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3D Porous HA/TCP Composite Scaffolds for Bone Tissue Engineering

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Abstract

Calcium phosphates (apatites) are considered as a research frontier for bone regeneration applications by virtue of similarity to the mineral constituent of bone, suitable biocompatibility and remarkable osteogenesis ability. In this regard, the biodegradability and mechanical properties of monophasic apatites, typically hydroxyapatite (HA) and tricalcium phosphate (TCP), are imperfect and do not fulfill some requirements. To overcome these drawbacks, 3D porous HA/TCP composite scaffolds prepared by conventional and more recently, 3D printing techniques have shown to be promising since their bioperformance is adjustable by the HA/TCP ratio and pores. Despite the publication of several reviews on either 3D porous scaffolds or biphasic calcium phosphates (BCPs), no review paper has to our knowledge focused on 3D porous BCP scaffolds. This paper comprehensively reviews the production methods, properties, applications and modification approaches of 3D porous HA/TCP composite scaffolds for the first time. In addition, new insights are introduced towards developing HA/TCP scaffolds with more impressive bioperformance for further tissue engineering applications, including those with different interior and exterior frameworks, patient-specific specifications and drugs (or other biological factors) loading.

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Keywords: Biphasic calcium phosphates (BCPs); 3D printing; Interconnected porous structure; Cellular activity; Bioactivity; Doping

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1. Introduction

The human aging and general longevity of the world's population surge bone-associated illnesses, including osteoporosis, bone cancer and neoplasm. They are considered as critical issues in orthopedics and have significantly increased the demand for bone replacement and regeneration approaches. Autologous bone transplantation is believed to be a convenient way for the bone regeneration operation. However, limited availability, second surgery requirement and long-term pain restrict their extensive applications [1, 2], making it essential to develop alternatives. Natural-origin and synthetic bone grafting powders and granulates are promising alternatives to address the limitations of transplantation, albeit for small bone defects. Nonetheless, the therapeutic treatment of large segmental and load-bearing defects seeks 3D porous tissue engineering scaffolds offering large and interconnected pores as well as mechanical integrity for facilitating the healing process.

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The tissue engineering technology relies upon 3D porous scaffolds acting as platforms for cells to adhere, differentiate and proliferate towards bone regeneration. In this regard, biocompatibility is the most essential requirement to ensure detrimental biological responses in the body. Biocompatible substances do not cause toxicity, inflammation, allergy, immunologic reactions and cancer. In addition, an ideal 3D bone tissue scaffold have to possess two distinct characteristics (Fig. 1), including 1) interconnected porous structure with suitable pore sizes from micropores to macropores to support cell activities, supply nutrients and promote vascularization and 2) mechanical characteristics close to the adjacent bone to maintain mechanical support in the course of healing and to avoid the stress shielding effect [3, 4].

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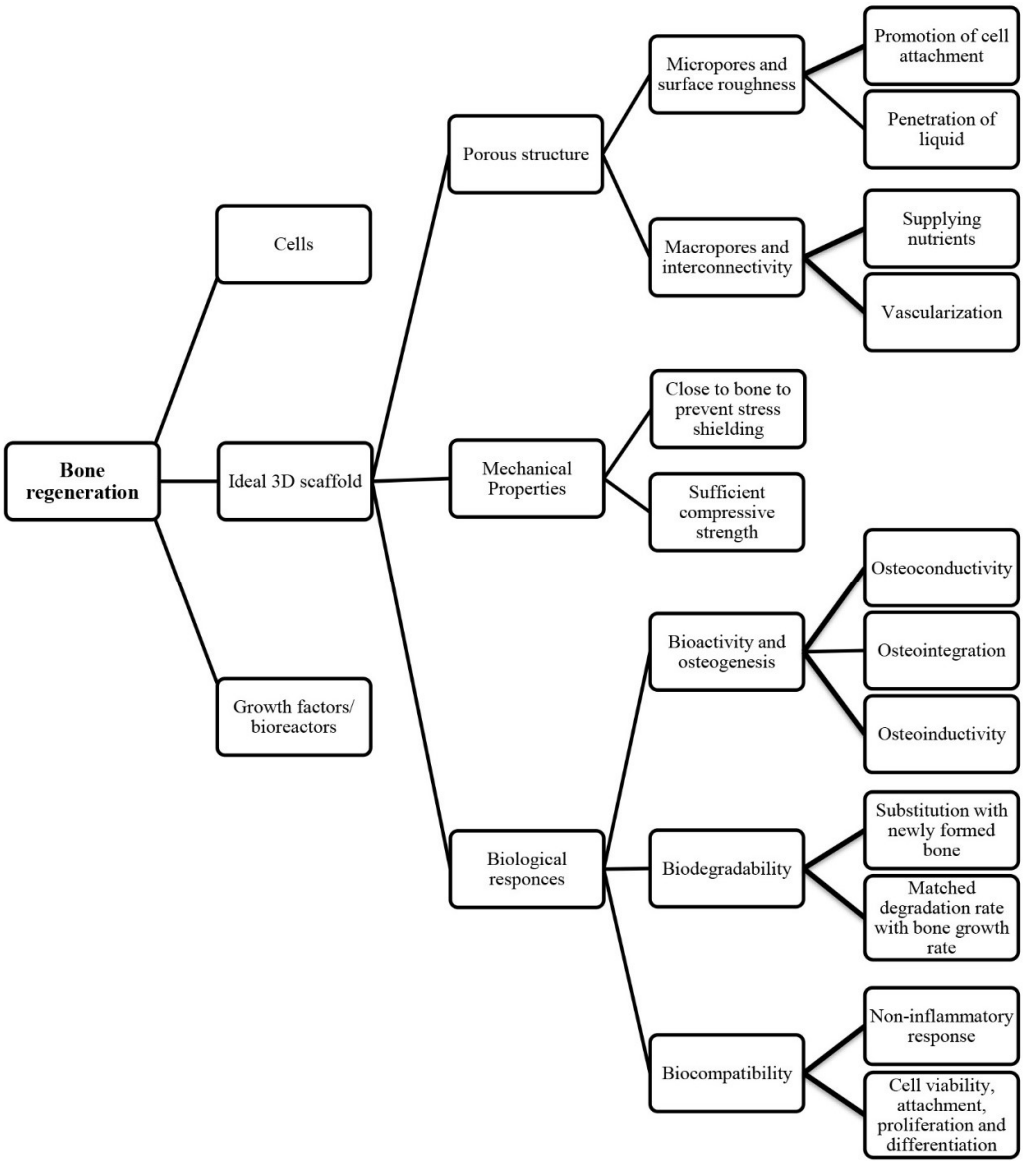

Fig. 1. Requirements of scaffolds for bone tissue reconstruction.

