), (c) PLGA/HA composites (top view), and (d) PLGA/HA composites (front view) manufactured by SLS (Adapted from Ref. [107]).

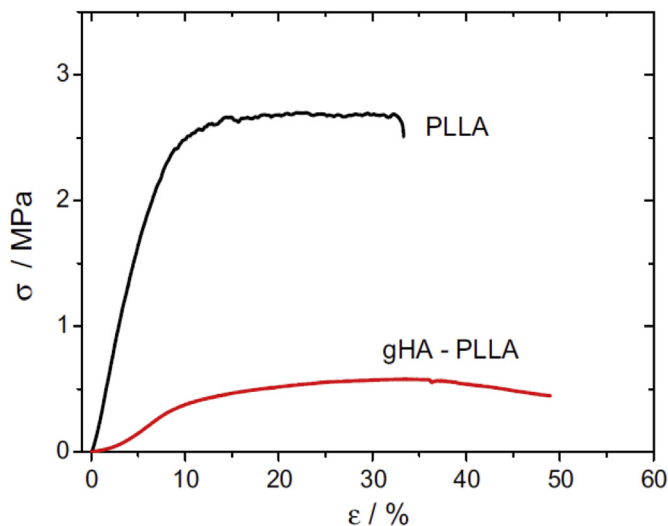


Fig. 8. The stress-strain behaviour for pure PLLA and gHA-PLLA composite (Adapted from Ref. [114]).

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

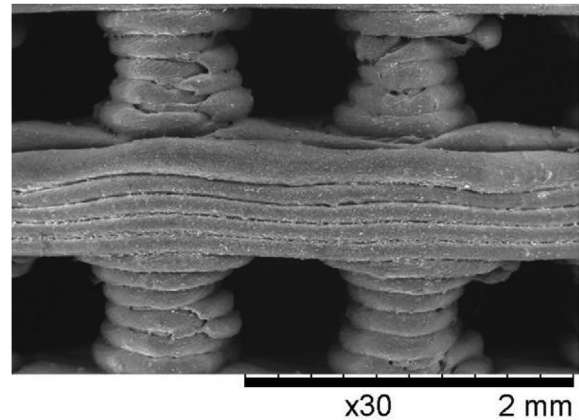


Fig. 9. PLA scaffolds manufactured by FDM (Adapted from Ref. [123]).

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

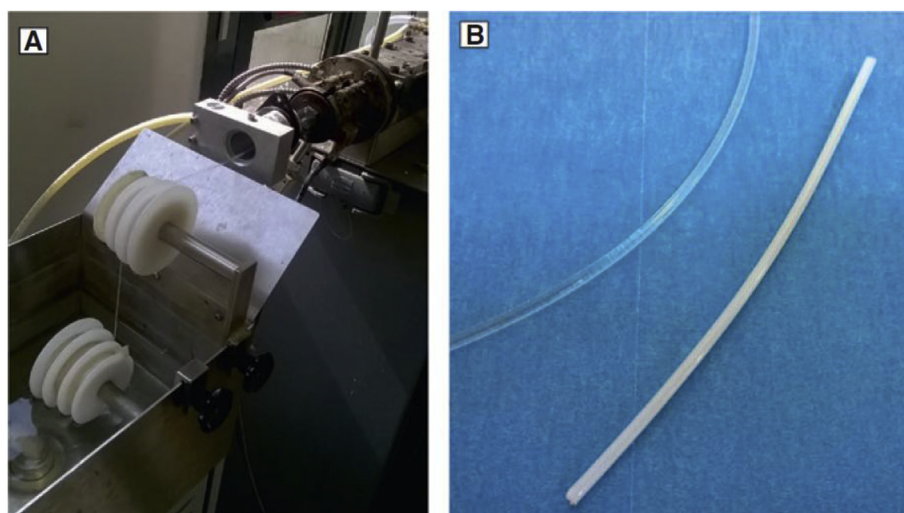


Fig. 10. a) Extrusion process of PLA/HA composites, and b) PLA and PLA/HA filament (white one) (Adopted from Ref. [131]).

can reach 16,000 K. The gas flowing such as He, H<sub>2</sub>, N<sub>2</sub>, 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.

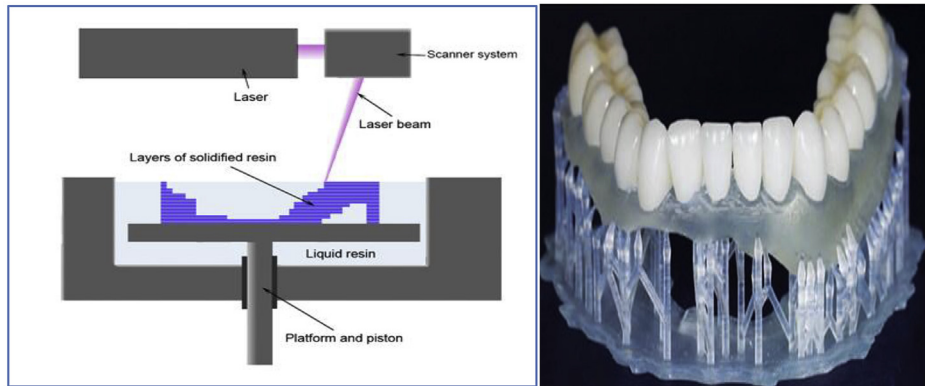
As a new generation of materials, biodegradable polymers offer excellent biomedical applications ranging from wound management to drug delivery [230]. Table 9 summarized the biomedical applications of synthetic polymer-ceramic composites with the greatest history of usage.

## 3. Summary and future research directions

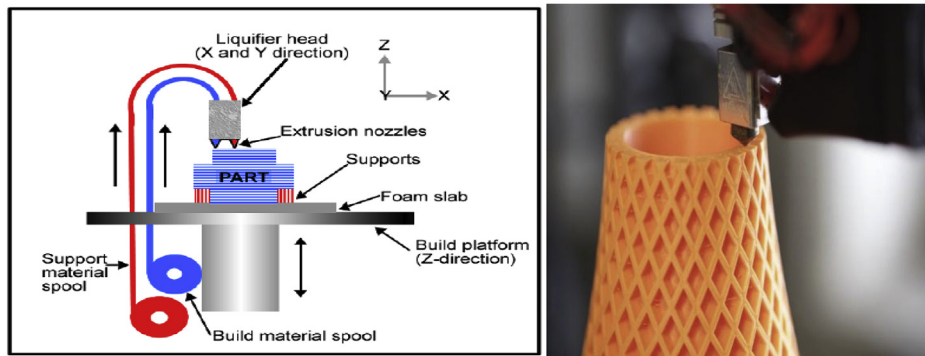
According to previous studies, various parameters should be considered as requirements for the achievement of successful implants and scaffolds.

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

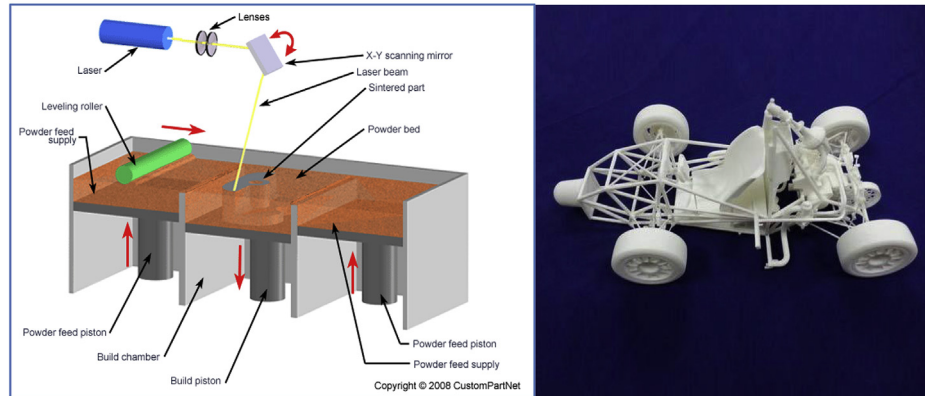
(a)



(b)



(c)



(d)

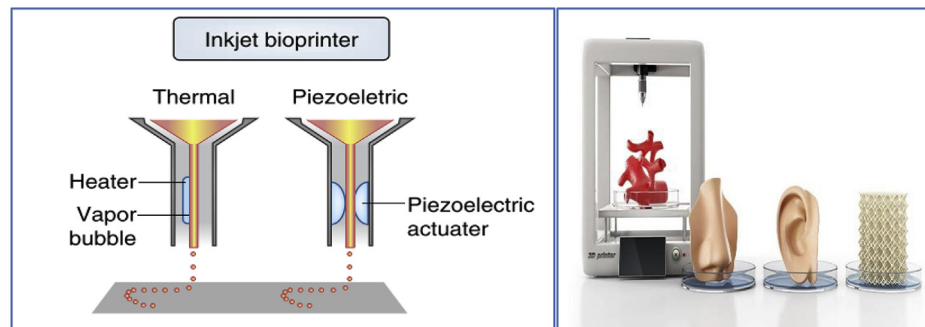


Fig. 11. Diagrams of: (a) SLA, (b) FDM, (c) SLS, (d) inkjet bioprinting and their models (Adapted from Refs. [132–139]).



