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## An overview of polyester/hydroxyapatite composites for bone tissue repairing

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## ABSTRACT

**Objectives:** The polyester/hydroxyapatite (polyester/HA) composites play an important role in bone tissue repairing, mostly because they mimic the composition and structure of naturally mineralized bone tissue. This review aimed to discuss commonly used geometries of polyester/HA composites, including microspheres, membranes, scaffolds and bulks, and their applications in bone tissue repairing and to discuss existed restrictions and developing trends of polyester/HA.**Methods:** The current review was conducted by searching Web of Science, and Google Scholar for relevant studies published related with polyester/HA composites. Selected studies were analyzed with a focus on the fabrication techniques, properties (mechanical properties, biodegradable properties and biological properties) and applications of polyester/HA composites in bone repairing.**Results:** A total of 111 articles were introduced to discuss the review. Different geometries of polyester/HA composites were discussed. In addition, properties and applications of polyester/HA composites were evaluated. The addition of HA into polyester can adjust the mechanical and biodegradability of composites. Besides, the addition of HA into polyester can improve its osteogenic abilities. The results showed that polyester/HA composites can ideal candidate for bone tissue repairing.**Conclusion:** Polyester/HA composites have many remarkable properties, such as appropriate mechanical strength, biodegradability, favorable biological properties. Diverse geometries of polyester/HA composites have been used in bone repairing, drug delivery and implant fixation. Further work needs to be done to investigate existed restrictions, including the controlled degradation rate, controlled drug release performance, well-matched mechanical properties, and novel fabrication techniques.**The translational potential of this article:** The present review reveals the current state of the polyester/HA composites used in bone tissue repairing, contributing to future trends of polyester/HA composites in the forthcoming future.

## 1. Introduction

Bone-related diseases derive from skeletal diseases, infections, congenital malformations or trauma, which can lead to permanent damage to many patients and make the treatment of bone-related disease a clinical challenge [1]. Nowadays, the golden standard for treating bone defect is autograft or allograft [2]. Autograft is more attractive because

there is no immune reaction in therapy. Whereas, the development of autograft is hampered by restricted availability and potential morbidity at donor sites. Allograft is more readily available, but there is a risk of disease transmission, immunogenicity and high incidence of non-union healing [1].

To solve problems mentioned above, as an alternative strategy, artificial bone repairing materials have been developed [3–6]. The

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commonly used bone repairing materials mainly include polymer materials, inorganic materials, metals and their composites [7]. Among polymer materials, polyesters such as poly(lactic acid) (PLA) [8], polycaprolactone (PCL) [9,10], poly(lactide-co-glycolide) (PLGA) [11,12], Poly(L-Lactic Acid) (PLLA) [13] and their composites have attracted much attention because of their excellent biodegradability and biocompatibility. These polymers have no toxicity to human body and with America Food and Drug Administration (FDA) approval. They can degrade within body gradually, with no residue, no stimulation and no toxic side effects to tissues. In addition, through adjusting molecular weight, choosing different polymerization methods and forming methods, the degradation rate and the mechanical properties of these biodegradable polymers can be controlled and adjusted to fulfill various clinical needs. However, there are some drawbacks with polyester, single polyester material has low mechanical strength, no biological activity, and the degraded acid products are not conducive to the growth of cells and tissues.

To handle with the above-mentioned problems, commonly, the addition of bioceramic components into polyester can significantly improve its mechanical strength, bioactivity and regulate the acidic microenvironment brought from the acidic degradation products of polyesters to induce bone formation and prevent the inflammatory reactions [14]. Hydroxyapatite [ $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ , HA] has a similar inorganic composition with natural bone tissues along with high mechanical strength, bioactivity, osteoinductivity, and osteoconductivity [15–17]. In addition, its medical products such as screws [18], plates [19] strongly connect to natural bone *in vivo*. These characteristics make HA an ideal biomaterial for bone repairing and common bioactive filler used in biocomposites.

To meet different needs of clinical applications, biocomposites have been produced in variety of geometries such as microsphere, membrane, scaffold and bulk. A series of techniques have been adopted to fabricate polyester/HA composites, including electrospinning [20], three-dimensional printing (3DP) [21], freezing emulsions [22], solvent evaporation method [23], injection molding [24], and forging [25], etc (Fig. 1). This review attempts to present a comprehensive study on polyester/HA composites. It will provide a comprehensive compendium regarding the main aspects of polyester/HA research, including the

fabricating techniques, properties such as mechanical properties, biodegradable properties, biological abilities and applications of the polyester/HA composites. Furthermore, future trends of polyester/HA composite such as improving mechanical properties, controlling degradation rates and the functionalization of the polyester/HA composite will be discussed. We hope that this review can and, therefore, stimulate their future development and biomedical applications.

## 2. Fabrication techniques to control various geometries of polyester/HA composites

To achieve desired bone repairing effect, polyester/HA composites have been fabricated into diverse geometries to satisfy different requirements during bone repairing process. Table 1 Summarizes various geometries and fabrication techniques for polyester/HA composites.

### 2.1. Microsphere

Microspheres are kinds of materials which in the form of spherical particles or hollow spheres. It is suitable for bone defect filling. The main advantage of this kind of material is injectable. Compared to 3D scaffolds, they can be used to repair bone defects with noninvasive or minimally invasive surgeries. Besides, it can fill irregularly shaped bone defects easily [26]. Due to their stable properties, they can be used as protective carriers for various biological factors, drugs and cells when used in bone repairing process. Furthermore, microspheres have high specific surface area, so they can provide large attachment surface for cells and promote the transformation of nutrients and oxygen through the space layered by microspheres. Therefore, they can be widely applied in bone tissue repairing and pharmaceutical fields. Since microspheres have great physical and biological properties, many techniques have been adopted to fabricate different kinds of microspheres.

#### 2.1.1. In-situ biomimetic mineralized deposition method

In-situ biomimetic mineralized deposition method is to immerse polyester microspheres in certain aqueous solution and utilize strong affinity of materials towards  $\text{Ca}^{2+}$  in solution [27,28]. Through this method, a uniform mineralization layer can be formed on the surface of polyester microsphere.

Aminated modified PLA/nanocrystalline HA (EPLA/nHA) composite microspheres were constructed for drug delivery via the biomimetic mineralized deposition method [29]. Firstly, EPLA microspheres were immersed in  $\text{Ca}(\text{NO}_3)_2$  solution. Secondly, the mineralization and crystallization process of nHA crystals on the surface of EPLA microspheres is achieved by separating the  $\text{Ca}^{2+}$ -absorbed microspheres from the solution and then immersing them in  $\text{K}_2\text{HPO}_4$  solution. Lastly, the EPLA/nHA composite microspheres were obtained by filtration.

#### 2.1.2. Freezing emulsions

Freezing emulsion method is a way which used to fabricate porous microspheres through controlling the freezing of emulsions. During freezing, emulsified droplets are converted into solid microspheres and solvent phase is removed through freeze drying. The frozen solvent microspheres are trapped in the matrix of water - soluble polymer, which supports the polymer matrix to remain solidified until it is removed by the succeeding freeze - drying process. Therefore, there is no problem of microsphere accumulation during solvent removal.