Various biomaterials have been utilized to manufacture 3D porous scaffolds, including medical-grade metals, ceramics, polymers and their composites. In this regard, bioceramics have the advantages of being remarkably biocompatible, bioactive and bioresorbable. For instance, bioglasses [5, 6], calcium silicates [7, 8], calcium-magnesium silicates [9, 10] and

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calcium phosphates (CaPs) [11, 12] have been successfully used for this purpose. Among the different bioceramics, CaPs have drawn noticeable attention due to their remarkable similarity to the human bone mineral, explaining their excellent biocompatibility [13]. Also, the release of their constituting ions (phosphate and calcium ions) effectively leads to the stimulation of new bone formation and healing. However, CaP scaffolds suffer from inadequate mechanical, osteoinductive and antibacterial properties. Even regarding their advantageous characteristics, mono-phasic CaPs (typically hydroxyapatite, HA and tricalcium phosphates, TCPs) do not mostly satisfy the needs of an ideal scaffold. Because HA and TCPs exhibit an inappropriate degradation rate and mechanical strength, respectively [14, 15]. To overcome the mentioned challenges, the application of composites constituted of those two phases (biphasic calcium phosphates, BCPs) has been widely investigated to manufacture 3D porous scaffolds. Because properties of BCP scaffolds are between those of HA and TCP based on the rule of mixtures, meaning that they benefit from a promising combination of the degradability of TCP and bioactivity of HA. In this regard, the HA/TCP ratio, porosity and pore geometry of the scaffolds are the most significant parameters that dramatically affect their mechanical and biological features. Nonetheless, the achievement of interconnected porous CaPs, similar to the structure of a healthy bone, with continuous mechanical support during the healing process is still challenging.

BCPs have been widely used in different forms, such as dense granules and powders as well as 3D porous structures. The dense forms are appropriate for filling bone cavities caused by tumors and bone cysts, where high stability and mechanical support are required. Also, 3D porous HA/TCP scaffolds are preferred in order for fast bone formation due to the capability of a porous structure in facilitating cell attachment, proliferation and differentiation [16]. There are comprehensive review papers on BCPs in the literature, covering their different aspects [14,

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17-19]. Nevertheless, to our knowledge, no review paper on 3D porous HA/TCP composite scaffolds has been published until now. This issue is accordingly considered in this paper in terms of fabrication methods, properties like mechanical, degradation, apatite-formation ability, cytocompatibility and osteogenesis ability, as well as approaches utilized to improve their biofunctionality.

2. Calcium phosphates: HA and TCP

As one of the main constitutes of bone, CaPs exhibit an appropriate potential to be involved in the bone reconstruction process owing to their appropriate biocompatibility, osteoconductivity and availability. CaPs have been successfully used in orthopedics and dentistry to treat defects, reconstruct craniomaxillofacial tissues and so on. Moreover, CaPs have been utilized in the form of coating and filler to enhance the bioperformance of metals and polymers, respectively [20]. HA, $Ca_{10}(PO_4)_6(OH)_2$ and TCP, $Ca_3(PO_4)_2$ including β-TCP and α-TCP are prominent CaPs employed in biomedical applications. β-TCP (stable at temperatures < 1125 °C) and α-TCP (stable polymorphism at temperatures > 1125 °C) are mostly employed as macroporous/dense blocks and CaP cements, respectively, for bone tissue regeneration [21, 22]. HA demonstrates superior structural support during the bone healing period as a result of its lower biodegradability compared to TCP, where the degradation rate of these CaP phases is ranked as HA << β-TCP < α-TCP [23]. Composites of these phases, BCPs, benefit from moderate and adjustable degradability, bioactivity and mechanical properties. Accordingly, they have been extensively studied for bone tissue reconstruction in different forms, including powder, microsphere, granulate, block, scaffold and so on.

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3. Fabrication methods of 3D porous HA/TCP composite scaffolds

To fabricate an ideal 3D porous scaffold, there are porous, mechanical and biological requirements. For bone tissue reconstruction, a structure of at least 50 vol% porosity with an interconnected pore size of 200-800 µm is well-established to be promising [9, 24]. Several routes have been employed to manufacture 3D porous HA/TCP biphasic scaffolds, as schematically shown in Fig. 2. Also, Table 1 tabulates the pore specification, advantages and limitations associated with these processes.