**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

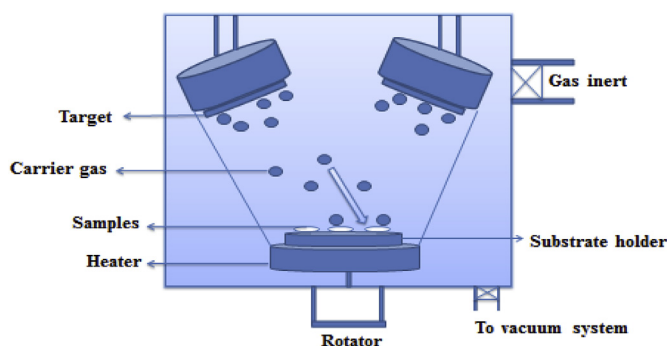


Fig. 12. Schematic of a sputtering technique.

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.

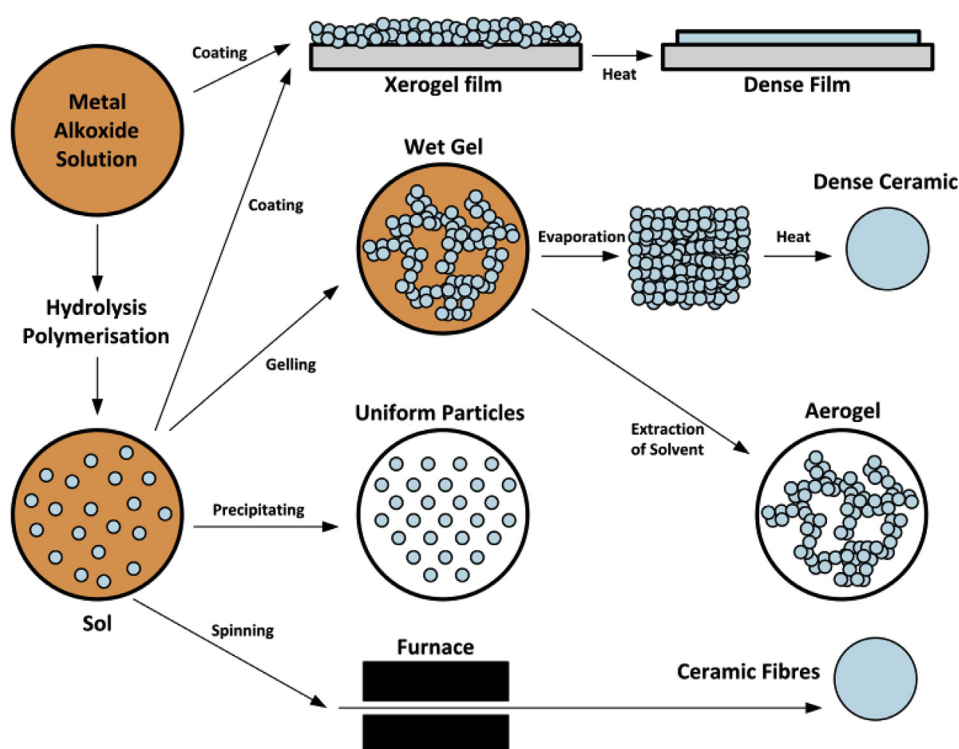


Fig. 13. Schematic of the sol-gel technology (Adapted from Ref. [166]).

**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 <sub>p</sub>	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 <sub>p</sub> & PLLA/g-HA <sub>p</sub>	Precipitation	2016 [193]
PLA/HA	3D printing	2016 [194]
PEEK/HA <sub>p</sub>	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 <sub>p</sub>	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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### References