Moreover, porosity of the microspheres can be tuned simply through varying the internal emulsion phase or the concentration of the freeze - drying conditions. In addition, unique aligned porous microspheres can be achieved by applying a high temperature gradient across the emulsion droplets [30]. Aligned porous PCL/HA composite microspheres have been fabricated by Kim et al. [22] using freezing emulsions method. In this method, firstly, PCL/HA solutions with different HA ratios were poured into the fabricated PVA aqueous solution and stirred at room temperature. The beaker containing the mixed solution was then

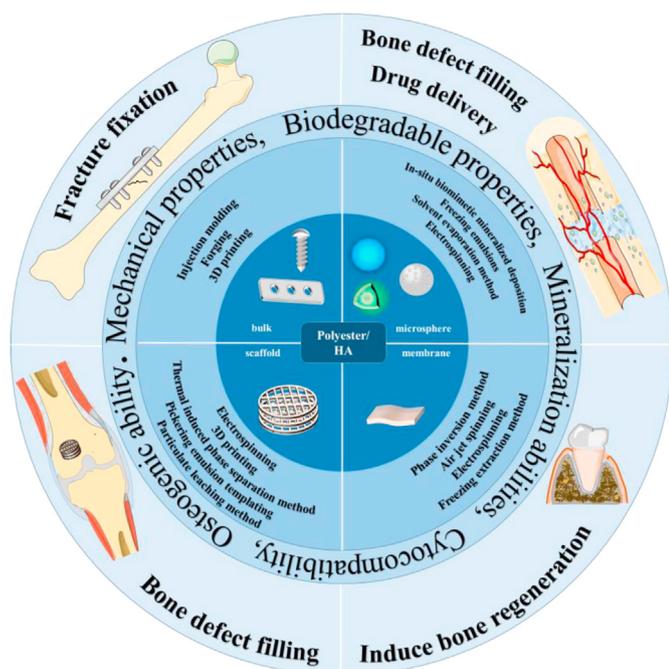


Fig. 1. Geometries, fabrication techniques, properties and applications for polyester/HA composites.

**Table 1**  
Fabrication techniques of different geometries for polyester/HA composites.

Types	Fabrication methods	Categories of polyester	Remarks for fabrication methods	Ref
<b>Microsphere</b>	In-situ biomimetic mineralized deposition method Freezing emulsions	PLA	*Form uniform mineralization layer. *Long mineralization time.	[29]
		PCL	*Varying the concentration of the freeze-drying conditions or the internal emulsion phase, the porosity in the microparticles can be tuned. *Unique aligned porous microparticles can be achieved by applying a high temperature gradient across the emulsion droplets.	[22]
	Solvent evaporation method	PCL	*Fabricate microspheres by removing the volatile solvent of dispersed phase from the emulsion. *Size of the microspheres can be controlled within the nanometer range.	[31]
		PLGA	*Simpler and more convenient. *The condition of microspheres fabricating was mild and applicable to adding the bioactive substance.	[32]
		PLA	*Does not need any large equipment and has a low running cost. *Based on the use of pressurized gas being dispensed at extreme velocity.	[36]
	Phase inversion method	PCL	*Simple operation, simple membrane making process and easy control of membrane structure. *Polymer changes from liquid to solid by adding non-solvent into the polymer.	[35]
		PLA	*Present a high surface-to-volume ratio. *Controllable porosity. *Excellent mechanical properties.	[42]
Air jet spinning	PLA	*The solvent and the polymer crystallize in the polymer-poor phase and the polymer-rich phase, respectively.	[45]	
	PLLA			
<b>Scaffold</b>	Electrospinning	PCL	*Have an extremely high surface-volume ration and a complex porous structure	[55]

**Table 1 (continued)**

Types	Fabrication methods	Categories of polyester	Remarks for fabrication methods	Ref
<b>Bulk</b>	3DP	PLA, PCL	with excellent pore-inter connectivity. *Fabricate personalized biological scaffolds with high dimensional accuracy and complex structure. *Customized shape, tailored pore size/porosity, tuned mechanical properties. *Flexibility in materials handling and processing *High mechanical properties.	[21]
		PLA		[60]
		PLLA	*Achieve polymer foams with porosity over 95%and pore diameter from 1 to 100 μm.	[61]
	Thermal induced phase separation technique	PLLA	*Simplicity and versatility.	[65]
		PLG	*Adjusting the size and proportion of the soluble particles, scaffold with different properties can be fabricated.	[66]
	Injection molding	PCL	*Materials with specific shapes and sizes.	[24]
PLLA		*Obtain forgings with certain mechanical properties, certain shape and size. *Porosity and other defects generated during the preparation of materials can be eliminated.	[25]	
	3DP	PLA	*Simple operation.	[67]

immersed in liquid nitrogen and frozen for 1 h to completely freeze the emulsion, then freeze dried for 12 h to remove the organic phase and water, and finally the microspheres were obtained by filtering and washing.

**2.1.3. Solvent evaporation method**

Solvent evaporation method is a method to fabricate microspheres by removing the volatile solvent of dispersed phase from the emulsion. The size of the microspheres can be controlled within nanometer range. Usually, the solvent evaporation method is based on the properties of the solvent and the polymer to produce oil/water (O/W), oil/water/oil (O/W/O), water/oil (W/O), water/oil/water (W/O/W), and emulsion systems. After the stable emulsion is formed, the organic solvent is diffused into the continuous phase and evaporated through the interface between the continuous phase and the air by means of heating, decompressing extraction or continuous stirring. Meanwhile, the microspheres are solidified gradually and the final microspheres along with the drug - loaded microspheres can be obtained through filtration, cleaning and drying.

Cheng et al. [31] fabricated hollow poly (lactic-co-glycolic acid)/-HA/calcium carbonate (PLGA/HA/CC) microsphere via emulsion solvent evaporation method. Firstly, PLGA was dissolved in dichloromethane to

form homogeneous solution. Then, a well dispersed slurry was obtained by adding HA particles into above mentioned solution with stirring. Subsequently, the slurry was added into poly (vinyl alcohol) (PVA) solution. Finally, solid PLGA/HA/CC microspheres were collected through washing and lyophilizing (Fig. 2).

#### 2.1.4. Electrospinning

Electrospinning is a method of forming microspheres by means of high voltage electrostatic field. In electrostatic field, the polymer liquid at low velocity delivered to the top of the capillary, a high voltage is applied to the top of the capillary and electrode. Because electrostatic charges concentrate on the surface of the droplet which suspended at the top of the capillary tube, the mutual repulsion of the same charges elongate the droplet, and at the appropriate voltage and velocity, the droplet deforms into a cone. A trickle of liquid arises at the top of the cone and splits into numerous tiny droplets. Finally, microspheres are formed through quickly dried or cooled liquid polymer droplets. Liu et al. [32] fabricated 3, 4 - dihydroxyphenylalanine - insulin - like growth factor -1 (DOP-A-IGF-1) coated HA/PLGA microspheres by electrospinning. Firstly, HA/PLGA solutions with different HA proportions were fabricated. Then, the fabricated working solution was absorbed with a syringe and placed in the propeller. Meanwhile, the receiving solution was placed under the nozzle. The target microsphere can be fabricated by adjusting the voltage, distance between the nozzle and the receiving solvent, and the propulsion speed.

## 2.2. Membrane

Membrane materials have been widely applied to meet different clinical needs, Guide bone regeneration (GBR) membrane such as artificial periosteum membrane is often used to induce bone tissue regeneration in defect sites. In dental field, GBR is an effective approach for bone tissue augmentation to address insufficient bone volume around dental implants [33]. Besides, artificial periosteal materials were

developed based on the structural and functions of the periosteum. It not only provides stable space for new bone formation but also prevent soft tissues from penetrating into bone defects areas and assist anatomical bone reconstruction.