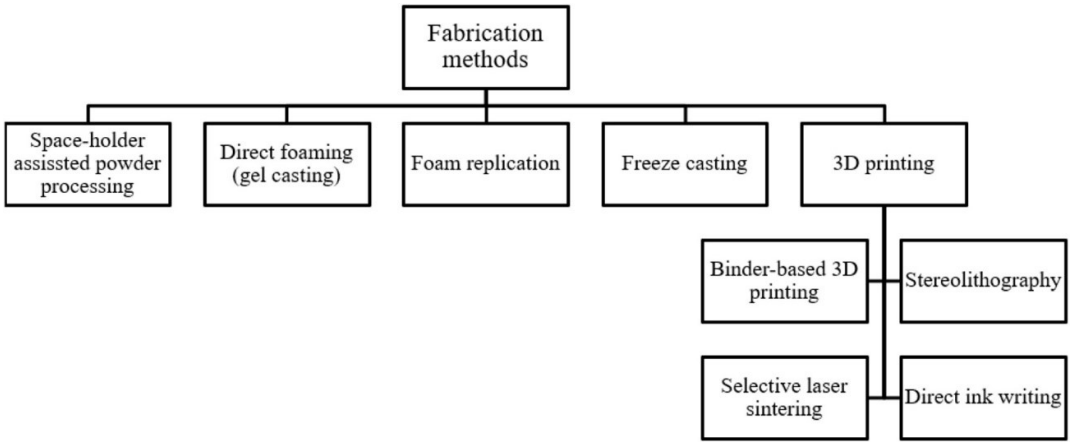

Fig. 2. Manufacturing methods of 3D porous HA/TCP bone tissue engineering scaffolds.

Table 1. Porosity, pore size, advantages and limitations of the different methods used to fabricate 3D porous HA/TCP bone tissue engineering scaffolds

Fabrication method	Porosity (%)/pore size (µm)		Compressive strength (MPa)	Advantages	Limitations	References
	Reported for HA/TCP scaffolds	Method capability				
Space holder-assisted powder processing	40-55/15-100	Up to 80/15-700	4.0-15.6	Simplicity; Cost-effective; High porosity	Uncontrolled shrinkage during sintering; Insufficient mechanical strength for load-bearing applications	[25-29]

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Direct foaming (gel casting)	80-85/200-1200	16-90/10-1300	1.6-6.7	Usable for different materials; Near net shape method; High porosity; Low shrinkage	Implement of chemical and toxic materials; High cost of materials; Low interconnectivity	[30-32]
Foam replication	Up to 91/0.6-700	Up to 97/0.6-900	0.1-8.0	Simple and low cost; High porosity and interconnectivity with a structure close to bone	Low mechanical properties	[33, 34]
Freeze casting	31-73/100-200	Up to 90/0-220	0.4-36.4	Simplicity; Usable for different materials; Structural controllability; Higher mechanical properties compared to the above methods; Environmentally friendly	Complexity of templating and controllability; Poor mechanical properties; Commonly low porosity and small pore size	[35-37]
3D printing	20-80/50-4000	Up to 90/5-5000	0.1-50.0	Complex structure fabrication; Adjustable porosity and pore size; Good surface finish; Possibility for the incorporation of biological agents	Relatively expensive; Constricted thickness of layers; Challenge of elimination of trapped unprocessed powder in small pores	[27, 38-40]

3.1. Space holder-assisted powder processing

The space holder strategy is considered as a conventional method for the manufacture of porous scaffolds, by which a broad range of porosity with tunable pore geometries and sizes can be obtained. The space holder method mainly involves four steps, including 1) preparing a mixture of starting ceramic and space-holding powders, 2) compaction of the prepared mixture, 3) post heat treatment or washing of the compact to eliminate the space-holder particles,

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yielding a green scaffold with the final shape of the scaffold but insufficient mechanical strength and 4) consolidation of the green scaffold via sintering [25, 41].

This route has been employed to manufacture 3D porous HA/TCP composite scaffolds [28, 42]. In this regard, starting materials normally include CaP powder, space holder and binder. The preliminary CaP powder can be either a mixture of HA+TCP, BCP or metastable non-stoichiometric CaPs like Ca-deficient HA (CDHA). The latter is transformed into a desirable combination of HA and TCP after subsequent heat treatment. Space holders used to fabricate 3D porous HA/TCP composite scaffolds are sucrose and polyethylene glycol (PEG), whereas other porogens like sodium chloride, ammonium bicarbonate and carbon have the potential for this purpose [43-45]. Polyvinyl alcohol (PVA) is the most common binder employed for HA/TCP scaffolds production, although polymethylmethacrylate and vegetable oil can be considered as other options [46, 47]. The sintering process is normally conducted at temperatures between 1000 ℃ and the melting points of the constitutes (the melting point of HA and TCP is 1650 ℃ and 1670 ℃, respectively). The porosity and pore sizes of HA/TCP scaffolds manufactured by this route are adjustable by controlling the initial geometry and relative amount of the starting ceramic and space-holding powders, as well as the sintering process. Typically, HA/TCP scaffolds with 40-55% porosity and 15-100 μm pore size have been fabricated via this technique.

3.2. Direct foaming (gel casting)

Direct foaming, invented in the 1970s [48], is another technique to fabricate highly porous 3D ceramic scaffolds, mostly with cellular structures. In the direct foaming method, a colloidal sol or powder suspension is turned into foams by using a blowing agent to introduce bubbles and then pores after consolidation. Subsequent densification is also followed to ensure

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the strength of the scaffolds. One of the most used methods of direct foaming to manufacture porous scaffolds is gel casting. This process is summarized as *in situ* polymerization of monomers in a casting mold to produce a stable 3D network (gel) which is then sintered for burning out the polymer and fabricating a 3D ceramic scaffold with high porosity. The main attraction of gel casting is the possibility to achieve spherical macropores connected to each other by window-like pores [49].

The employment of the gel casting method to fabricate HA/TCP scaffolds has been pointed out [30, 31]. Typically, an initial slurry is produced by mixing CaP powder (a mixture of HA+TCP, BCP or metastable CaP powders), dispersant (mostly ammonium polymethacrylate or replacements like fructose [50], ammonium polycarbonate [51] and polyethyleneimine [52]), monomers (mainly methacrylamide or other acrylamides [53]) and initiators like ammonium persulfate. The addition of catalysts (mostly tetramethylethylene diamine) and surfactants are optional. In the next step, the slurry is molded and polymerized. A two-step heat treatment process consisting of the initial removal of resins, typically at 500 ℃, and strengthening the structure mostly at about 1200-1300 ℃ is then conducted. Using this approach for HA/TCP scaffolds fabrication, the porosity of about 80-85% and pore sizes of 200-1200 μm have been reported.