- [1] M. Niinomi, Recent metallic materials for biomedical applications, *Mater. Trans.* A 33 (3) (2002) 477–486.
- [2] W. Cao, L.L. Hench, Bioactive materials, *Ceram. Int.* 22 (6) (1996) 493–507.
- [3] S.V. Dorozhkin, M. Epple, Biological and Medical Significance of Calcium Phosphates, Weinheim, (2002), pp. 3130–3146.
- [4] H.W. Denissen, K.d. Groot, Immediate dental root implants from synthetic dense calcium hydroxylapatite, *J. Prosthet. Dent.* 42 (5) (1979) 551–556.
- [5] L.C.C.W.E. Brown, A new calcium phosphate, water-setting cement, *Cem. Res. Prog.* (1986) 351–379.
- [6] S. Bose, S. Tarafder, Calcium phosphate ceramic systems in growth factor and drug delivery for bone tissue engineering: a review, *Acta Biomater.* 8 (4) (2012) 1401–1421.
- [7] R.Z. Legeros, J.P. Legeros, 16 - Hydroxyapatite A2 - Kokubo, Tadashi, *Bioceramics and Their Clinical Applications*, Woodhead Publishing, 2008, pp. 367–394.
- [8] L. Xiao-Ming, C. Rong-Rong, S. Lian-Wen, E.A. Katerina, F. Yubo, F. Qing-Ling, C. Fuz-Hai, W. Fumio, 3D-Printed biopolymers for tissue engineering application, *Int. J. Polym. Sci.* 2014 (2) (2014) 137–149.
- [9] S.A. Catledge, M.D. Fries, Y.K. Vohra, W.R. Lacefield, J.E. Lemons, S. Woodard, R. Venugopalan, Nanostructured ceramics for biomedical implants, *J. Nanosci. Nanotechnol.* 2 (3–4) (2002) 293–312.
- [10] R.Z. Legeros, Calcium phosphate materials in restorative dentistry: a review, *Adv. Dent. Res.* 2 (1) (1988) 164–180.
- [11] W. Paul, C.P. Sharma, Ceramic drug delivery: a perspective, *J. Biomater. Appl.* 17 (4) (2003) 253–264.
- [12] Y. Zhang, M. Zhang, Calcium phosphate/chitosan composite scaffolds for controlled in vitro antibiotic drug release, *J. Biomed. Mater. Res.* 62 (3) (2002) 378–386.
- [13] S.V. Dorozhkin, Calcium orthophosphates as bioceramics: state of the art, *J. Funct. Biomater.* 1 (1) (2010) 22–107.
- [14] T.R. Cuadrado, T.A. Abraham, Propiedades mecánicas de Biomateriales, in: R. Sastre, S. De Aza, J. San Román (Eds.), *Cooperación Iberoamericana*, CYTED, Biomateriales para la salud, 2004, pp. 151–171.
- [15] M.P. Ginebra, F.C. Driessens, J.A. Planell, Effect of the particle size on the micro and nanostructural features of a calcium phosphate cement: a kinetic analysis, *Biomaterials* 25 (17) (2004) 3453–3462.
- [16] L.L. Hench, Major elements in the human body, *J. Am. Ceram. Soc.* 81 (1998) 1705.
- [17] M. Shojai, M. Khorasani, E. Khoshdargi, A. Jamshidi, Research on hydroxyapatite based composite materials, *Acta Biomater.* 9 (2013) 7591–7621.
- [18] H. A. H. A. M. Y, Sequential histological Examination and morphometric analysis of osteogenesis in the pores of porous hydroxyapatite with attachment of vascularization periosteum, *J. Japan Cranio-Max-Fac. Surg.* 21 (4) (2005) 259–270.
- [19] I. Ono, T. Tateshita, M. Satou, T. Sasaki, M. Matsumoto, N. Kodama, Treatment of large complex cranial bone defects by using hydroxyapatite ceramic implants, *Plast. Reconstr. Surg.* 104 (2) (1999) 339–349.
- [20] L.L. Hench, Bioceramics: from concept to clinic, *J. Am. Ceram. Soc.* 74 (7) (1991) 1487–1510.
- [21] K. de Groot, Clinical applications of calcium phosphate biomaterials: a review, *Ceram. Int.* 19 (5) (1993) 363–366.
- [22] A.M. Ektessabi, M. Hamdi, *Surf. Coating. Technol.* 10 (2002) 153.
- [23] W. Suchanek, M. Yoshimura, Processing and properties of hydroxyapatite-based biomaterials for use as hard tissue replacement implants, *J. Mater. Res.* 13 (1) (2001) 94–117.
- [24] P. Mandracci, F. Mussano, P. Rivolo, S. Carossa, Surface treatments and functional coatings for biocompatibility improvement and bacterial adhesion reduction in dental implantology, *Coatings* 6 (1) (2016).
- [25] G.B. Zhang, E.D. Myers, G.G. Wallace, M. Brandt, F.P. Choong, Bioactive coatings for orthopaedic implants—recent trends in development of implant coatings, *Int. J. Mol. Sci.* 15 (7) (2014).
- [26] J.V. Loghem, Y.A. Yutskovskaya, W.M. Philip Werschler, Calcium hydroxylapatite: over a decade of clinical experience, *J. Clin. Aesthetic Dermatol.* 8 (1) (2015) 38–49.
- [27] M. Todo, S.D. Park, K. Arakawa, Y. Takenoshita, Relationship between microstructure and fracture behavior of bioabsorbable HA/PLLA composites, *Compos. Appl. Sci. Manuf.* 37 (12) (2006) 2221–2225.
- [28] R.A. Surmenev, M.A. Surmeneva, A.A. Ivanova, Significance of calcium phosphate coatings for the enhancement of new bone osteogenesis – a review, *Acta Biomater.* 10 (2) (2014) 557–579.
- [29] M.A. Surmeneva, M.V. Chaikina, V.I. Zaikovskiy, V.F. Pichugin, V. Buck, O. Prymak, M. Epple, R.A. Surmenev, The structure of an RF-magnetron sputter-deposited silicate-containing hydroxyapatite-based coating investigated by high-resolution techniques, *Surf. Coating. Technol.* 218 (2012) 39–46.
- [30] K.C. Ang, K.F. Leong, C.K. Chua, M. Chandrasekaran, Compressive properties and degradability of poly( $\epsilon$ -caprolactone)/hydroxyapatite composites under accelerated hydrolytic degradation, *J. Biomed. Mater. Res. A* 80 (3) (2007) 655–660.
- [31] J. Liuyun, X. Chengdong, J. Lixin, X. Lijuan, Degradation behavior of hydroxyapatite/poly(lactic-co-glycolic) acid nanocomposite in simulated body fluid, *Mater. Res. Bull.* 48 (10) (2013) 4186–4190.
- [32] Z. Hong, P. Zhang, C. He, X. Qiu, A. Liu, L. Chen, X. Chen, X. Jing, Nano-composite of poly(L-lactide) and surface grafted hydroxyapatite: mechanical properties and biocompatibility, *Biomaterials* 26 (32) (2005) 6296–6304.
- [33] C. Verheyen, C. Klein, J. Deblieckhogervorst, J. Wolke, C. Vanblitterswijk, K. Degroot, Evaluation of hydroxylapatite poly(L-lactide) composites - physico-chemical properties, *J. Mater. Sci. Mater. Med.* 4 (1) (1993) 58–65.
- [34] A. Mina, A. Castaño, J.C. Caicedo, H.H. Caicedo, Y. Aguilar, Determination of physical properties for  $\beta$ -TCP + chitosan biomaterial obtained on metallic 316L substrates, *Mater. Chem. Phys.* 160 (2015) 296–307.
- [35] A. Rakovsky, I. Gotman, E. Rabkin, E.Y. Gutmanas, beta-TCP-poly(lactide) composite scaffolds with high strength and enhanced permeability prepared by a modified salt leaching method, *J. Mech. Behav. Biomed. Mater.* 32 (2014) 89–98.
- [36] L. Zheng, F. Yang, H. Shen, X. Hu, C. Mochizuki, M. Sato, S. Wang, Y. Zhang, The effect of composition of calcium phosphate composite scaffolds on the formation of tooth tissue from human dental pulp stem cells, *Biomaterials* 32 (29) (2011) 7053–7059.
- [37] B. Rai, M.E. Oest, K.M. Dupont, K.H. Ho, S.H. Teoh, R.E. Goldberg, Combination of platelet-rich plasma with polycaprolactone-tricalcium phosphate scaffolds for segmental bone defect repair, *J. Biomed. Mater. Res. A* 81 (4) (2007) 888–899.
- [38] R.Z. LeGeros, S. Lin, R. Rohanizadeh, D. Mijares, J.P. LeGeros, Biphasic calcium phosphate bioceramics: preparation, properties and applications, *J. Mater. Sci. Mater. Med.* 14 (3) (2003) 201–209.
- [39] G. Daculsi, R.Z. LeGeros, E. Nery, K. Lynch, B. Kerebel, Transformation of biphasic calcium phosphate ceramics in vivo: ultrastructural and physicochemical characterization, *J. Biomed. Mater. Res.* 23 (8) (1989) 883–894.
- [40] M.V. Thomas, D.A. Puleo, Calcium sulfate: properties and clinical applications, *J. Biomed. Mater. Res. B Appl. Biomater.* 88B (2) (2008) 597–610.
- [41] S. Sali, Natural Calcium Carbonate for Biomedical Applications, (2016) arXiv.org.
- [42] L. Pröbster, J. Diehl, Slip-casting alumina ceramics for crown and bridge restorations, *Quintessence Int.* 23 (1) (1992) 25–31.
- [43] E. Medvedovski, Alumina–mullite ceramics for structural applications, *Ceram. Int.* 32 (4) (2006) 369–375.
- [44] I. Denry, J.R. Kelly, State of the art of zirconia for dental applications, *Dent. Mater.* 24 (3) (2008) 299–307.
- [45] P.F. Manicone, P. Rossi Iommetti, L. Raffaelli, An overview of zirconia ceramics: basic properties and clinical applications, *J. Dent.* 35 (11) (2007) 819–826.
- [46] T. Kokubo, Bioactive glass ceramics: properties and applications, *Biomaterials* 12 (2) (1991) 155–163.
- [47] M. Dziadek, J. Pawlik, E. Menaszek, E. Stodolak-Zych, K. Cholewa-Kowalska, Effect of the preparation methods on architecture, crystallinity, hydrolytic degradation, bioactivity, and biocompatibility of PCL/bioglass composite scaffolds, *J. Biomed. Mater. Res. B Appl. Biomater.* 103 (8) (2015) 1580–1593.
- [48] G.E. Vargas, L.A. Haro Durand, V. Cadena, M. Romero, R.V. Mesones, M. Mackovic, S. Spallek, E. Spiecker, A.R. Boccaccini, A.A. Gorustovich, Effect of nano-sized bioactive glass particles on the angiogenic properties of collagen based composites, *J. Mater. Sci. Mater. Med.* 24 (5) (2013) 1261–1269.
- [49] E. Tamjid, R. Bagheri, M. Vossoughi, A. Simchi, Effect of particle size on the in vitro bioactivity, hydrophilicity and mechanical properties of bioactive glass-reinforced polycaprolactone composites, *Mater. Sci. Eng. C* 31 (7) (2011) 1526–1533.
- [50] P. Fabbri, V. Cannillo, A. Sola, A. Dorigato, F. Chiellini, Highly porous polycaprolactone-45S5 Bioglass® scaffolds for bone tissue engineering, *Compos. Sci. Technol.* 70 (13) (2010) 1869–1878.
- [51] V. Maquet, A.R. Boccaccini, L. Pravata, I. Notinger, R. Jerome, Porous poly(alpha-hydroxyacid)/Bioglass composite scaffolds for bone tissue engineering. I: preparation and in vitro characterisation, *Biomaterials* 25 (18) (2004) 4185–4194.
- [52] A.R. Boccaccini, V. Maquet, Bioresorbable and bioactive polymer/Bioglass® composites with tailored pore structure for tissue engineering applications, *Compos. Sci. Technol.* 63 (16) (2003) 2417–2429.
- [53] J.J. Blaker, J.E. Gough, V. Maquet, I. Notinger, A.R. Boccaccini, In vitro evaluation of novel bioactive composites based on Bioglass-filled polylactide foams for bone tissue engineering scaffolds, *J. Biomed. Mater. Res. A* 67 (4) (2003) 1401–1411.
- [54] K.A. Athanasiou, G.G. Niederauer, C.M. Agrawal, Sterilization, toxicity, biocompatibility and clinical applications of polylactic acid/polyglycolic acid copolymers, *Biomaterials* 17 (2) (1996) 93–102.
- [55] G. Prestwich, H. Matthew, Hybrid, composite, and complex biomaterials, *Ann. NY Acad. Sci.* 961 (2002) 106–108.
- [56] C.H. Lee, A. Singla, Y. Lee, Biomedical applications of collagen, *Int. J. Pharm.* 221 (1) (2001) 1–22.