However, there are some drawbacks to GBR membranes, such as lack of sufficient mechanical strength, bioactivities and suitable degradation profile [34]. To overcome these problems, polyester/HA composites have been fabricated as GBR membranes to realize excellent bone regeneration effect. There are several methods have been developed to fabricate polyester/HA composite membranes including phase inversion methodology, air jet spinning, electrospinning and freeze extraction method.

#### 2.2.1. Phase inversion method

Phase inversion method is one of the most used film forming methods because of its simple operation, making process and easily controlling the structure of membrane. Phase inversion is mainly a process in which the polymer changes from liquid to solid by adding non-solvent into the polymer. This curing process is firstly initiated by the transformation of a homogeneous liquid into two layered liquids. When the stratification reaches a certain degree, one of the liquids solidifies and finally forms a solid body.

Functionalized PCL/HA composite membranes for bone repairing were fabricated by Basile et al. [35] using solvent - non phase inversion methodology. Firstly, HA nano - whiskers were predispersed into a little amount of  $\text{CHCl}_3$  through sonication, and the dispersion was then added to the polymer solution with stirring for 30 s. Secondly, the mixture was poured into a glass petridish and then the dish was immersed in a hexane contained bath rapidly. A thin skin was formed by the gradual solidification at the interface between the polymer solution and the hexane. Finally, the hardened polymer membrane was received 2 h later.

#### 2.2.2. Air jet spinning (AJS)

As a fresh and facile composite fabricating technique, air jet spinning (AJS) can produce multifunctional materials used in tissue repairing and

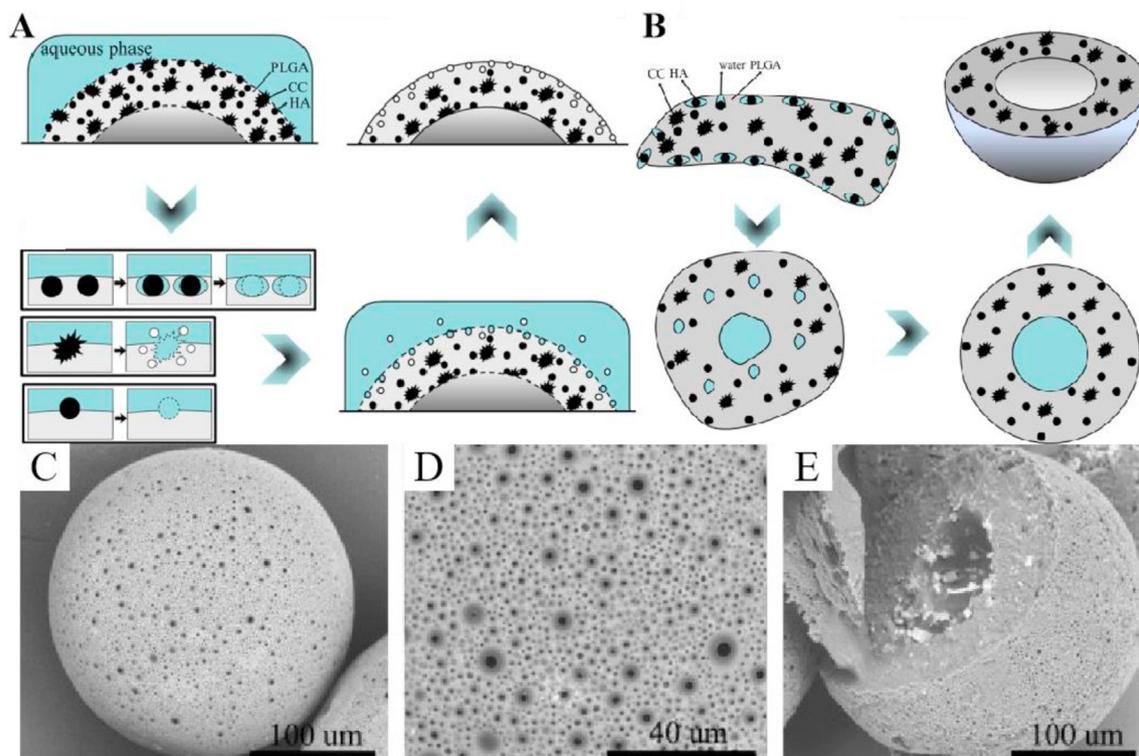


Fig. 2. (A) Formation process of superficial open macropores and (B) hollow structure in PLGA/HA/CC microspheres. (C-E) SEM images of PLGA/HA/CC microsphere: (C, D) morphologies images and (E) cross-section images [31].

tissue engineering fields from biodegradable polymers to bioactive ceramics. Compared with electrospinning, AJS has the advantages of not requiring large equipment and low operating cost. It stretches a polymer solution into thin fibers by forcing a pressurized gas out of the nozzle at high velocity. Meanwhile, the solvent starts evaporating and the fibers are deposited onto a substrate gradually.

Abdalla et al. [36] fabricated PLA/HA hybrid nanocomposite membrane by AJS. For the preparation of the solution, PLA was dissolved in dichloromethane (DCM) solvent. Then the synthetic HA powder was mixed with the fabricated PLA solution and stirred for 24 h. These solutions were deposited using a custom designed airbrush spraying device at room temperature. Then, hybrid nanocomposite membrane was achieved (Fig. 3).

### 2.2.3. Electrospinning

As an emerging and booming technology to fabricate micro-/nano-fibers, electrospinning technique has arisen great attentions [37–39]. Electrospinning is a unique fiber fabricating process [39]. Under the action of electric field, when the electric field force of the droplet at the tip of the needle is greater than its surface tension, the droplet will change from spherical to conical shape called "Taylor cone", and fibers are produced by the cone tip extension [40]. It can produce materials with high specific surface area which provides more space for cell attachment. In addition, the excellent mechanical properties of the electrospinning membrane ensure that it can withstand the mechanical forces during regeneration process [41].

According to the research of Chuan et al. [42], taking poly(D-lactic acid) (PDLA) grafting and enantiomer PLA as raw materials, composite nanofiber membranes which are based on stereocomplex PLA and compatible with bone marrow stem cells (BMSCs) were fabricated by electrospinning technology. For the preparation process, mixture was made by dissolving HA and PLA into a solvent. Afterwards, nanofiber membranes were fabricated by an FM-1206 electrospinning machine with collected distance of 12 cm, electrospinning voltage of 18–19.5 KV, flow rate of 1.1–1.5 ml/h, and total collection time of 4 h for each membrane.

### 2.2.4. Freezing extraction method

The freeze extraction method based on the solvent and the polymer crystallize respectively in the polymer-rich phase and the polymer-poor phase, producing a similar effect to phase separation [43]. Thus, a porous morphology can be achieved by removing the crystallized solvent with the help of a good solvent. To enhance the bioactivity, these membranes can be modified by plasma treatment [44]. According to the research of

Deplaine et al. [45], PLLA/HA composite membranes with various HA content for bone regeneration were fabricated using freezing extraction method. Firstly, dispersed HA nano-powder in dioxane by ultrasonic technology. Secondly, PLLA was added into the mixture and stirred until completely dissolved. Thirdly, poured the PLLA/HA solution into the Teflon molds and frozen with liquid nitrogen. Lastly, the porous structure was obtained by extracting dioxane in a cold ethanol bath. After extraction, membranes were dried in air atmosphere.

## 2.3. Scaffold

Scaffolds are one of the most common orthopedic application materials. The 3D structure is conducive to fill the bone defect arising from postoperative defect, trauma, infection, neoplasm and failed arthroplasty [46]. Besides, 3D scaffolds can well mimic the structure of extracellular matrix (ECM) which is beneficial to cell adhesion and migration [47,48]. Porous 3D construction is conducive to the transport of nutrients, intravascular growth and waste discharge [49]. Thus, polyester/HA composite scaffolds are widely used in bone repairing and bone tissue engineering fields. Herein, we briefly introduce some common strategies for fabricating polyester/HA composite scaffolds.