3.3. Foam replication

The foam replication method to manufacture porous 3D ceramic scaffolds with high interconnected and large-scaled pores has been used since their invention in 1963 by Schwartzwalder and Somers [54]. The foam replication method consists of coating a polymeric template with a ceramic slurry, burning out of the polymeric template and subsequent sintering of the green scaffold. Despite the inevitable crack formation owing to the inconsistent thermal

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expansion coefficients of the ceramic slurry and foam, the simplicity, controllability and understandability of this method make it an interesting approach to produce 3D porous scaffolds [55, 56].

Fabrication of 3D porous HA/TCP scaffolds through the foam replication method has been reported by researchers [57-60]. In this regard, mixed HA+TCP, BCP or CDHA powders and a binder (usually PVA with the potential application of polyethylene glycol (PEG) [61] and guar gum [62]) are added into a liquid to produce the slurry. Afterward, a sacrificial polymeric sponge, mostly from polyurethane (PU), is coated with the slurry, sintered optionally at 400-600 ℃ for the removal of the polymeric sponge and then sintered at 900-1350 ℃ for densification. The structure of the scaffolds obtained from this route is characterized as up to 90% porosity and pore sizes between 70-700 μm. Also, the decrease of the solid loading (the amount of solids suspended in a slurry) and sintering temperature, besides using larger powders result in larger pores and higher porosity.

In some cases, the combination of classic fabrication methods is a suitable approach to pick the best characteristics of each method and to meet the further required characteristics of scaffolds. Typically, the production of ceramic scaffolds by a combined arrangement of foam replication and gel casting is noticeable. In this strategy, the slurry is produced based on the gel casting method, coated on a sponge polymer and heated for removing the sacrificial sponge followed by subsequent sintering. The implementation of the gel casting method combined with the foam replication process to fabricate 3D porous HA/TCP scaffolds has been also reported [33, 63, 64]. The scaffold obtained by this method exhibited porosity up to 75% and the pore dimension of 150-400 μm.

3.4. Freeze casting

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Freeze casting, also named freeze drying or ice templating, has been used since the 2000s [65] to fabricate porous structures using various materials, including ceramics, polymers and metals. The freeze casting method provides a simple, low cost and environment-friendly way of producing porous 3D scaffolds with controllability over porosity. The structure of the freeze-casted scaffolds includes macropores in the body of the scaffolds and micropores in walls. In general, freeze casting consists of four steps: (1) mixing initial ingredients (powders, solvent and additives) to produce a solution, slurry, gel or sol, (2) solidification, (3) sublimation of the solvent resulting in the pore formation and (4) final post-treatments. This method develops macropores in the body of the scaffold and micropores into the wall. The only drawback of freeze casting is that controlling all parameters to obtain the suitable morphology and porosity is complicated [66, 67].

The application of freeze casting as an approach to fabricate 3D porous HA/TCP scaffolds has been reported [37, 68]. In this regard, either BCP, metastable CaP or mixed HA+TCP powders, dispersants (such as Darvan, Texaphor and HaiRun) and binders (mainly PVA with the potential application of gelatin [69], Na_2SiO_3 [70], silk fibroins [71] and sugar alcohol [72]) are loaded into a freezing vehicle which is mostly water or camphene. Camphor naphthalene [73] and tert-butyl alcohol [74] can be potential supplements as the freezing vehicle. The green scaffold is sintered at about 1200-1300 ℃ for strengthening and solidification, giving the common pore sizes of 100-200 μm with the maximum porosity of about 70-80% in HA/TCP scaffolds.

3.5. 3D printing

The classic methods used for manufacturing 3D porous HA/TCP scaffolds encounter many challenges which are listed in Table 1. These drawbacks are mainly associated with

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inadequately interconnected pores and the use of some toxic organic substances which are not entirely removed sometimes, deteriorates bioperformance. Contrary to the classic fabrication methods, the 3D printing technology has paved a way to develop scaffolds with adjustable porosity, controllable pore size, complex shape, improved precision and desirable surface finish [75]. This additive manufacturing technique involves building 3D scaffolds layer-by-layer to establish a 3D porous structure based on a digital stereolithography file [76, 77]. Also, the development of a functionally-graded porous scaffold for the treatment of tissues like bone with a gradient porous structure is another capability of 3D printing to match the mechanical stiffness and strength of the 3D-printed scaffolds and target tissue [78]. The 3D printing technology has made the incorporation and delivery of growth factors and drugs more convenient, resulting in the improvement of new bone growth in the scaffolds. Considering the significance of porosity, pore size and interconnectivity in delivery applications, 3D-printed scaffolds demonstrate a higher efficiency owing to their tunable pore structure [79]. Despite the significant features offered by the 3D printing technology, drawbacks like the restricted availability of biomaterials with desired properties and stability as well as the relatively long manufacturing time have slowed the clinical translation of 3D-printed scaffolds, which required further investigations [80]. Selective laser sintering (SLS), binder-based 3D printing, direct-ink writing and stereolithography (SLA) are common 3D printing routes used to fabricate 3D porous HA/TCP composite scaffolds, as compared in Table 2 from different viewpoints.