- [57] S. Young, M. Wong, Y. Tabata, A.G. Mikos, Gelatin as a delivery vehicle for the controlled release of bioactive molecules, *J. Contr. Release* 109 (1) (2005) 256–274.
- [58] K. Rezwan, Q.Z. Chen, J.J. Blaker, A.R. Boccaccini, Biodegradable and bioactive porous polymer/inorganic composite scaffolds for bone tissue engineering, *Biomaterials* 27 (18) (2006) 3413–3431.
- [59] L.S. Nair, C.T. Laurencin, Biodegradable polymers as biomaterials, *Prog. Polym. Sci.* 32 (8) (2007) 762–798.
- [60] D. Puppi, F. Chiellini, A.M. Piras, E. Chiellini, Polymeric materials for bone and cartilage repair, *Prog. Polym. Sci.* 35 (4) (2010) 403–440.
- [61] A. López-Noriega, E. Quinlan, N. Celikkin, F.J. O'Brien, Incorporation of polymeric microparticles into collagen-hydroxyapatite scaffolds for the delivery of a pro-osteogenic peptide for bone tissue engineering, *Apl. Mater.* 3 (1) (2015).
- [62] A. Przekora, K. Palka, G. Ginalska, Biomedical potential of chitosan/HA and chitosan/ $\beta$ -1,3-glucan/HA biomaterials as scaffolds for bone regeneration—A comparative study, *Mater. Sci. Eng. C* 58 (2016) 891 Materials for biological applications.
- [63] J. Qin, Z. Zhong, J. Ma, Biomimetic synthesis of hybrid hydroxyapatite nanoparticles using nanogel template for controlled release of bovine serum albumin, *Mater. Sci. Eng. C* 62 (2016) 377 Materials for biological applications.
- [64] N. Sultana, M. Mokhtar, M.I. Hassan, R.M. Jin, F. Roozbahani, T.H. Khan, Chitosan-based Nanocomposite Scaffolds for Tissue Engineering Applications, *Materials and Manufacturing Processes*, (2014).
- [65] T. Niemela, Effect of beta-tricalcium phosphate addition on the in vitro degradation of self-reinforced poly-L,D-lactide, *Polym. Degrad. Stab.* 89 (3) (2005) 492–500.
- [66] B.L. Eppley, Biomechanical testing of alloplastic PMMA cranioplasty materials, *J. Craniofac. Surg.* 16 (1) (2005) 140–143.
- [67] M. Lampin, R. Warocquier-Clérout, C. Legris, M. Degrange, M.F. Sigot-Luizard, Correlation between substratum roughness and wettability, cell adhesion, and cell migration, *J. Biomed. Mater. Res.* 36 (1) (1997) 99–108.
- [68] C. Ambrose, T. Clanton, Bioabsorbable implants: review of clinical experience in orthopedic surgery, *Ann. Biomed. Eng.* 32 (1) (2004) 171–177.
- [69] M. Baro, E. Sánchez, A. Delgado, A. Perera, C. Évora, In vitro–in vivo characterization of gentamicin bone implants, *J. Contr. Release* 83 (3) (2002) 353–364.
- [70] R. Li, D. Yao, Preparation of single poly(lactic acid) composites, *J. Appl. Polym. Sci.* 107 (5) (2008) 2909–2916.
- [71] G. Narayanan, V.N. Vernekar, E.L. Kuyinu, C.T. Laurencin, Poly (lactic acid)-based biomaterials for orthopaedic regenerative engineering, *Adv. Drug Deliv. Rev.* 107 (2016) 247–276.
- [72] S.R. Shah, A.M. Tataru, R.N. Souza, A.G. Mikos, F.K. Kasper, Evolving strategies for preventing biofilm on implantable materials, *Mater. Today* 16 (5) (2013) 177–182.
- [73] A.J. Lasprilla, G.A. Martinez, B.H. Lunelli, A.L. Jardini, R.M. Filho, Poly-lactic acid synthesis for application in biomedical devices - a review, *Biotechnol. Adv.* 30 (1) (2012) 321–328.
- [74] C. Migliaresi, A. De Lollis, L. Fambri, D. Cohn, The effect of thermal history on the crystallinity of different molecular weight PLLA biodegradable polymers, *Clin. Mater.* 8 (1) (1991) 111–118.
- [75] C. Crecelius, Soft tissue trauma, *Atlas Oral Maxillofac. Surg. Clin.* 21 (1) (2013) 49–60.
- [76] J.D. Currey, The design of mineralised hard tissues for their mechanical functions, *J. Exp. Biol.* 202 (23) (1999) 3285–3294.
- [77] G.A. Holzapfel, Biomechanics of soft tissue, *The Handbook of Materials Behavior Models*, vol. 3, 2001, pp. 1049–1063.
- [78] K. Van de Velde, P. Kiekens, Biopolymers: overview of several properties and consequences on their applications, *Polym. Test.* 21 (4) (2002) 433–442.
- [79] B.D. Ulery, L. Nair, C.T. Laurencin, Biomedical applications of biodegradable polymers, *J. Polym. Sci. B Polym. Phys.* (2011) 832–864.
- [80] F. Haghghat, S.A.H. Ravandi, Mechanical properties and in vitro degradation of PLGA suture manufactured via electrospinning, *Fibers Polym.* 15 (1) (2014) 71–77.
- [81] F. Sadat Tabatabaei Mirakabad, K. Nejati-Koshki, A. Akbarzadeh, M.R. Yamchi, M. Milani, N. Zarghami, V. Zeighamian, A. Rahimzadeh, S. Alimohammadi, Y. Hanifehpour, S.W. Joo, PLGA-based nanoparticles as cancer drug delivery systems, *Asian Pac. J. Cancer Prev. APJCP* 15 (2) (2014) 517–535.
- [82] J.C. Kleinschmidt, L.J. Marden, D. Kent, N. Quigley, J.O. Hollinger, A multiphase system bone implant for regenerating the calvaria, *Plast. Reconstr. Surg.* 91 (4) (1993) 581–588.
- [83] G. Gonzalez, C. Albano, J. Palacios, PLLA-HA Composites: Synthesis and Characterization, (2012), pp. 241–243.
- [84] R. Drumright, P.R. Gruber, D.E. Henton, Poly(lactic Acid) Technology, (2000).
- [85] M.S. Lopes, A.L. Jardini, R.M. Filho, Poly (lactic acid) production for tissue engineering applications, *Procedia Eng.* 42 (Supplement C) (2012) 1402–1413.
- [86] R.L. Flores, H. Liss, S. Raffaelli, A. Humayun, K.S. Khouri, P.G. Coelho, L. Witek, The technique for 3D printing patient-specific models for auricular reconstruction, *J. Cranio-Maxillofacial Surg.* 45 (6) (2017) 937–943.
- [87] S.V. Dorozhkin, Calcium orthophosphate-based biocomposites and hybrid biomaterials, *J. Mater. Sci.* 44 (9) (2009) 2343–2387.
- [88] J.F. Mano, R.A. Sousa, L.F. Boesel, N.M. Neves, R.L. Reis, Bioinert, biodegradable and injectable polymeric matrix composites for hard tissue replacement: state of the art and recent developments, *Compos. Sci. Technol.* 64 (6) (2004) 789–817.
- [89] D.E. Henton, P. Gruber, J. Lunt, J. Randall, Natural Fibers, Biopolymers, and Biocomposites, Boca Raton, (2005), pp. 527–577.
- [90] S.S. Ray, M. Okamoto, Biodegradable polylactide and its nanocomposites: opening a new dimension for plastics and composites, *Macromol. Rapid Commun.* 24 (14) (2003) 815–840.
- [91] I. Pillin, N. Montrelay, A. Bourmaud, Y. Grohens, Effect of thermo-mechanical cycles on the physico-chemical properties of poly(lactic acid), *Polym. Degrad. Stab.* 93 (2) (2008) 321–328.
- [92] H. Younes, D. Cohn, Phase separation in poly(ethylene glycol)/poly(lactic acid) blends, *Eur. Polym. J.* 24 (8) (1988) 765–773.
- [93] T. Maharana, B. Mohanty, Y.S. Negi, Melt–solid polycondensation of lactic acid and its biodegradability, *Prog. Polym. Sci.* 34 (1) (2009) 99–124.
- [94] H. Tsuji, S. Miyauchi, Poly(l-lactide): VI Effects of crystallinity on enzymatic hydrolysis of poly(l-lactide) without free amorphous region, *Polym. Degrad. Stab.* 71 (3) (2001) 415–424.
- [95] J. Yul Lim, S.-H. Kim, S. Lim, Y. Ha Kim, Improvement of Flexural Strengths of Poly(L-lactic Acid) by Solid-State Extrusion, 2. Extrusion through Rectangular Die, (2003).
- [96] P.E. Haers, R. Suuronen, C. Lindqvist, H. Sailer, Biodegradable polylactide plates and screws in orthognathic surgery: technical note, *J. Cranio-Maxillo-Fac. Surg. Official Publ. Eur. Assoc. Cranio-Maxillo-Fac. Surg.* 26 (2) (1998) 87–91.
- [97] K. Hamad, M. Kaseem, H. Yang, F. Deri, Y. Ko, Properties and medical applications of polylactic acid: a review, *Express Polym. Lett.* 9 (5) (2015).
- [98] O.M. Bostman, Absorbable implants for the fixation of fractures, *J. Bone Joint Surg. Am.* 73 (1) (1991) 148–153.
- [99] J.W. Leenslag, A.J. Pennings, R.R.M. Bos, F.R. Rozema, G. Boering, Resorbable materials of poly(l-lactide). VI. Plates and screws for internal fracture fixation, *Biomaterials* 8 (1) (1987) 70–73.
- [100] W.H. Akeson, S.L.Y. Woo, L. Rutherford, R.D. Coutts, M. Gonsalves, D. Amiel, The effects of rigidity of internal fixation plates on long bone remodeling: a bio mechanical and quantitative histological study, *Acta Orthop. Scand.* 47 (3) (1976) 241–249.
- [101] S. Hanafusa, Y. Matsusue, T. Yasunaga, T. Yamamuro, M. Oka, Y. Shikinami, Y. Ikada, Biodegradable plate fixation of rabbit femoral shaft osteotomies. A comparative study, *Clin. Orthop. Relat. Res.* (315) (1995) 262–271.
- [102] H.R. Lin, C.J. Kuo, C.Y. Yang, S.Y. Shaw, Y.J. Wu, Preparation of macroporous biodegradable PLGA scaffolds for cell attachment with the use of mixed salts as porogen additives, *J. Biomed. Mater. Res.* 63 (3) (2002) 271–279.
- [103] L. Singh, V. Kumar, B.D. Ratner, Generation of porous microcellular 85/15 poly (dl-lactide-co-glycolide) foams for biomedical applications, *Biomaterials* 25 (13) (2004) 2611–2617.
- [104] A.R. Boccaccini, J.J. Blaker, V. Maquet, R.M. Day, R. Jérôme, Preparation and characterisation of poly(lactide-co-glycolide) (PLGA) and PLGA/Bioglass® composite tubular foam scaffolds for tissue engineering applications, *Mater. Sci. Eng. C* 25 (1) (2005) 23–31.
- [105] F.G. Torres, S.N. Nazhat, S.H. Sheikh Md Fadzullah, V. Maquet, A.R. Boccaccini, Mechanical properties and bioactivity of porous PLGA/TiO<sub>2</sub> nanoparticle-filled composites for tissue engineering scaffolds, *Compos. Sci. Technol.* 67 (6) (2007) 1139–1147.
- [106] P. Zhang, Z. Hong, T. Yu, X. Chen, X. Jing, In vivo mineralization and osteogenesis of nanocomposite scaffold of poly(lactide-co-glycolide) and hydroxyapatite surface-grafted with poly(l-lactide), *Biomaterials* 30 (1) (2009) 58–70.
- [107] C. Shuai, B. Yang, S. Peng, Z. Li, Development of composite porous scaffolds based on poly(lactide-co-glycolide)/nano-hydroxyapatite via selective laser sintering, *Int. J. Adv. Manuf. Technol.* 69 (1) (2013) 51–57.
- [108] M.J. Hargis, B.P. Grady, Effect of sample size on isothermal crystallization measurements performed in a differential scanning calorimeter: a method to determine avrami parameters without sample thickness effects, *Thermochim. Acta* 443 (2) (2006) 147–158.
- [109] M.C. Kuo, C.M. Tsai, J.C. Huang, M. Chen, PEEK composites reinforced by nano-sized SiO<sub>2</sub> and Al<sub>2</sub>O<sub>3</sub> particulates, *Mater. Chem. Phys.* 90 (1) (2005) 185–195.
- [110] Y.H. Lai, M.C. Kuo, J.C. Huang, M. Chen, On the PEEK composites reinforced by surface-modified nano-silica, *Mater. Sci. Eng. A* 458 (1) (2007) 158–169.
- [111] T.D. Lam, T.V. Hoang, D.T. Quang, J.S. Kim, Effect of nanosized and surface-modified precipitated calcium carbonate on properties of CaCO<sub>3</sub>/polypropylene nanocomposites, *Mater. Sci. Eng. A* 501 (1) (2009) 87–93.
- [112] P.-L. Lin, H.-W. Fang, T. Tseng, W.-H. Lee, Effects of hydroxyapatite dosage on mechanical and biological behaviors of polylactic acid composite materials, *Mater. Lett.* 61 (14) (2007) 3009–3013.
- [113] M. Todo, S.D. Park, K. Arakawa, Y. Takenoshita, Relationship between micro-structure and fracture behavior of bioabsorbable HA/PLLA composites, *Composites Part A* 37 (12) (2006) 2221–2225.
- [114] D. Santos, D.M. Silva, P.S. Gomes, M.H. Fernandes, J.D. Santos, V. Sencadas, Multifunctional PLLA-ceramic fiber membranes for bone regeneration applications, *J. Colloid Interface Sci.* 504 (2017) 101–110.
- [115] L. Guan, J.E. Davies, Preparation and characterization of a highly macroporous biodegradable composite tissue engineering scaffold, *J. Biomed. Mater. Res. A* 71 (3) (2004) 480–487.
- [116] D.W. Huttmacher, Scaffold design and fabrication technologies for engineering tissues — state of the art and future perspectives, *J. Biomater. Sci. Polym. Ed.* 12 (1) (2001) 107–124.
- [117] Y. Jung, S. Kim, S.-S. Kim, H.J. You, B.S. Kim, S. Kim, Y.H. Kim, Tissue Engineered Bone Formation with Polymer/ceramic Composites by Press-and-baking Method, (2005).
- [118] W. Zongliang, W. Yu, I. Yoshihiro, Z. Peibiao, C. Xuesi, A comparative study on the in vivo degradation of poly(L-lactide) based composite implants for bone fracture fixation, *Sci. Rep.* 6 (1) (2016).
- [119] X. Liu, P.X. Ma, Polymeric scaffolds for bone tissue engineering, *Ann. Biomed. Eng.* 32 (3) (2004) 477–486.
- [120] S.M. Peltola, F.P.W. Melchels, D.W. Grijpma, M. Kellomki, A review of rapid