### 2.3.1. Electrospinning

As mentioned before, electrospinning can produce fibers from nanoscale to microscale continuously [50–52]. Scaffolds produced by electrospinning with porous 3D network structure and excellent pore interconnection [53,54], which will facilitate the migration of cells into the electrospinning scaffold and the transportation of nutrients. These characters make electrospinning become one of the most effective method to produce bone repairing scaffold materials.

Hu et al. [55] fabricated PLA/HA@polydopamine (PLA/HA@PDA) composite scaffold via electrospinning technique. A well dispersed HA@PDA suspension solution was obtained by putting HA@PDA nanoparticles into 20 ml CHCl<sub>3</sub>/DMF mixed solvent with ultrasonic treatment. Then, homogeneous PLA/HA@PDA electrospinning solution was obtained through putting PLA particles into solution mentioned above and oscillated. The electrospinning machine was used to fabricate the PLA, PLA/HA and PLA/HA@PDA composite nanofibers via adjusting the collected distance, electrospinning time, humidity, electrospinning voltage, injection rate and environment temperature (Fig. 4).

### 2.3.2. 3D printing (3DP)

3DP technology, also be called as rapid prototyping and additive fabricating, using the principle of ordinary printer [56]. Through

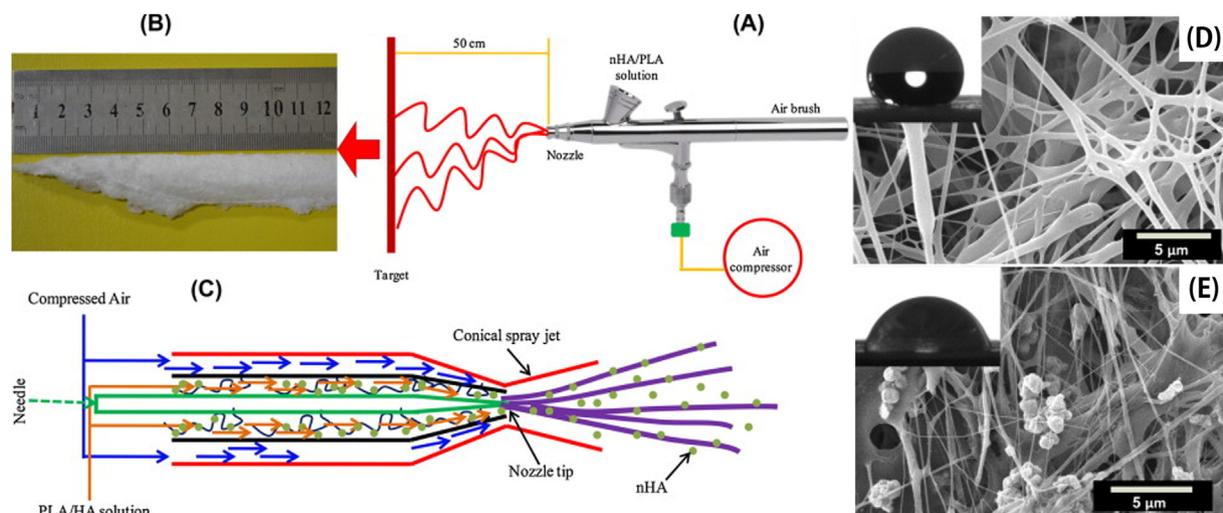


Fig. 3. (A–C) Schematic diagram: (A) Air jet apparatus, (B) collected mat and (C) fabrication process diagram. (D) H-PLA and (E) H-PLA/HA<sub>0.3</sub> membrane composite mats [36].

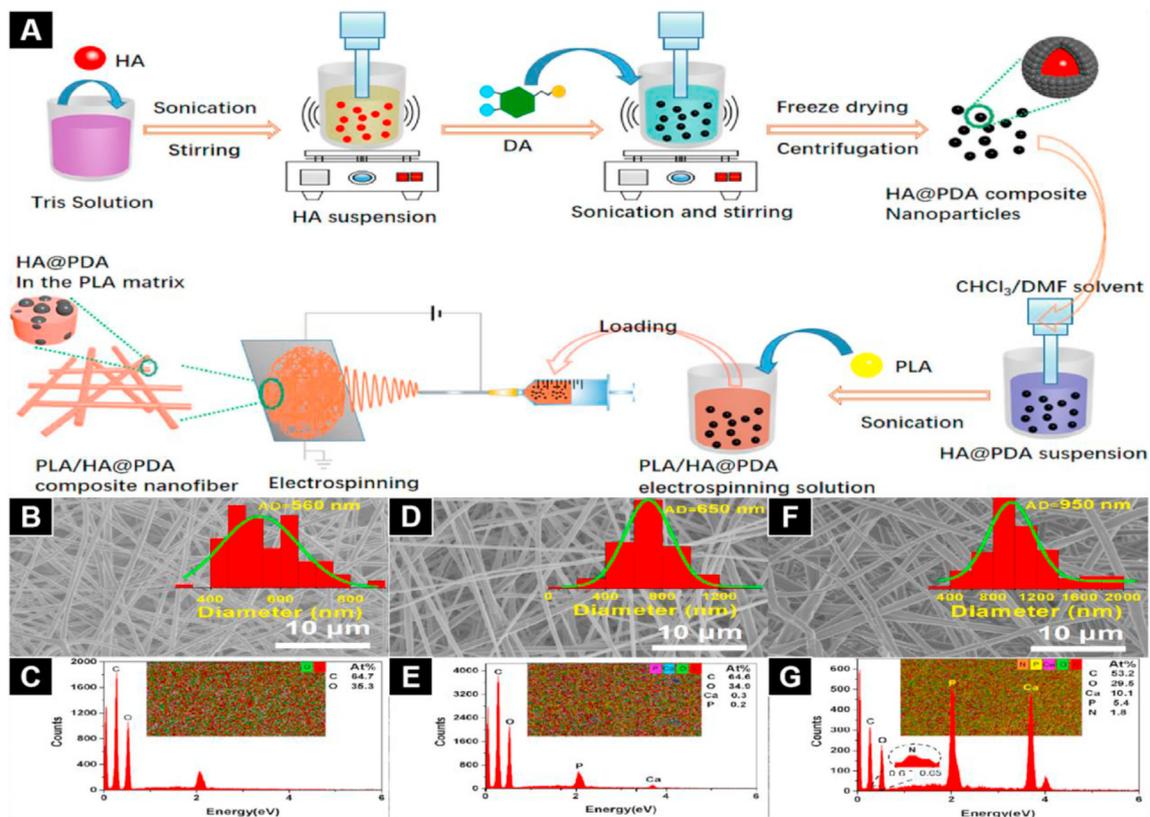


Fig. 4. (A) Schematic illustration of the fabrication method for PLA/HA@PDA composite nanofiber scaffold. SEM (B, D, F) and energy spectrum (C, E, G) of PLA (B, C), PLA/HA (D, E), and PLA/HA@PDA (F, G) composite nanofibers [55].

controlling the computer, materials are accumulated layer by layer, and finally the 3D model in the computer is turned into a physical object [57]. It can fabricate personalized biological scaffolds with high dimensional accuracy and complex structures. Materials fabricated by 3DP technique have the following advantages: customized pore size/porosity, tailored shape and tunable mechanical properties, etc. [58]. Thus, it is an attractive and promising technology in the fabrication of bone repairing materials [59]. Hassanajili et al. [21] fabricated PCL/PLA/HA composite scaffolds using 3DP technology. The morphology, porosity, degradation rate and mechanical properties of the composite scaffolds can be controlled by optimizing synthesis parameters.