Table 2. Porosity, pore size, advantages and limitations of the various 3D printing methods used to fabricate 3D porous HA/TCP bone tissue engineering scaffolds

Fabrication method	Porosity (%)/pore size (μm)	Advantages	Limitations	References

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	Reported for HA/TCP scaffolds	**Method capability**			
Binder-based 3D printing	30-68/300-1200	Up to 60/40-1600	Accessible and cost-effective; Rapid processing; Negligible thermal effect on ceramic powder during printing	Insufficient mechanical strength for load-bearing applications; Inferior powdery surface finish	[27, 81]
Direct-ink writing	45-67/150-620	Up to 90/5-650	Suitable resolution; Feasibility of manufacturing highly loaded slurries	Need for exact control over ink properties; Expensive apparatus	[38, 82]
Selective laser sintering	60-80/800-1200	Up to 80/30-2500	Rapid processing; Fabrication of sophisticated pore geometry; No organic phase involved	High temperature of the process; Inferior powdery surface finish; Expensive apparatus; Shrinkage during sintering	[83, 84]
Stereolithography	20-80/50-4000	Up to 90/20-5000	Excellent resolution and accuracy; Construction of scaffolds with complex geometry	Usage of mostly toxic resins; Shrinkage during polymerization	[84, 85]

3.5.1. Binder-based 3D printing technique

Sachs et al. [86] first introduced binder-based 3D printing in 1993. In this 3D printing process, a binder is sprayed by printheads on appointed zones of a surface filled with a ceramic powder layer, thereby consolidating the selected area of the ceramic layer. Then, a new powder layer is loaded on the previous one, and this process is repeated to complete the whole part. Loos and unprocessed powder particles in the vicinity of the 3D-printed part are then removed. As a usual post-treatment process, sintering is also applied to the 3D-printed part to eliminate the excessive organic binder and give higher mechanical strength [39, 76]. The utilization of

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inexpensive materials, no need for additional support and rapid speed of the system are some of the advantages of this method, whereas the relatively poor mechanical strength as a result of weak bonding between the powders as well as the curbed accuracy and resolution are considered as its main drawbacks [27].

3D porous HA/TCP scaffolds have been manufactured by this technique [81, 87-89]. HA and TCP (alternatively, BCP or metastable CaP) powders are mixed to form a smooth and homogenous powder bed. PVA and phosphoric acid are typical binders used to manufacture HA/TCP scaffolds, whereas citric acid can be another candidate [90]. It should be noted that the type of the polymeric binder affects the resolution and properties of the 3D-printed scaffolds; hence, the selection of the appropriate binder is critical [87]. The green printed part is followed by a one-step heating regime at temperatures higher than 1000 ℃ for the binder removal and sintering [81, 89]. The binder-based 3D printing technique could generate a broad range of porosity, 30-68%, micropore and macropore sizes of 2-30 μm and 300-1200 μm, respectively, in 3D porous HA/TCP scaffolds. In this method, the size of the binder and preliminary CaP powders controls the macropore and micropore geometry, respectively [87].

3.5.2. Direct-ink writing

Direct-ink writing or robocasting was first devised by Cesarano et al. [91] in 1997. As a slurry-based 3D printing method, ink deposition is employed to construct 3D structures with a complex geometry. In this process, a ceramic-organic slurry is made as the ink. Binders and, in particular cases for more convenient flow, lubricants are the ingredients of an appropriate ink for this technique. However, due to the low content of the ceramic powders in the prepared ink, it is prone to be rapidly dried, leading to microcrack formation in the 3D-printed part. Therefore, the main concern of the robocasting technique is the optimization of the ink [92].

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The ink containing the desired ceramic composition is extruded through a nozzle that moves to write the structure layer-by-layer directly. At the end of the process, for eliminating the organic phase and improving the mechanical strength of the green structure, sintering at a relatively high temperature is performed [27, 39, 93].

The fabrication of 3D porous HA/TCP composite scaffolds by direct-ink writing has been widely investigated in the literature [82, 94-96]. For this purpose, a ceramic ink containing a dispersed HA+TCP, BCP or metastable CaP powder is used to print a scaffold layer-by-layer. Pluronic F-127 is normally used as the solution as it shows a reverse thermal property. This mater at low temperatures is a fluid and at room temperature is a gel, allowing a convenient dispersion of the ceramic powder. Also, Darvan 821A containing ammonium polyacrylate and hydroxypropyl methylcellulose [94] can be considered as another potent candidate for this purpose. Moreover, the employment of a polymeric porogen, acting as an artificial defect, results in higher porosity with pore sizes close to that of the used porogen. Polymethylmethacrylate (PMMA) has been used as the porogen to induce 67% porosity in a 3D printed HA/TCP scaffold fabricated by the robocasting technique [95]. Also, this method is a versatile approach for the incorporation of drugs, where the sintering process can be replaced by a cross-linking step to avoid the destruction of the loaded drugs [97]. The organic burning-out process is conducted at 400-600 ℃ with subsequent sintering at 1100-1200 ℃ normally. The scaffolds fabricated by this technique exhibited 45-67% porosity and 150-620 μm pore size.

3.5.3. Selective laser sintering (SLS)

SLS as a 3D printing method was first patented in 1986 by Deckard and Beaman [98]. In the SLS technique, a laser selectively irradiates a powder layer to fuse or sinter. Then, a new

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powder layer is then dispersed on the previous layer for subsequent laser treating. A 3D-designed part is constructed layer-by-layer by repeating this process [39, 76]. In the case of weak sintering properties of the powder, a sacrificial binder is often added to the powder, which is removed in the debinding process. Numerous complex structures like tissue engineering scaffolds with sophisticated pore structures can be fabricated by the SLS method [27, 99]. In addition, SLS can normally produce layers with the thickness of 100-150 μm, whereas finer structures can be established by using thinner layers and smaller powder sizes. However, the inferior quality of the 3D-printed parts developed by this technique in terms of structural integrity, accuracy and surface roughness has impeded their extensive applications [76].