- prototyping techniques for tissue engineering purposes, *Ann. Med.* 40 (4) (2008) 267–280.
- [121] E. Sachlos, J.T. Czernuszka, Making Tissue Engineering Scaffolds Work. Review: the application of solid freeform fabrication technology to the production of tissue engineering scaffolds, *Eur. Cell. Mater.* 5 (2003) 29–40.
- [122] A.E. Jakus, R.N. Shah, Multi and mixed 3D-printing of graphene-hydroxyapatite hybrid materials for complex tissue engineering, *J. Biomed. Mater. Res. A* 105 (1) (2017) 274–283.
- [123] F.S. Senatov, K.V. Niaza, M.Y. Zadorozhnyy, A.V. Maksimkin, S.D. Kaloshkin, Y.Z. Estrin, Mechanical properties and shape memory effect of 3D-printed PLA-based porous scaffolds, *J. Mech. Behav. Biomed. Mater.* 57 (2016) 139–148.
- [124] J.E. Trachtenberg, J.K. Placone, B.T. Smith, J.P. Fisher, A.G. Mikos, Extrusion-based 3D printing of poly(propylene fumarate) scaffolds with hydroxyapatite gradients, *J. Biomater. Sci. Polym. Ed.* 28 (6) (2017) 532–554.
- [125] G.-H. Wu, S.-h. Hsu, Review: polymeric-based 3D printing for tissue engineering, *J. Med. Biol. Eng.* 35 (3) (2015) 285–292.
- [126] I. Chiulan, A.N. Frone, C. Brandabur, D.M. Panaitescu, Recent advances in 3D printing of aliphatic polyesters, *Bioengineering (Basel, Switzerland)* 5 (1) (2017).
- [127] F.P.W. Melchels, J. Feijen, D.W. Grijpma, A review on stereolithography and its applications in biomedical engineering, *Biomaterials* 31 (24) (2010) 6121–6130.
- [128] I. Zein, D.W. Hutmacher, K.C. Tan, S.H. Teoh, Fused deposition modeling of novel scaffold architectures for tissue engineering applications, *Biomaterials* 23 (4) (2002) 1169–1185.
- [129] S. Kumar, Selective laser sintering: a qualitative and objective approach, *J. Miner. Met. Mater. Soc. (TMS)* 55 (10) (2003) 43–47.
- [130] Y.-J. Seol, H.-W. Kang, S.-J. Lee, A. Atala, J.-J. Yoo, Bioprinting technology and its applications, *Eur. J. Cardio. Thorac. Surg.* 46 (3) (2014) 342–348.
- [131] C. Esposito Corcione, F. Gervaso, F. Scalera, F. Montagna, T. Maiullaro, A. Sannino, A. Maffezzoli, 3D printing of hydroxyapatite polymer-based composites for bone tissue engineering, *J. Polym. Eng.* (2017) 741.
- [132] D. Vyas, D. Udyawar, A review on current state of art of bioprinting, in: L.J. Kumar, P.M. Pandey, D.I. Wimpenny (Eds.), *3D Printing and Additive Manufacturing Technologies*, Springer Singapore, Singapore, 2019, pp. 195–201.
- [133] T.A. Sidambe, Biocompatibility of advanced manufactured titanium implants—a review, *Materials* 7 (12) (2014).
- [134] 3D Bio-printing Approaches for Tissue Engineering Applications, By Liam Critchley. <https://www.azom.com/article.aspx?ArticleID=13810>.
- [135] 3D Rapid Prototyping Selective Laser Sintering SLS Services. <https://www.indiamart.com/proddetail/3d-rapid-prototyping-selective-laser-sintering-sls-services-19899095048.html>.
- [136] Selective Laser Sintering. <https://www.custompartnet.com/wu/selective-laser-sintering>.
- [137] Stereolithography: The Future of Dental Fabrication. <http://decisionsindustry.com/article/stereolithography-future-dental-fabrication/>.
- [138] Stereolithography (SLA). <https://www.tth.com/3d-printing/sla-prototyping/>.
- [139] Fused Deposition Modeling (FDM).
- [140] C. Liu, Z. Xia, J.T. Czernuszka, Design and development of three-dimensional scaffolds for tissue engineering, *Chem. Eng. Res. Des.* 85 (7 A) (2007) 1051–1064.
- [141] F.P.W. Melchels, J. Feijen, D.W. Grijpma, A poly( d, l-lactide) resin for the preparation of tissue engineering scaffolds by stereolithography, *Biomaterials* 30 (23) (2009) 3801–3809.
- [142] V.M. Sean, A. Anthony, 3D bioprinting of tissues and organs, *Nat. Biotechnol.* 32 (8) (2014) 773.
- [143] N. Sears, D. Seshadri, P. Dhavalikar, E. Cosgriff-Hernandez, A Review of Three-dimensional Printing in Tissue Engineering, Mary Ann Liebert, Inc., New Rochelle, 2016, pp. 298–310.
- [144] X. Wang, M. Jiang, Z. Zhou, J. Gou, D. Hui, 3D printing of polymer matrix composites: a review and prospective, *Compos. B* 110 (2017) 442–458.
- [145] O. Mohamed, S. Masood, J. Bhowmik, Optimization of fused deposition modeling process parameters: a review of current research and future prospects, *Adv. Manuf.* 3 (1) (2015) 42–53.
- [146] J. Kruth, X. Wang, T. Laoui, L. Froyen, Lasers and materials in selective laser sintering, *Assemb. Autom.* 23 (4) (2003).
- [147] A. Mazzoli, Selective laser sintering in biomedical engineering, *Med. Biol. Eng. Comput.* 51 (3) (2012) 1–12.
- [148] P. Bajaj, R.M. Schweller, A. Khademosseini, J.L. West, R. Bashir, 3D biofabrication strategies for tissue engineering and regenerative medicine, *Annu. Rev. Biomed. Eng.* 16 (2014) 247–276.
- [149] K.W. Binder, A.J. Allen, J.J. Yoo, A. Atala, Drop-on-demand inkjet bioprinting: A primer, *Gene Ther. Regul.* 06 (01) (2011) 33–49.
- [150] S. Yang, K.-F. Leong, Z. Du, C.-K. Chua, The design of scaffolds for use in tissue engineering. Part I. Traditional factors, *Tissue Eng.* 7 (6) (2001) 679–689.
- [151] A. Butscher, M. Bohner, N. Doebelin, S. Hofmann, R. Müller, New depowdering-friendly designs for three-dimensional printing of calcium phosphate bone substitutes, *Acta Biomater.* 9 (11) (2013) 9149–9158.
- [152] R. Matsuzaki, M. Ueda, M. Namiki, T.-K. Jeong, H. Asahara, K. Horiguchi, T. Nakamura, A. Todoroki, Y. Hirano, Three-dimensional printing of continuous-fiber composites by in-nozzle impregnation, *Sci. Rep.* 6 (2016) 23058.
- [153] Z. Bin, S. Baekhoon, N. VuDat, B. Doyoung, 3D printing of high-resolution PLA-based structures by hybrid electrohydrodynamic and fused deposition modeling techniques, *J. Microchem. Microeng.* 26 (2) (2016) 025015.
- [154] S. Shaffer, K. Yang, J. Vargas, M.A. Di Prima, W. Voit, On reducing anisotropy in 3D printed polymers via ionizing radiation, *Polymer* 55 (23) (2014) 5969–5979.
- [155] K. Van Dijk, H.G. Schaeken, C.H.M. Marée, J. Verhoeven, J.C.G. Wolke, F.H.P.M. Habraken, J.A. Jansen, Influence of Ar pressure on r.f. magnetron-sputtered Ca5(PO4)3OH layers, *Surf. Coating. Technol.* 76–77 (1995) 206–210.
- [156] K. Van Dijk, H.G. Schaeken, J.C.G. Wolke, C.H.M. Marée, F.H.P.M. Habraken, J. Verhoeven, J.A. Jansen, Influence of discharge power level on the properties of hydroxyapatite films deposited on Ti6Al4V with RF magnetron sputtering, *J. Biomed. Mater. Res.* 29 (2) (1995) 269–276.
- [157] Y. Han, K. Xu, G. Montay, T. Fu, J. Lu, Evaluation of nanostructured carbonated hydroxyapatite coatings formed by a hybrid process of plasma spraying and hydrothermal synthesis, *J. Biomed. Mater. Res.* 60 (4) (2002) 511–516.
- [158] R.B. Heimann, Thermal spraying of biomaterials, *Surf. Coating. Technol.* 201 (5) (2006) 2012–2019.
- [159] Y. Yang, K.-H. Kim, J.L. Ong, A review on calcium phosphate coatings produced using a sputtering process—an alternative to plasma spraying, *Biomaterials* 26 (3) (2005) 327–337.
- [160] N. W -Aa, A. Thaveedeetrakul, B. Virote, Effect of Sputtering Power on in Vitro Bioactivity of Zirconia Thin Films Obtained by DC Unbalanced Magnetron Sputtering, (2012).
- [161] M. Dinu, A. Emil Kiss, A.C. Parau, V. Braic, C. Vitelaru, M. Braic, I. Pana, M. Balaceanu, A. Vladescu, Influence of Thermal Treatment on the Roughness, Corrosion Resistance and Wettability of Hydroxyapatite Films Deposited by RF Magnetron Sputtering, (2013).
- [162] E.O. López, A. Mello, H. Sendão, L.T. Costa, A.L. Rossi, R.O. Ospina, F.F. Borghi, J.G. Silva Filho, A.M. Rossi, Growth of crystalline hydroxyapatite thin films at room temperature by tuning the energy of the RF-magnetron sputtering plasma, *ACS Appl. Mater. Interfaces* 5 (19) (2013) 9435.
- [163] V.F. Pichugin, R.A. Surmenev, E.V. Shesterikov, M.A. Ryabtseva, E.V. Eshenko, S.I. Tverdokhlebov, O. Prymak, M. Epple, The preparation of calcium phosphate coatings on titanium and nickel–titanium by rf-magnetron-sputtered deposition: composition, structure and micromechanical properties, *Surf. Coating. Technol.* 202 (16) (2008) 3913–3920.
- [164] J. Shin, K. Lee, J. Koh, H. Son, H. Kim, H.P. Lim, K. Yun, G. Oh, S. Lee, H. Oh, K. Lee, G. Hwang, S.W. Park, Hydroxyapatite coatings on nanotubular titanium dioxide thin films prepared by radio frequency magnetron sputtering, *J. Nanosci. Nanotechnol.* 13 (8) (2013) 5807–5810.
- [165] R.A. Surmenev, A review of plasma-assisted methods for calcium phosphate-based coatings fabrication, *Surf. Coating. Technol.* 206 (2011) 2035–2056.
- [166] R.A. Surmenev, M.A. Surmeneva, K.E. Evdokimov, V.F. Pichugin, T. Peitsch, M. Epple, The influence of the deposition parameters on the properties of an rf-magnetron-deposited nanostructured calcium phosphate coating and a possible growth mechanism, *Surf. Coating. Technol.* 205 (12) (2011) 3600–3606.
- [167] S. Takayanagi, T. Yanagitani, M. Matsukawa, Unusual growth of polycrystalline oxide film induced by negative ion bombardment in the capacitively coupled plasma deposition, *Appl. Phys. Lett.* 101 (23) (2012).
- [168] S. Takuya, O. Kazuhiko, W. Akira, The effect of implant surfaces sputter-coated with hydroxyapatite target, *J. Hard Tissue Biol.* 22 (1) (2013) 67–77.
- [169] T. Crouzier, K. Ren, C. Nicolas, C. Roy, C. Picart, Layer-by-layer films as a biomimetic reservoir for rhBMP-2 delivery: controlled differentiation of myoblasts to osteoblasts, *Small* 5 (5) (2009) 598–608.
- [170] H. Matthias, H. Christian, Nanomaterials in preventive dentistry, *Nat. Nanotechnol.* 5 (8) (2010) 565.
- [171] A.R. Boccaccini, S. Keim, R. Ma, Y. Li, I. Zhitomirsky, Electrophoretic deposition of biomaterials, *J. R. Soc. Interface* 7 (5) (2010) 581–613.
- [172] F. Chen, W.M. Lam, C.J. Lin, G.X. Qiu, Z.H. Wu, K.D.K. Luk, W.W. Lu, Biocompatibility of electrophoretic deposition of nanostructured hydroxyapatite coating on roughen titanium surface: in vitro evaluation using mesenchymal stem cells, *J. Biomed. Mater. Res. B Appl. Biomater.* 82 (1) (2007) 183–191.
- [173] K. Gross, C. Chai, G. Kannangara, B. Ben-Nissan, L. Hanley, Thin hydroxyapatite coatings via sol–gel synthesis, *Official Journal of the European Society for Biomaterials* 9 (12) (1998) 839–843.
- [174] P. Layrolle, A. Ito, T. Tateishi, Sol-gel synthesis of amorphous calcium phosphate and sintering into microporous hydroxyapatite bioceramics, *J. Am. Ceram. Soc.* 81 (6) (1998) 1421–1428.
- [175] K.S. Joshy, S. Snigdha, S. Thomas, Chapter 16 - plasma modified polymeric materials for scaffolding of bone tissue engineering, in: S. Thomas, M. Mozetič, U. Cvelbar, P. Špatenka, P.K. M (Eds.), *Non-Thermal Plasma Technology for Polymeric Materials*, Elsevier, 2019, pp. 439–458.
- [176] E. Petrovicova, L.S. Schadler, Thermal spraying of polymers, *Int. Mater. Rev.* 47 (4) (2002) 169–190.
- [177] P.s.p. Anon, Plasma spraying process, (2010), (2010) Available at: <http://www.zircotec.com/page/plasma-spray-processing/39> (accessed April 2011).
- [178] D. AS, N. YuV, F. YuA, Vliánie naprãženiã smeniã na podložke na teksturu, magnetnye svojstva i morfologiju poverhnosti plenok nikelã, *Geteromagnitnaã Mikroelektronika* 13 (25) (2012).
- [179] D. AS, N. YuV, F. YuA, Vliánie naprãženiã smeniã na strukturu, morfologiu i magnetnye svojstva plenok nikelã, polužennyy magnetronnym raspyleniem na postoãnnom toke, *Nanoinženeriã* 2 (24) (2013).
- [180] P. Asanithi, S. Chaiyakun, P. Limsuwan, Growth of silver nanoparticles by DC magnetron sputtering, *J. Nanomater.* 2012 (2012) Article Number: 79.
- [181] E. Slavcheva, G. Ganske, U. Schnakenberg, Sputtered Pd as hydrogen storage for a chip-integrated microenergy system, *Sci. World J.* 2014 (2014).
- [182] E. Slavcheva, G. Ganske, G. Topalov, W. Mokwa, U. Schnakenberg, Effect of sputtering parameters on surface morphology and catalytic efficiency of thin platinum films, *Appl. Surf. Sci.* 255 (13) (2009) 6479–6486.
- [183] E.P. Slavcheva, Magnetron sputtered iridium oxide as anode catalyst for PEM hydrogen generation, *Macedonian J. Chem. Chem. Eng.* 30 (1) (2011) 45–54.
- [184] N. YuV, D. AS, F. YuA, Formirovanie teksturnykh plenok ferromagnitnykh 3-d metallov s različnoj kristallografičeskoj orientaciej i mikrostrukturam stroeniem metodom magnetronnogo raspyleniã na postoãnnom toke, *Nelinejnij Mir* 2 (5)