Fused deposition modelling (FDM) is another usual 3DP method. The working principle of FDM is to melt filaments of thermoplastic materials through the nozzle and then the liquid material in the molten state is squeezed out and solidified. PLA/HA scaffolds using HA microsphere as inorganic fillers were fabricated by Corcione et al. [60] through FDM. Firstly, composite PLA/HA filament used for 3D printing was made through a twin-screw counter rotating extruder. After that, 3D samples were then fabricated through a FDM printer under the set parameters.

### 2.3.3. Thermal induced phase separation method

The aim of thermal induced phase separation method is to dissolve the polymer in the solvent with high boiling point and low volatility at high temperature to form a uniform solution. Then, phase separation was achieved by freezing solution. Finally, the volatile reagent was used to extract the high boiling point solvent to obtain the material with certain structure and shape.

Thermal induced phase separation technique has been adopted by Szustakiewicz et al. [61] to fabricate PLLA/HA composites. Briefly, the composites of PLLA/HA were obtained in 1,4-dioxane with stirring for 24 h. Then, added NaCl into PLLA/HA solution and held the mixture in a freezer. Afterwards, transferred the frozen samples to freeze-dryer vessel and removed the solvent. Salt can be removed by putting the dried

samples in demineralized water. After leaching, the scaffolds with pre-supposed structure were obtained.

### 2.3.4. Pickering emulsion templating

Pickering emulsion is a kind of solid particle-stabilized emulsion [61–63], which can keep the emulsion stable through the barrier formed by solid particles almost irreversibly adsorption on the liquid–liquid interfaces to prevent coalescence [64]. The preparation process can be divided into two parts: firstly, a pickering emulsion was fabricated. Secondly, the emulsion continuous phase was solidified. In order to investigate the possibility of materials used for bone repairing and bone tissue engineering, PLLA/HA composite scaffolds have been fabricated by Hu et al. [65] via solvent evaporation from templating water-in-oil (W/O) pickering emulsions. Firstly, the calculated amount of HA nanoparticles was dispersed in  $\text{CH}_2\text{Cl}_2$  solution of PLLA through ultrasonication. Secondly, a W/O pickering emulsion was obtained by adding water into the above-mentioned dispersion with homogenization treatment. Thirdly, samples were fabricated by pouring the pickering emulsion into cylindrical molds and placed it in a shaker to allow solvents to evaporate. Lastly, the residual solvent was removed by drying the fabricated scaffolds in a vacuum oven at room temperature.

### 2.3.5. Particulate leaching method

Particle leaching is a common method for preparing porous scaffolds. Usually, soluble particles are added into the scaffold materials, after the composite material is formed, scaffold with porous structure can be obtained by washing the soluble particles with corresponding solvent. By adjusting the size and proportion of the soluble particles, scaffold with different pore size and porosity can be fabricated. Boehler et al. [66] fabricated PLG/HA composite scaffold using particle leaching method with salt as the soluble particles. Briefly, PLG microspheres were created with emulsion method. Then, the mixtures of HA, PLG and NaCl with various ratios were pressed to 1000 psi in a 5 mm KBr die using a carver

press. High pressure CO<sub>2</sub> gas in a pressure vessel was used to equilibrate the scaffolds and fuse scaffolds during pressure release. Lastly, salt removal was carried out by leaching the scaffolds in water.

## 2.4. Bulk

Fracture often occurred in children and the old, it's the continuity of the phalanx structure completely or partially broken. When a fracture occurs, a fixation device is usually used to keep the fracture in place in order to avoid further injury and restore motor function. Bulk materials with proper mechanical strength make it suitable for fixing fracture sites. Recently, bulk materials with remarkable mechanical properties have been developed by different methods.

### 2.4.1. Injection molding

Injection molding is a common and simple material forming technology, which allows materials with specific shapes and sizes. Injecting the fabricated materials into the mold, and the materials cool down with time or the solvent evaporates, then, materials with ideal characters can be fabricated.

Zhang et al. [24] fabricated an osteo-regenerative, fast-fixing, biomechanically robust bone screws via injection molding based on PCL matrix. Firstly, the dried PCL - diol and 4, 4-methylenebis (phenyl isocyanate) (MDI) were poured into a vessel and followed by reacting at 85 °C for 2h to form a polyurethane (PU) oligomer. Then HA nanoparticles were dispersed into the solution to form composite solution. Subsequently, the composite solution was placed in a designed silicon mold to achieve the shape memory polymer/HA (SMP/HA) screw (Fig. 5).

### 2.4.2. Forging

Forging is a kind of machining method which uses forging machinery to exert pressure on materials and causes plastic deformation of materials to obtain forgings with certain mechanical property, shape and size. Through forging, porosity and other defects generated during the preparation of materials can be eliminated, the microstructure can be optimized, and the mechanical properties of materials can be improved.

According to Shikinami et al. [25], PLLA/HA forged composites were used to fabricate bioresorbable devices. For preparation process, the method of adding ethanol dropwise into a PLLA/dichloromethane solution was adopted to precipitate polymer solution to collect the small granules of uniformly distributed HA microparticles within a PLLA matrix. Then, a thick billet was made by extruding these granules. After this, a thin billet without fibrillation was achieved by forging billet mentioned above through a process for compression molding. Lastly, a lathe was used to cut thin billet into devices with various sizes and shapes.

### 2.4.3. 3D printing (3DP)

As mentioned before, 3DP technology has great flexibility in material fabricating. According to Yeon et al. [67], PLA/HA/silk composites have been fabricated for internal bone fracture fixation. For preparation process, HA was mixed with PLA to fabricate PLA/HA filament. After that, the fabricated PLA/HA mixture was placed in a filament maker and dispensed it via a steel nozzle at 170 °C to make the PLA/HA composite filaments. Then, the achieved composite filaments were heated to 170 °C. Finally, the extrusion process was carried via a ceramic nozzle using a 3D printer.

## 3. Properties of polyester/HA composites and their controlling methods

Materials used in bone repairing must meet some restrictive conditions, such as appropriate mechanical strength, biodegradation rate and biological properties. Different preparation methods and the amount of HA component will affect the properties of polyester/HA composites [68]. Table 2 summarizes the properties and controlling methods of polyester/HA composites.