The SLS route has been employed to manufacture 3D porous HA/TCP biphasic scaffolds [83, 100]. It has been reported that the utilization of a polymeric binder in the HA/TCP powder mixture would mitigate problems associated with the high temperature of direct laser sintering, which is referred as the indirect SLS technique [100]. In this technique, the binder is melted, adheres adjacent CaP powder particles and finally is removed in a heating process. This gives rise to the improvement of the powder particles arrangement and hence densification. The decrease of the subsequent sintering temperature and thereby preventing the undesirable transition of β-TCP to α-TCP and wavy deformation of 3D HA/TCP scaffolds are other beneficial consequences [100, 101]. Also, it should be pointed out that the type of the binder, as well as its amount, affects the inner structure and porosity of the 3D-printed scaffolds. Epoxy resins are the most frequently used binder in constructing HA/TCP scaffolds by the indirect SLS technique [100]. Through this mechanism, it has been realized that the addition of 1 wt% polylactic-co-glycolic acid (PLGA) and polylactic acid (PLA) to HA/β-TCP scaffolds during the SLS fabrication improves hardness by 87 and 105 Hv, respectively [101]. The HA/TCP

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scaffolds developed by this technique demonstrated 60-80% porosity and 800-1200 μm pore size.

3.5.4. Stereolithography (SLA)

Stereolithography is a prominent 3D printing route that uses the photopolymerization principle to construct 3D objects. SLA utilizes a concentrated light source or a digital light projector with a particular wavelength, typically ultraviolet (UV), to cure and solidify molecular chains layer-by-layer with respect to the STL file. Ceramic stereolithography involves preparing a ceramic slurry composed of ceramic powders with micron/nanometric sizes, a photocurable polymer, surfactants and additives. A concentrated light irradiates the slurry, polymerizes the organic phase and results in surrounded ceramic particles with a cross-linked organic network [76, 85]. Furthermore, additives like dispersants can mitigate problems associated with the SLA process, such as the scattering phenomenon of tiny ceramic powders, which augments the production time and decreases the dimensional accuracy as well as the depth of cure. Also, additives can stabilize the ceramic pastes and prevent particle agglomeration [76]. Generally, heat treatment is applied to the 3D-printed green part to remove the polymeric phase and consolidate the ceramic particles.

HA/TCP composite scaffolds fabricated by this technique exhibit a hierarchical controllable porous structure [85, 102]. Polyfunctional acrylic resins and waxcast are photocurable polymers used in HA/TCP fabrication by this method, whereas 1,6-Hexanediol diacrylate, 1,1,1-Trimethylolpropane triacrylate and polyfunctional acrylic resins have the potential for this intention [103, 104]. Typically, the debinding process is executed at 600-650 °C with subsequent sintering at temperatures higher than 1000 °C. HA/TCP porous scaffolds

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fabricated by the SLA technique demonstrate a controllable hierarchical porous feature with 20-80% porosity and pore sizes from nanometers to 4000 μm.

Digital light processing (DLP) is a newly developed SLA route that cures a resin layer by using a digital projector screen for flashing a two-dimensional pattern across the entire platform [105, 106]. This process has been also utilized to manufacture 3D porous HA/TCP composite scaffolds [107]. In this respect, materials comprising HA+TCP powder, a photosensitive resin and a photoinitiator were polymerized by light to form the green scaffold. The dispersion media, including acrylic monomers as a photosensitive resin and phenylbis phosphine oxide as a photoinitiator, are common for the manufacture of porous ceramic scaffolds, including HA/TCP ones [105, 106, 108]. This method could construct HA/TCP scaffolds of different pore shapes like cubic and diamond with the pore size of 800-1400 μm.

Mask image projection-based stereolithography (MIP-SL) is another common 3D printing technique for ceramics including HA/TCP scaffolds, which uses a high-resolution light projection to solidify a ceramic slurry composed of photopolymers and bioceramics. The sintering process is typically applied to eliminate the photocurable polymer and fusion of the ceramic powder [85]. The MIP-SL process has been employed for the fabrication of HA/TCP scaffolds with a hierarchical controllable porous structure of 20-80% porosity.

3.6. Morphological comparison of 3D porous HA/TCP composite scaffolds fabricated by different processes

3D porous HA/TCP scaffolds developed by different approaches exhibit varied morphology and thus properties. Space holder-assisted powder processing as a cost-effective technique is able to produce highly porous HA/TCP scaffolds. Space-holding particles and

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voids among HA+TCP powder particles generate macropores and micropores, respectively (Fig. 3a) [28]. In direct foaming and gel casting, pores are formed owing to the removal of bubbles and polymers used in the slurry or gel, respectively. Therefore, pores are not highly interconnected but are spherical (Fig. 3b) [30]. The pore structure of scaffolds processed by the foam replication method, in addition to the fabrication parameters and the thickness of the slurry layer coated on the sacrificial foam, strongly depends on the pore configuration of the template used. These scaffolds mostly contain highly interconnected pore structures with large pore sizes (Fig. 3c) [64]. The pore formation in scaffolds manufactured by freeze casting is also due to the sublimation of the freezing vehicle, which mostly leads to lamellar pore structures since solidification is mostly directional (Fig. 3d, e) [37]. Comparatively, the 3D printing method is the most promising method to fabricate complex structures with sophisticated pore geometries (Fig. 3f) [82].