- (2013).
- [185] A.A. Ivanova, M.A. Surmeneva, R.A. Surmenev, D. Depla, Influence of deposition conditions on the composition, texture and microstructure of RF-magnetron sputter-deposited hydroxyapatite thin films, *Thin Solid Films* 591 (2015) 368–374.
- [186] J.O. Akindoyo, M.D.H. Beg, S. Ghazali, H.P. Heim, M. Feldmann, Impact modified PLA-hydroxyapatite composites – thermo-mechanical properties, *Compos. A. Appl. Sci. Manuf.* 107 (2018) 326–333.
- [187] Y. Zhang, K. Dong, F. Wang, H. Wang, J. Wang, Z. Jiang, S. Diao, Three dimensional macroporous hydroxyapatite/chitosan foam-supported polymer micelles for enhanced oral delivery of poorly soluble drugs, *Colloids Surfaces B Biointerfaces* 170 (2018) 497–504.
- [188] F.E. Baştan, M. Atiq Ur Rehman, Y.Y. Avcu, E. Avcu, F. Üstel, A.R. Boccaccini, Electrophoretic co-deposition of PEEK-hydroxyapatite composite coatings for biomedical applications, *Colloids Surfaces B Biointerfaces* 169 (2018) 176–182.
- [189] K. Ozeki, T. Masuzawa, H. Aoki, Fabrication of hydroxyapatite thin films on polyetheretherketone substrates using a sputtering technique, *Mater. Sci. Eng. C* 72 (2017) 576–582.
- [190] A. Naik, D.V. Shepherd, J.H. Shepherd, S.M. Best, R.E. Cameron, The effect of the type of HA on the degradation of PLGA/HA composites, *Mater. Sci. Eng. C* 70 (2017) 824–831.
- [191] X. Jing, H.-Y. Mi, L.-S. Turng, Comparison between PCL/hydroxyapatite (HA) and PCL/halloysite nanotube (HNT) composite scaffolds prepared by co-extrusion and gas foaming, *Mater. Sci. Eng. C* 72 (2017) 53–61.
- [192] J.O. Akindoyo, M.D.H. Beg, S. Ghazali, H.P. Heim, M. Feldmann, Effects of surface modification on dispersion, mechanical, thermal and dynamic mechanical properties of injection molded PLA-hydroxyapatite composites, *Compos. A. Appl. Sci. Manuf.* 103 (2017) 96–105.
- [193] Z. Wang, Y. Wang, Y. Ito, P. Zhang, X. Chen, A comparative study on the in vivo degradation of poly(L-lactide) based composite implants for bone fracture fixation, *Sci. Rep.* 6 (2016) 20770.
- [194] K.V. Niaza, F.S. Senatov, S.D. Kaloshkin, A.V. Maksimkin, D.I. Chukov, 3D-printed scaffolds based on PLA/HA nanocomposites for trabecular bone reconstruction, *J. Phys. Conf.* 741 (1) (2016) 012068.
- [195] J.W. Durham, A. Rabiei, Deposition, heat treatment and characterization of two layer bioactive coatings on cylindrical PEEK, *Surf. Coating Technol.* 301 (2016) 106–113.
- [196] G. Gherzi, F.C. Pavia, G. Conoscenti, G.A. Mannella, S. Greco, S. Rigogliuso, V.L. Carrubba, V. Brucato, PLLA scaffold via TIPS for bone tissue engineering, *Chem. Eng. Trans.* 49 301-306.
- [197] Y. Nishida, R. Domura, R. Sakai, M. Okamoto, S. Arakawa, R. Ishiki, M.R. Salick, L.-S. Turng, Fabrication of PLLA/HA composite scaffolds modified by DNA, *Polymer* 56 (2015) 73–81.
- [198] A. Naik, S.M. Best, R.E. Cameron, The influence of silanisation on the mechanical and degradation behaviour of PLGA/HA composites, *Mater. Sci. Eng. C* 48 (2015) 642–650.
- [199] M. Persson, G.S. Lorite, H.E. Kokkonen, S.-W. Cho, P.P. Lehenkari, M. Skrifvars, J. Tuukkanen, Effect of bioactive extruded PLA/HA composite films on focal adhesion formation of preosteoblastic cells, *Colloids Surfaces B Biointerfaces* 121 (2014) 409–416.
- [200] T. Endoğan, V. Hasirci, N. Hasirci, Preparation and Characterization of Chitosan and PLGA-based Scaffolds for Tissue Engineering Applications, (2014).
- [201] J. Liuyun, X. Chengdong, J. Lixin, X. Lijuan, Effect of HA with different grain size range on the crystallization behaviors and mechanical property of HA/PLGA composite, *Thermochim. Acta* 565 (2013) 52–57.
- [202] M.-J. Kim, Y.-H. Koh, Synthesis of aligned porous poly( $\epsilon$ -caprolactone) (PCL)/hydroxyapatite (HA) composite microspheres, *Mater. Sci. Eng. C* 33 (4) (2013) 2266–2272.
- [203] A.B. Kutikov, J. Song, An amphiphilic degradable polymer/hydroxyapatite composite with enhanced handling characteristics promotes osteogenic gene expression in bone marrow stromal cells, *Acta Biomater.* 9 (9) (2013) 8354–8364.
- [204] A. Abdal-hay, F.A. Sheikh, J.K. Lim, Air jet spinning of hydroxyapatite/poly(lactic acid) hybrid nanocomposite membrane mats for bone tissue engineering, *Colloids Surfaces B Biointerfaces* 102 (2013) 635–643.
- [205] C. Albano, G. Gonzalez, J. Palacios Gutiérrez, A. Karam, M. Covis, PLLA-HA Vs. PLGA-HA Characterization and Comparative Analysis, (2013).
- [206] S. Tanodekaew, S. Channasanon, P. Kaewkong, P. Uppanan, P.L.A.-H.A. Scaffolds, Preparation and Bioactivity, (2013).
- [207] J. Liuyun, X. Chengdong, C. Dongliang, J. Lixin, P. xiubing, Effect of n-HA with different surface-modified on the properties of n-HA/PLGA composite, *Appl. Surf. Sci.* 259 (2012) 72–78.
- [208] X. Li, H. Liu, J. Wang, C. Li, Preparation and characterization of PLLA/nHA nonwoven mats via laser melt electrospinning, *Mater. Lett.* 73 (2012) 103–106.
- [209] Z.-L. Mou, L.-J. Zhao, Q.-A. Zhang, J. Zhang, Z.-Q. Zhang, Preparation of porous PLGA/HA/collagen scaffolds with supercritical CO<sub>2</sub> and application in osteoblast cell culture, *J. Supercrit. Fluids* 58 (3) (2011) 398–406.
- [210] L. Lao, Y. Wang, Y. Zhu, Y. Zhang, C. Gao, Poly(lactide-co-glycolide)/hydroxyapatite nanofibrous scaffolds fabricated by electrospinning for bone tissue engineering, *J. Mater. Sci. Mater. Med.* 22 (8) (2011) 1873–1884.
- [211] G. Socol, A.M. Macovei, F. Mirouiu, N. Stefan, L. Duta, G. Dorcioman, I.N. Mihailescu, S.M. Petrescu, G.E. Stan, D.A. Marcov, A. Chiriac, I. Poata, Hydroxyapatite thin films synthesized by pulsed laser deposition and magnetron sputtering on PMMA substrates for medical applications, *Mater. Sci. Eng., B* 169 (1) (2010) 159–168.
- [212] C. Delabarde, C.J.G. Plummer, P.E. Bourban, J.A.E. Månson, Solidification behavior of PLLA/nHA nanocomposites, *Compos. Sci. Technol.* 70 (13) (2010) 1813–1819.
- [213] B.J. Papenburg, L.A.M. Bolhuis-Versteeg, D.W. Grijpma, J. Feijen, M. Wessling, D. Stamatiulis, A facile method to fabricate poly(l-lactide) nano-fibrous morphologies by phase inversion, *Acta Biomater.* 6 (7) (2010) 2477–2483.