### 3.1. Mechanical properties

Mechanical properties refer to the mechanical characteristics of materials under various external loads and different environments. Proper mechanical strength is essential in bone repairing, since high mechanical

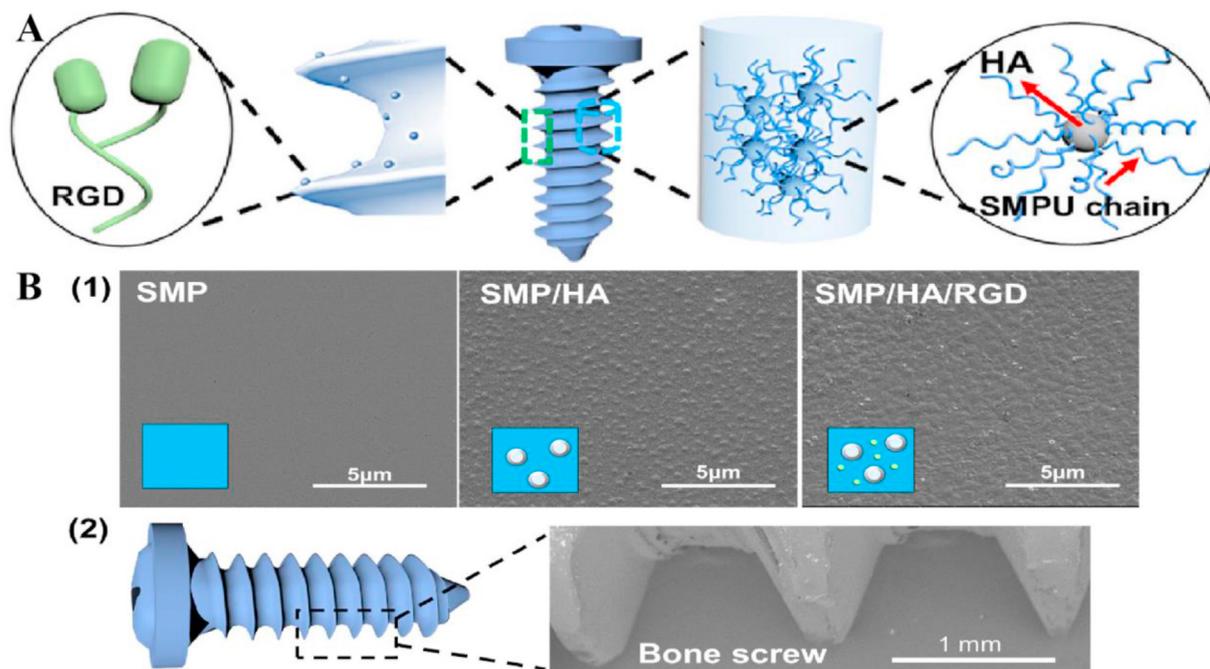


Fig. 5. Components in the shape memory polymer composite (SMPC) screw (A) and (B) SEM images of: (1) shape memory polymer composite (SMPC) and its composites; (2) SMPC screw; insert schematic of corresponding surface [24].

**Table 2**  
Properties and controlling methods of polymer/HA composites.

Properties	Preparing methods	Current situation	Strategies	Remarks for properties	Ref
Mechanical properties	Phase separation technique	*Adding HA increases the brittleness and decrease the toughness of the composite.	*Choose polyesters with high crosslinking degree or high molecular weight.	*Proper mechanical strength is essential in bone repairing.	[72]
Biodegradable properties	Electrospinning	*Through drug releasing, structure design or surface treatment to promote bone repairing and achieve the unification of degradation rate and bone repairing rate.	*Choose or synthesis materials that are naturally degradable.	*Be self-degraded in the body, and do not produce toxic substances, do not need to be removed again, to avoid secondary injury.	[77]
Mineralization abilities	Electrospinning	*Apatite formed on the surface of composites	*Calcium or phosphorus was added to the material to induce the precipitation of element ions to form HA.	*Favorable for calcium and phosphonium ion deposition.	[80]
Cytocompatibility	3D printing	*Nanoscale material structure is more conducive to cell adhesion and migration.	*Plasma surface modification, dopamine modification and surface chemical grafting are beneficial to promote the cytocompatibility of materials. *Pore forming materials are beneficial to fabricate materials with porous structure.	*The cytocompatibility is the primary condition for the material to be used as biomedical materials.	[87]
Osteogenic ability	3D printing	*Higher osteogenic ability can be found in HA-adopted composites.	*The osteogenic differentiation rate can be improved by releasing inducing factors.	*Promote bone regeneration and shorten healing time.	[92]

strength of material may cause stress shielding, while the low mechanical strength of materials may make the materials fail to achieve good supporting effect [69]. Generally, single polyester material is hard to meet the mechanical requirements for bone repairing, while the addition of HA could efficiently increase the mechanical properties of composite biomaterials [70]. Composite materials with different mechanical properties can be prepared by adjusting the proportion of HA. Besides, the performance of the interface between HA and polyester matrix can greatly influence the mechanical properties of composites [71]. The key to ensure the effective transfer of load from the polymer matrix to HA is to ensure a good interfacial bonding between them. Good interfacial bonding can reduce stress concentration and improve the mechanical properties of composites.

Wei et al. [72] fabricated HA/PLLA composite scaffolds using a phase separation technique. The results showed that the compressive modulus of HA/PLLA composite scaffolds increased with the content of HA increased. Besides, when the content of HA increased to 30%, the compressive modulus of the composite material increased significantly. Furthermore, when the ratio of HA to PLLA was 50:50, the compression modulus reached 8.3 MPa.

### 3.2. Biodegradable properties

Biodegradation of materials *in vivo* can avoid secondary surgical injury and can provide growth space for new bone [73]. However, too fast or too slow degradation rate is detrimental to bone repairing. Besides, during every stage of bone repairing process, the rate of bone repairing is different. This means it is essential to fabricate materials which the degradation rate can match the bone repairing rate [21]. Research has shown that the addition of HA into polyester can hinder the degradation of the composite [74]. Generally, with the increase of water absorption, the degradation degree will be deepened and the degradation rate will be accelerated [75,76]. Usually, phosphate buffered saline (PBS) solution was used to study the degradation behavior of the developed composite scaffolds [77,78].

According to the research of Song et al. [77], compared with pure PLGA film, composite film has higher weight loss. The addition of hydroxyapatite grafted poly(L-lactide) (HA-g-PLLA) nanoparticles into electrospinning PLGA fiber membrane enhanced the hydrophilicity and water absorption of the whole material. In addition, the addition of HA-g-PLLA nanoparticles could prevent the matrix crystallization to a certain extent, which was conducive to degradation. Thus, increasing the

content of HA-g-PLLA nanoparticles can accelerate the rate of weight loss.

### 3.3. Biological properties

#### 3.3.1. Mineralization abilities

Simulated body fluid (SBF) is a fluid that mimics the plasma and pH value of human body. It is widely used to test the mineralization ability of synthetic materials and indirectly evaluates the osteogenic ability or bone-bonding ability of materials, which is an effective method to predict the osteogenic activity of materials *in vivo* [79]. The addition of HA into polymer matrix could accelerate the formation of apatite on composite biomaterials [80].

According to Bhattacharjee et al. [80], non-mulberry silk fibroin grafted poly (ε-caprolactone)/HA (NSF - PCL/HA) nanofibrous scaffold has been fabricated via electrospinning technique. The nanofibrous matrices was incubated in SBF solution for 2 and 3 weeks and shaken continuously in a water bath at 37 °C for immersion study. Compared to nHA/NSF-PCL composite scaffolds, there was less amount of CaP precipitation visible on NSF-PCL scaffold. Indicated that the incorporation of HA component has a good effect on osteogenesis.

The novel polyester/HA composites were competitive candidates for bone repairing with enhance mechanical properties, tunable biodegradable properties and well biological properties. However, the matching of degradation rate and osteogenesis rate remains to be further studied. Therefore, more researches should be conducted to shed light on this tissue.

#### 3.3.2. Cytocompatibility

The first requirement for biomedical materials is that they are harmless to living organisms. It is important to test the biological properties of composites. Generally, the cytocompatibility of a material is characterized by seeding it with cells and testing how the cells react to the material. Usually, MG63 [81], Human bone marrow cells (HBMSCs) [82], osteoblastic MC3T3-E1 cells [83], rat bone marrow cells (rBMSCs) [84], Saos-2 osteoblast-like cells [85], primary human osteoblasts [86] were used to detect the cytocompatibility of polyester/HA composites.