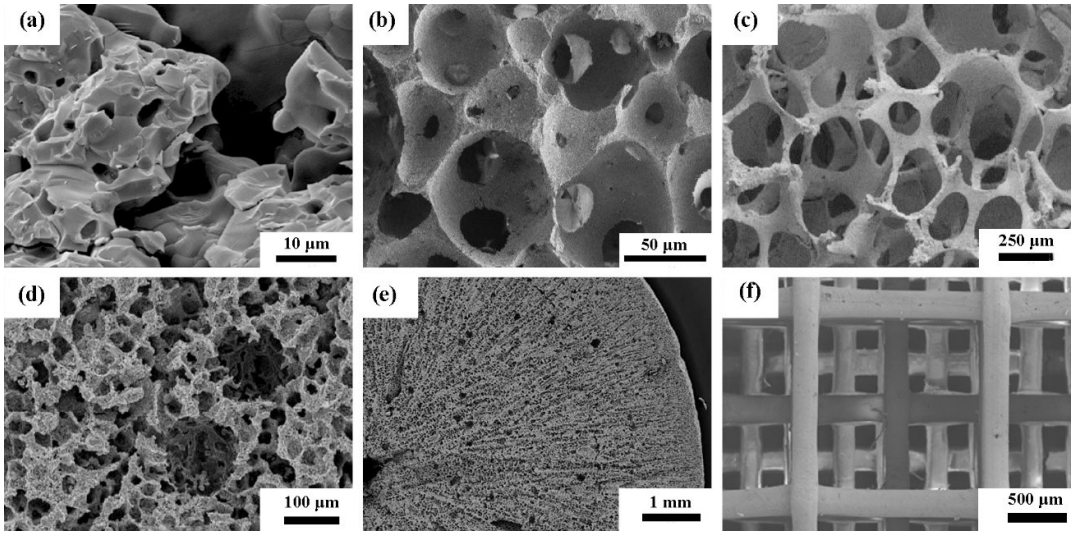

Fig. 3. Scanning electron microscopy (SEM) micrograph of 3D porous HA/TCP composite scaffolds fabricated by different techniques: (a) space holder-assisted powder processing, reprinted from Ref. [28], (b) direct

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foaming, reprinted from Ref. [30], (c) foam replication, reprinted from Ref. [64], (d, e) freeze casting (high and low magnifications, respectively), reprinted from Ref. [37] and (f) 3D printing, reprinted from Ref. [82].

3D porous HA/TCP scaffolds fabricated by various 3D printing techniques present distinct morphologies and properties. The binder-based 3D printing technique exhibits a powdery surface finish with relatively weak mechanical strength, where small gaps can be found between powder particles, as shown by yellow circles in Fig. 4a. This method is not capable of generating high porosity in HA/TCP composite scaffolds compared to the other 3D printing techniques. However, macropores with irregular geometries can be formed by this method, as marked by a red circle in Fig. 4a [87]. Direct-ink writing is the most frequently 3D printing route used to develop 3D porous HA/TCP composite scaffolds due to its potential to construct scaffolds with an outstanding resolution (Fig. 4b, c) [82]. SLS can fabricate HA/TCP scaffolds with a large variety of porosity and pore sizes, up to 90% porosity and 4 mm pore size, respectively, which is a specific ability among the different production techniques (Fig. 4d) [107]. Precise control over the ink preparation and extrusion is critical to obtain HA/TCP scaffolds with a desired architecture. Highly porous HA/TCP scaffolds with complex geometries have been produced by the SLS method. However, the powdery surface finish and considerable shrinkage during the sintering process are its main drawbacks.

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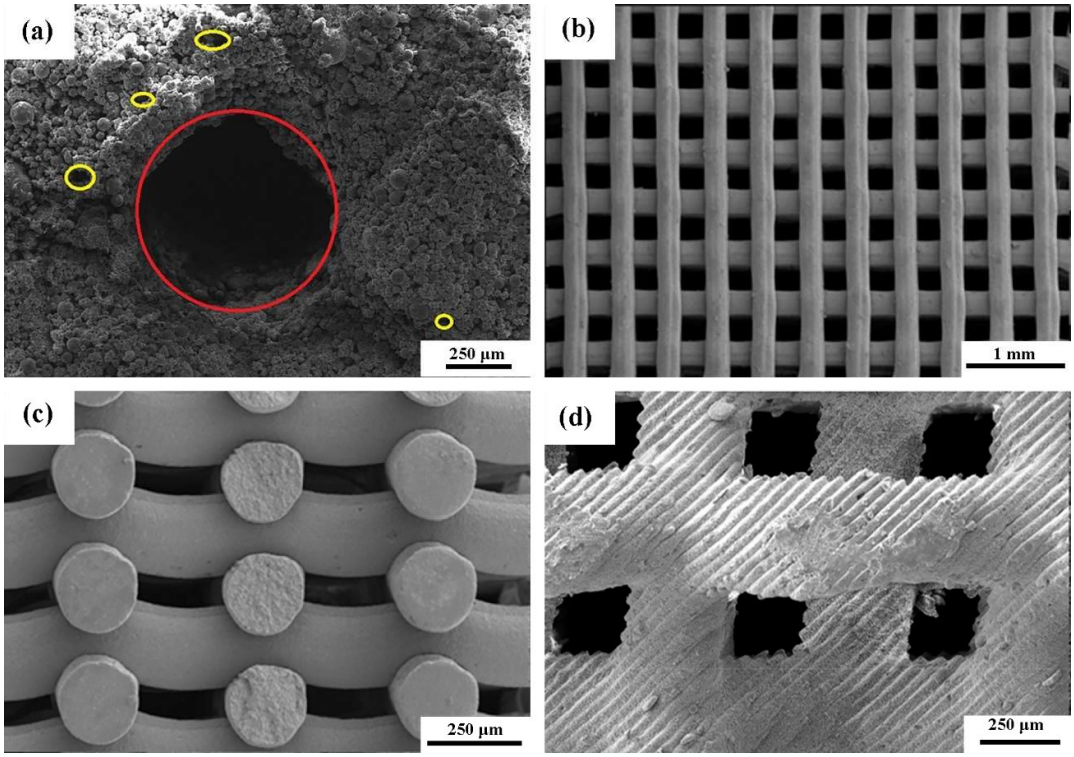

Fig. 4. Morphology of HA/TCP scaffolds manufactured by different 3D printing techniques: (a) binder-based 3D printing method, reprinted from Ref. [87], (b, c) direct-ink writing (top and cross-section views, respectively) , reprinted from Ref. [82] and (d) SLA, reprinted from Ref. [107].