- [214] H. Deplaine, J.L.G. Ribelles, G.G. Ferrer, Effect of the content of hydroxyapatite nanoparticles on the properties and bioactivity of poly(l-lactide) – hybrid membranes, *Compos. Sci. Technol.* 70 (13) (2010) 1805–1812.
- [215] R. Fang, E. Zhang, L. Xu, S. Wei, Electrospun PCL/JPLA/HA Based Nanofibers as Scaffold for Osteoblast-like Cells, (2010).
- [216] S. Eosoly, D. Brabazon, S. Lohfeld, L. Looney, Selective laser sintering of hydroxyapatite/poly- $\epsilon$ -caprolactone scaffolds, *Acta Biomater.* 6 (7) (2010) 2511–2517.
- [217] B. Duan, M. Wang, W.Y. Zhou, W.L. Cheung, Z.Y. Li, W.W. Lu, Three-dimensional nanocomposite scaffolds fabricated via selective laser sintering for bone tissue engineering, *Acta Biomater.* 6 (12) (2010) 4495–4505.
- [218] S. Gay, S. Arostegui, J. Lemaitre, Preparation and characterization of dense nanohydroxyapatite/PLLA composites, *Mater. Sci. Eng. C* 29 (1) (2009) 172–177.
- [219] M.P. Prabhakaran, J. Venugopal, S. Ramakrishna, Electrospun nanostructured scaffolds for bone tissue engineering, *Acta Biomater.* 5 (8) (2009) 2884–2893.
- [220] T. Tian, D. Jiang, J. Zhang, Q. Lin, Fabrication of bioactive composite by developing PLLA onto the framework of sintered HA scaffold, *Mater. Sci. Eng. C* 28 (1) (2008) 51–56.
- [221] J. Zhao, L.Y. Guo, X.B. Yang, J. Weng, Preparation of bioactive porous HA/PCL composite scaffolds, *Appl. Surf. Sci.* 255 (5) (2008) 2942–2946 Part 2.
- [222] S.I. Jeong, E.K. Ko, J. Yum, C.H. Jung, Y.M. Lee, H. Shin, Nanofibrous poly(lactide acid)/hydroxyapatite composite scaffolds for guided tissue regeneration, *Macromol. Biosci.* 8 (4) (2008) 328–338.
- [223] L. Shor, S. Güçeri, X. Wen, M. Gandhi, W. Sun, Fabrication of three-dimensional polycaprolactone/hydroxyapatite tissue scaffolds and osteoblast-scaffold interactions in vitro, *Biomaterials* 28 (35) (2007) 5291–5297.
- [224] S.-S. Kim, M. Sun Park, O. Jeon, C. Yong Choi, B.-S. Kim, Poly(lactide-co-glycolide)/hydroxyapatite composite scaffolds for bone tissue engineering, *Biomaterials* 27 (8) (2006) 1399–1409.
- [225] J. Russias, E. Saiz, R.K. Nalla, K. Gryn, R.O. Ritchie, A.P. Tomsia, Fabrication and mechanical properties of PLA/HA composites: a study of in vitro degradation, *Mater. Sci. Eng. C* 26 (8) (2006) 1289–1295 Biomimetic and supramolecular systems.
- [226] C.R. Kothapalli, M.T. Shaw, M. Wei, Biodegradable HA-PLA 3-D porous scaffolds: effect of nano-sized filler content on scaffold properties, *Acta Biomater.* 1 (6) (2005) 653–662.
- [227] J.M. Williams, A. Adewunmi, R.M. Schek, C.L. Flanagan, P.H. Krebsbach, S.E. Feinberg, S.J. Hollister, S. Das, Bone tissue engineering using polycaprolactone scaffolds fabricated via selective laser sintering, *Biomaterials* 26 (23) (2005) 4817–4827.
- [228] K.H. Tan, C.K. Chua, K.F. Leong, C.M. Cheah, W.S. Gui, W.S. Tan, F.E. Wira, Selective laser sintering of biocompatible polymers for applications in tissue engineering, *Bio Med. Mater. Eng.* 15 (1–2) (2005) 113–124.
- [229] V.J. Chen, P.X. Ma, Nano-fibrous poly(l-lactide acid) scaffolds with interconnected spherical macropores, *Biomaterials* 25 (11) (2004) 2065–2073.
- [230] P.P. Rajendra, U.T. Sunil, U.S. Suresh, T.T. Jalinder, J.D. Abraham, Biomedical applications of poly(lactide acid), *Recent Pat. Regen. Med.* 4 (1) (2014) 40–51.
- [231] M. Dziadek, E. Menaszek, B. Zagrajczuk, J. Pawlik, K. Cholewa-Kowalska, New generation poly( $\epsilon$ -caprolactone)/gel-derived bioactive glass composites for bone tissue engineering: Part I. Material properties, *Mater. Sci. Eng. C* 56 (2015) 9–21.
- [232] Y.M. Shin, J.-S. Park, S.I. Jeong, S.-J. An, H.-J. Gwon, Y.-M. Lim, Y.-C. Nho, C.-Y. Kim, Promotion of human mesenchymal stem cell differentiation on bioresorbable polycaprolactone/biphase calcium phosphate composite scaffolds for bone tissue engineering, *Biotechnol. Bioproc. Eng.* 19 (2) (2014) 341–349.
- [233] J. Ren, K.A. Blackwood, A. Doustgani, P.P. Poh, R. Steck, M.M. Stevens, M.A. Woodruff, Melt-electrospun polycaprolactone strontium-substituted bioactive glass scaffolds for bone regeneration, *J. Biomed. Mater. Res.* A 102 (9) (2013) 3140–3153.
- [234] S.P.P. Patriza, W.H. Dietmar, M.S. Molly, A.W. Maria, Fabrication and in vitro characterization of bioactive glass composite scaffolds for bone regeneration, *Biofabrication* 5 (4) (2013) 045005.
- [235] B. Lei, K.-H. Shin, D.-Y. Noh, I.-H. Jo, Y.-H. Koh, H.-E. Kim, S.E. Kim, Sol-gel derived nanoscale bioactive glass (NBG) particles reinforced poly( $\epsilon$ -caprolactone) composites for bone tissue engineering, *Mater. Sci. Eng. C* 33 (3) (2013) 1102–1108.
- [236] J. Wei, F. Chen, J.-W. Shin, H. Hong, C. Dai, J. Su, C. Liu, Preparation and characterization of bioactive mesoporous wollastonite – polycaprolactone composite scaffold, *Biomaterials* 30 (6) (2009) 1080–1088.
- [237] M. Raucci, V. Guarino, L. Ambrosio, Polymeric Composites, Prepared by Sol-gel Method, with Spatial Gradients of Hydroxyapatite Bioactive Signals, (2009).
- [238] D.E. Cutright, E.E. Hunsuck, The repair of fractures of the orbital floor using biodegradable polylactic acid, *Oral Surg. Oral Med. Oral Pathol.* 33 (1) (1972) 28–34.
- [239] C.-W. Lou, C.-H. Yao, Y.-S. Chen, T.-C. Hsieh, J.-H. Lin, W.-H. Hsing, Manufacturing and properties of PLA absorbable surgical suture, *Textil. Res. J.* 78 (11) (2008) 958–965.
- [240] P. Saini, M. Arora, M.N.V.R. Kumar, Poly(lactide acid) blends in biomedical applications, *Adv. Drug Deliv. Rev.* 107 (2016) 47–59.
- [241] A. Rakovsky, I. Gotman, E. Rabkin, E.Y. Gutmanas,  $\beta$ -TCP-poly(lactide) composite scaffolds with high strength and enhanced permeability prepared by a modified salt leaching method, *J. Mech. Behav. Biomed. Mater.* 32 (2014) 89–98.
- [242] T. Lou, X. Wang, G. Song, Z. Gu, Z. Yang, Fabrication of PLLA/ $\beta$ -TCP nanocomposite scaffolds with hierarchical porosity for bone tissue engineering, *Int. J. Biol. Macromol.* 69 (2014) 464–470.