Liu et al. [87] cultured the rat BMSCs on 3D printed PCL/HA scaffold to test the cytocompatibility. The results showed that better proliferation behavior was found on PCL/HA scaffold than that on bare PCL scaffold. According to the fluorescence result, BMSCs were successfully attached to the scaffolds with the round shape after 1 day of cultivation. With time

passing, the number of cells on the scaffold showed an increasing trend, and the morphology of the cells was elongated and expanded. These results indicate that 3D printed bone scaffolds have good biocompatibility, and the addition of HA can promote the proliferation of BMSCs.

### 3.3.3. Osteogenic abilities

To evaluate the osteogenic abilities of the composite biomaterials, several osteogenic markers such as alkaline phosphatase (ALP) [88,89], alizarin red staining (ARS) [90], and the expression of some osteogenic genes [91] have been investigated. Another method to determine the osteogenic properties of materials is to characterize the amount of newly formed bone tissues. Usually, micro-CT scanning, and immunohistochemistry staining and sequential fluorescence staining are adopted to detect the new bone formation abilities.

Luis et al. [92] fabricated PCL/fibroin/HA porous scaffolds by superficial foaming for bone repairing (Fig. 6). A critical ovarian bone defect model was used for *in vivo* testing of the scaffold, and bone repairing ability was evaluated at the 7th and 14th week after implantation. The results found that there is an excellent biocompatibility between the scaffold and the host tissue, and no rejection or inflammatory reaction was observed during the experiment. In each group, foci of intramembranous ossification appeared in the 7th and 14th week after implantation. The ossification foci showed newly formed bone trabeculae with hypertrophic osteoblasts on the surface, surrounded by connective tissue and fragments of the scaffold. After 7 and 14 weeks of implantation, the histomorphological analysis of the defect area showed that the number of ossification foci of the PCL scaffold gradually increased with time. In addition, after the addition of HA, a greater number of ossification foci were found.

## 4. Applications of polyester/HA composites in bone repairing

### 4.1. Drug delivery system in bone tissue repairing

Yearly, great efforts have been made to develop novel therapeutic drugs for the treatment of various diseases, including bone tissue repairing [93,94]. However, because of their non-specific biological distribution and rapid eliminated from the body, the efficacy of these drugs are often diminished [95]. The application of controlled delivery approaches promising to keep drugs concentrated in target treatment sites, thus providing more competent and shorter drug treatment with better selectivity and fewer side effects [96–99]. Biodegradable polymeric microspheres are desired materials which suit for acting as drug

carriers, as larger specific surface area allows the microspheres loaded with more drugs, and they do not require surgical delivery and can be used directly by subcutaneous or intramuscular injection, simplifying the operation process. In addition, sustained and long-term drug release at specific lesion sites can promote tissue repairing and avoid various side effects of drugs [29]. Vukomanovic et al. [100] fabricated PLGA/HA core-shell nanosphere as drug delivery carrier. *In vitro* releasing of the active substances from the PLGA/HA drug carrier has been studied. Only 1.5% of the drugs were released in the first three days. From day 3 to day 11, the release of clindamycin-2-phosphate increased significantly, while the release rate of clindamycin was relatively slow. During the third week, the release pattern leveled off and the release rate of both form of clindamycin slowed down, and the drug releasing behavior could be maintained at week 4. These results indicated that PLGA/HA with core-shell structure is a promising composite material for local drug delivery in the treatment of infectious bone tissue diseases, thus achieving controlled drug release.

### 4.2. Bone tissue repairing

The main goal of bone regeneration engineering is to repair bone defect sites by fabricating functional replacements. Materials used for bone repairing can be defined as a synthesis or natural material appropriate for interacting with biological systems, with a function to augment, treat or replace bone defect sites. After the composite materials are implanted into the bone tissue, as the HA has an affinity for the bone tissue, it can induce the differentiation of undifferentiated mesenchymal cells into osteocytes. So, the addition of HA is beneficial to bone repairing.

Many techniques have been adopted to develop materials with different geometries for bone repairing. Membrane [101] and scaffold [102–104] are two common types of materials for bone repairing. Yang et al. [105] fabricated composite scaffold for promoting bone repairing and inhibiting bacterial infection using 3DP technique. PLGA particles and HA powders were mixed to form a uniform paste, then porous stereo-structured PLGA/HA scaffolds were fabricated layer-by-layer using 3D printer. *In vivo* study indicated that chitosan grafted PLGA/HA scaffold demonstrated great bone repairing effect (Fig. 7).

### 4.3. Anterior cruciate ligament (ACL) fixation

Anterior cruciate ligament (ACL) is the most important structure to stabilize the knee joint and the most vulnerable among the ligaments in

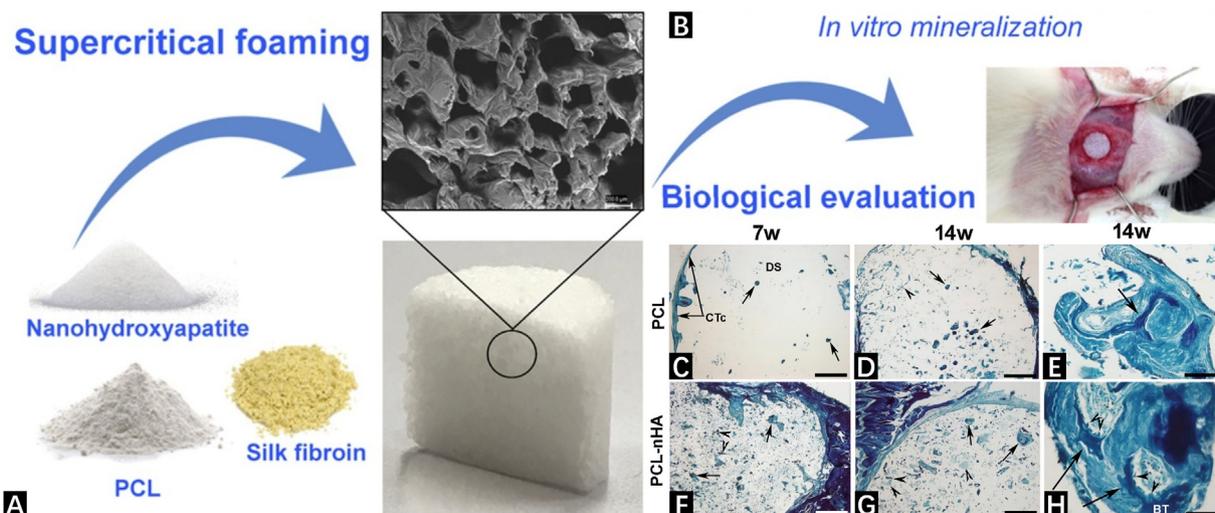
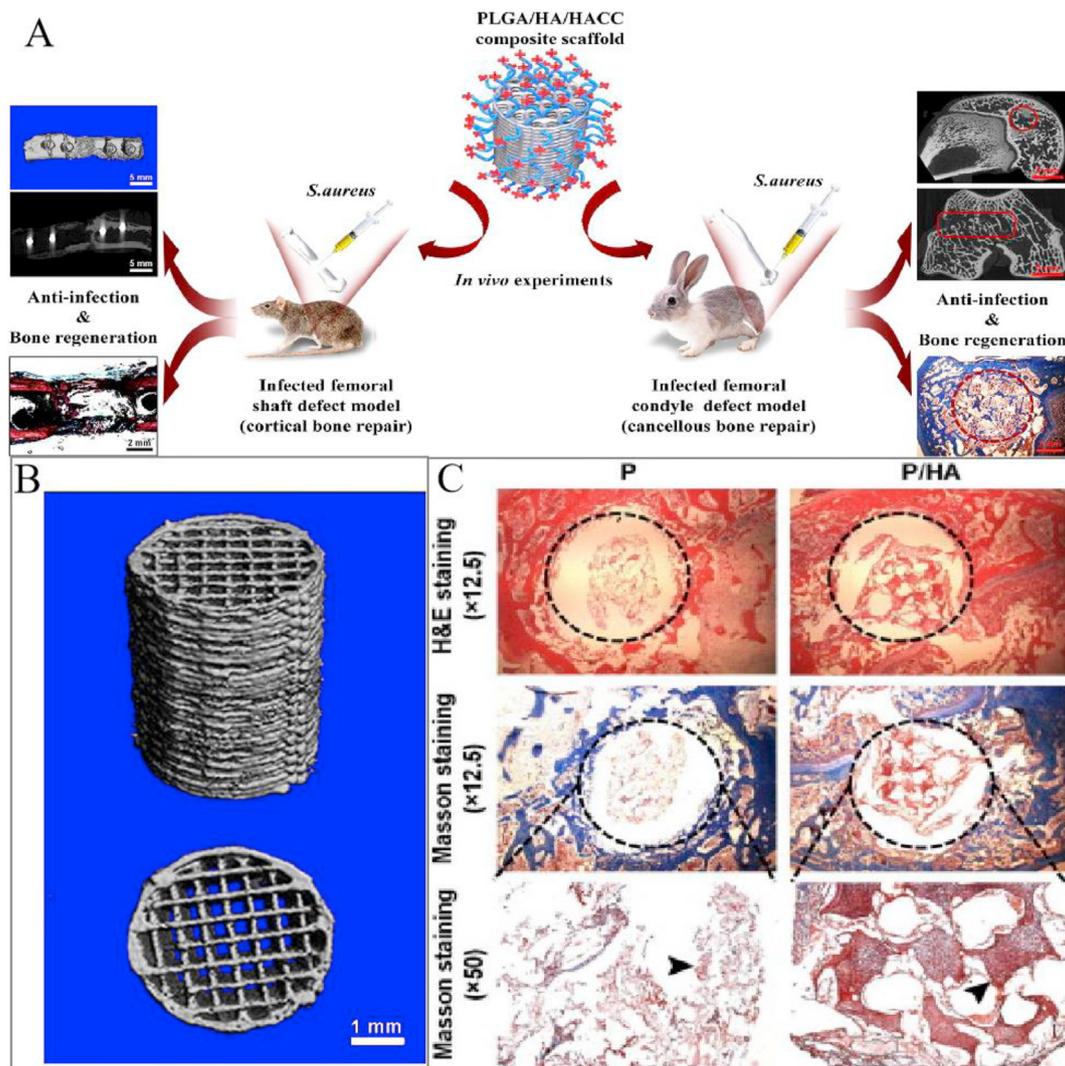


Fig. 6. Experimental flow graph (A, B) and Horizontal sections in panoramic view of the defect site in the different experimental groups, at 7 (C, F) and 14 (D, E, G, H) weeks after implantation [92].



**Fig. 7.** Schematic diagram of the experimental design and protocol (A). Micro - CT reconstructed images of the 3D-printed composite scaffolds (B). Histological images of rabbits at week 8 (C). The black circular regions indicate bone defect boundary. The black arrowheads indicate degraded scaffolds [105].

the knee [106,107]. After ACL rupture, the instability of the knee joint not only affects daily activities and sports, but also causes further damage to the structures inside the joint. Therefore, in order to restore the function and structure of the knee joint, it has become a consensus that the injured ACL needs to be reconstructed. Interface screw is commonly used in the process of anterior cruciate ligament reconstruction under arthroscopy. The addition of HA into polyester can enhance the whole mechanical strength. Zhu et al. [108] combined PLLA and HA to fabricated composites for interface healing using *in situ* polymerization method. The addition of HA can neutralize the acidic products degraded from PLLA, and the best biomechanical and biodegradable properties can be achieved when the content of HA is 20%. The results showed that the composite material provides a strong internal fixation and repair effect on fractures. It is also suitable for the repair of cancellous bone tissue and can be used as an internal material in orthopedics.

#### 4.4. Implant/fracture fixation

After the bone tumor is excised, the defect will affect the appearance and have negative psychological impact on the patient. Usually, polymethylmethacrylate bone cement [109], synthetic bone materials [110] and bone autograft are often be used to fill the bone cavity. After the excision, it is necessary to stabilize the implant especially when the cavity is concave- or hemispheric - shaped. According to the research of

Sakamoto et al. [111], unsintered PLLA and HA composite plates/screws were used to stabilize  $\beta$ -Tricalcium phosphate ( $\beta$ -TCP) bone implants. The results of the research indicated that the unsintered PLLA/HA composite plates/screws showed good performance in stabilizing hard-type  $\beta$ -TCP blocks in the reconstruction of bone tumor resections. In addition, polyester/HA composites can be used as fracture fixation materials, as they can be degraded *in vivo* gradually.

#### 5. Conclusion and outlooks

Polyester/HA composites have many remarkable properties, such as appropriate mechanical strength, biodegradability, favorable biological properties, good cell adhesion and interactions, induce tissue repairing, sustained drug releases, because they mimic the structure and composition of mineralized tissues. It has been confirmed that diverse polyester/HA composites fabricated into microparticles, microspheres, membranes, scaffolds and bulks have been used in bone tissue repairing, drug delivery and implant fixation. From the results of *in vivo* and *in vitro* experiments, it can be concluded that a satisfactory biocompatibility can be realized by good adhesion of the surrounding tissues to the surface of the composite implant after implantation.

Nowadays, there are many questions with regarding to the role of polyester/HA composites as reformative biomedical materials unanswered and unexplored. Much work is needed to analyze the different

behaviors of cells and their interaction with polyester/HA composites. Important but unsolved questions can be divided into the following aspects:

- (1) Although many methods have been put forward and studied to strengthen the mechanical strength of polyester/HA composites, the ultimate mechanical properties still unsatisfactory when compared to natural bone tissue. The existing strategies include crosslinking by chemical, physical and biological method, structure design, and improving anisotropic strength with aligned HA wires. More advanced processing methods need to be explored to enhance the mechanical properties of polyester/HA composites.
- (2) Different parts of bone tissue and different regeneration stages require diverse material degradation rates. Common methods used to control the degradation rate including change the molecular weight and crosslinking degree of polyester, the crystallinity and composite ratio of HA. However, due to the complexity of *in vivo* environment, regulated degradation rate at different regeneration stages is still a challenge. Thus, more studies should be carried to investigate the detailed degradation mechanism of polyester/HA composites *in vivo* for the development of bone tissue regeneration engineering.
- (3) In order to maximize the biological performance of polyester/HA composites, it is vital for composite materials mimic the nanoscale structure and chemical composition of the ECM as much as possible. Up to now, only devices like electrospinning and 3DP that can be used for simple mimicking have been developed. For the forthcoming future, applied devices might be expanded to wider fields and more breakthroughs are expected.
- (4) The further studies might focus on the structure design and functionalization of the polyester/HA composites to achieve better cell biocompatibility, biomechanical compatibility and more precise control of drug release performance. In summary, polyester/HA composites can be advanced biomaterials and have wider prospect in biomedical application fields with the advent of nanotechnology and materials forming techniques.

#### Declaration of competing interest

The authors declare no conflict of interest.

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