- [243] A.M. El-Kady, E.A. Saad, B.M.A. El-Hady, M.M. Farag, Synthesis of silicate glass/poly(l-lactide) composite scaffolds by freeze-extraction technique: characterization and in vitro bioactivity evaluation, *Ceram. Int.* 36 (3) (2010) 995–1009.
- [244] B. Damadzadeh, H. Jabari, M. Skrifvars, K. Airola, N. Moritz, P.K. Vallittu, Effect of ceramic filler content on the mechanical and thermal behaviour of poly-l-lactide acid and poly-l-lactide-co-glycolic acid composites for medical applications, *J. Mater. Sci. Mater. Med.* 21 (9) (2010) 2523–2531.
- [245] J. Filipowska, J. Pawlik, K. Cholewa-Kowalska, G. Tylko, E. Pamula, L. Niedzwiedzki, M. Szuta, M. Laczka, A.M. Osyczka, Incorporation of sol-gel bioactive glass into PLGA improves mechanical properties and bioactivity of composite scaffolds and results in their osteoinductive properties, *Biomed. Mater.* 9 (6) (2014) 065001.
- [246] E. Pamula, J. Kokoszka, K. Cholewa-Kowalska, M. Laczka, L. Kantor, L. Niedzwiedzki, G.C. Reilly, J. Filipowska, W. Madej, M. Kolodziejczyk, G. Tylko, A.M. Osyczka, Degradation, bioactivity, and osteogenic potential of composites made of PLGA and two different sol-gel bioactive glasses, *Ann. Biomed. Eng.* 39 (8) (2011) 2114–2129.
- [247] S.-S. Kim, K.-M. Ahn, M.S. Park, J.-H. Lee, C.Y. Choi, B.-S. Kim, A poly(lactide-co-glycolide)/hydroxyapatite composite scaffold with enhanced osteoconductivity, *J. Biomed. Mater. Res. A* 80A (1) (2006) 206–215.
- [248] V. Maquet, A.R. Boccaccini, L. Pravata, I. Notingher, R. Jérôme, Porous poly( $\alpha$ -hydroxyacid)/Bioglass® composite scaffolds for bone tissue engineering. I: preparation and in vitro characterisation, *Biomaterials* 25 (18) (2004) 4185–4194.
- [249] A.R. Amini, C.T. Laurencin, S.P. Nukavarapu, Bone tissue engineering: recent advances and challenges, *Crit. Rev. Biomed. Eng.* 40 (5) (2012) 363–408.
- [250] S.S. Kim, H. Utsunomiya, J.A. Koski, B.M. Wu, M.J. Cima, J. Sohn, K. Mukai, L.G. Griffith, J.P. Vacanti, Survival and function of hepatocytes on a novel three-dimensional synthetic biodegradable polymer scaffold with an intrinsic network of channels, *Ann. Surg.* 228 (1) (1998) 8–13.
- [251] L.-C. Gerhardt, K.L. Widdows, M.M. Erol, C.W. Burch, J.A. Sanz-Herrera, I. Ochoa, R. Stämpfli, I.S. Roqan, S. Gabe, T. Ansari, A.R. Boccaccini, The pro-angiogenic properties of multi-functional bioactive glass composite scaffolds, *Biomaterials* 32 (17) (2011) 4096–4108.
- [252] V. Maquet, A.R. Boccaccini, L. Pravata, I. Notingher, R. Jérôme, Preparation, characterization, and in vitro degradation of bioresorbable and bioactive composites based on Bioglass®-filled polylactide foams, *J. Biomed. Mater. Res. A* 66A (2) (2003) 335–346.
- [253] J.J. Blaker, J.E. Gough, V. Maquet, I. Notingher, A.R. Boccaccini, In vitro evaluation of novel bioactive composites based on Bioglass®-filled polylactide foams for bone tissue engineering scaffolds, *J. Biomed. Mater. Res. A* 67A (4) (2003) 1401–1411.