4. Properties of 3D porous HA/TCP composite scaffolds

To fabricate and employ a 3D load-bearing scaffold for bone regenerative applications, it is crucial to consider some functional requirements. In this chapter, the needs of an ideal scaffold, including mechanical properties, degradability, bioactivity, cell biocompatibility and osteogenic ability, are thoroughly discussed and linked to 3D porous HA/TCP composite scaffolds reported in the literature. Table 3 summarizes the fabrication route, structure, mechanical properties and bioperformance of different 3D porous HA/TCP composite scaffolds published in the literature.

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Table 3. Overview of the fabrication method, fabrication parameters, porosity, pore size, strength and biological performance of various 3D porous HA/TCP scaffolds

Composition	Fabrication parameters	Porosity (%)/pore size (µm)	Compressive strength (MPa)	Biological properties	References
HA/TCP (33/67)	Space holder: sucrose; Binder: PVA; Sintering at 1230 °C for 4 h	40/15	-	No infection and inflammation, formation of abundant osseous ECM[1]	[28]
HA/β-TCP (60/40)	Space holder: PEG; Binder: PVA; Sintering at 1000 °C for 4 h	54/-	15.6	-	[42]
HA/β-TCP (60/40)	Space holder	72/10-100	4.0	Rapid bone remolding	[29]
HA/β-TCP (60/40)	Direct foaming	80/200-400	6.7	Promoted bone formation capacity due to implementation of optimized concentration of PDRN[2] or rhBMP‑2[3] growth factors	[31]
HA/β-TCP (50/50)	Direct foaming (gel casting); Gelling agent: epoxy resin; Hardener: dipropylenetriamine; Sintering at 1250 °C for 2 h	85/698	1.6	Controllable degradation and superior cell activity	[30]
HA/β-TCP (26.9/73.1)	Direct foaming (gel casting); Sintering at 1100 °C for 4 h	80/100	-	Stability under static and orbital conditions in SBF solution and bioactivity	[33]
HA/β-TCP (28/72)	Foam replication; Sintering at 1350 °C for 10 min	-/100-500	-	Promoted cell activity due to preprocessing scaffolds with decellularized cell-derived ECM deposition	[57]
β-TCP + xHA nanofibers (x: 0, 1, 2, 3, 4 and 5 wt%)	Foam replication; Sintering at 1400 °C for 1 h	73/300-400	9.8	-	[64]
HA/β-TCP (80/20, 60/40, 40/60 and 20/80)	Foam replication; Sintering at 1100 °C for 2 h	63-73/150-400	5.3-7.9	-	[63]
HA/β-TCP/α-TCP (75/18/7)	Freeze casting; Freezing vehicle: camphene; Sintering at 1280 °C for 4 h	72/100-200	36.4	-	[37]

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HA/β-TCP (30/70, 50/50 and 70/30)	Freeze casting; Freezing vehicle: deionized water; Binder: PVA; Sintering at 1100 °C for 3 h	79.6 – 80.6/131.6 – 135.1	0.44-0.54	Suitable biodegradation, MG63 cell activity and bone regeneration capacity for HA/TCP: 30/70	[68]
HA/β-TCP (60/40)	Binder-based 3D printing; Binder: acrylic acid copolymer; Sintering at 1300 °C for 1 h	52-56/5-200	-	Acceptable cell viability and proliferation, high osteoclast activity	[89]
HA/TCP	Binder-based 3D printing; Binder: phosphoric acid; Sintering at 1200 °C for 5, 10 and 15 h	63-68/ 300	0.4-1.8	Significantly higher cell viability by BCP scaffold than pure HA and TCP	[81]
HA/β-TCP (60/40)	Binder-based 3D printing; Binder: PVA and phosphoric acid	50/800	1.21-2.81	Superior cell proliferation compared to pure HA and TCP; Higher biocompatibility of scaffolds with PVA as the binder than phosphoric acid	[87]
HA/β-TCP (100/0, 60/40 and 20/80)	Direct-ink writing; Ink organic phase: Pluronic F-127; Sintering at 1100 °C for 2 h	25-80/100-620	3.0-50.0	-	[82]
HA/β-TCP (70/30)	Direct-ink writing; Ink organic phase: Darvan 821 A; Sintering at 1200 °C for 30 min	50/-	45.6	-	[94]
HA/β-TCP (50/50)	Direct-ink writing; Ink organic phase: methacrylate-based photocurable resin; Sintering at 1200 °C for 6 h	33/600-800	25.1	-	[96]
HA/β-TCP (50:50)	Direct-ink writing; Modifier: sodium alginate solution; Drug: berberine	-/150-600	16.9	Enhanced antibacterial and bone-formation properties due to loading berberine	[97]
HA/β-TCP (100/0, 90/10, 70/30, 50/50, 30/70 and 0/100)	Selective laser sintering; Laser power: 12 W	61/800-1200	18.3 (for 70HA/30β-TCP)	Excellent osteoinductivity with favorable cell morphology in 70HA/30β-TCP scaffold	[83]
HA/TCP (70/30)	Indirect selective laser sintering; Binder: epoxy resin; Laser power: 1.8 W	80/5-1000	0.11	Higher osteoinductivity of the composite scaffold, boosted osteogenic marker expression	[100]

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HA/TCP (50/50)	Mask-based stereolithography; Photocurable polymer: polymer resin SI500; Sintering at 1050, 1150 and 1250 °C for 3 h	20-80/20-1000	15.0	Higher than 90% cell viability	[85]
(Sr+HA)/β-TCP (0/100, 20/80, 30/70 and 40/60)	Foam replication; Binder: PVA; Sintering at 900 °C for 4 h	80/70-135	-	Superior osteogenic property and cell activity compared to un-doped BCP scaffolds	[58]
HA/PCL coated HA/β-TCP (40/60)	Foam replication; Polymer sponge: PU; Binder: PVA; Densification sintering at 1200 °C for 2 h	90/400-700	2.1	Improved cell activity and gene expression (ALP[4] activity), HA formation	[60]
Collagen-coated HA/β-TCP (20/80)	Direct-ink writing; Ink organic phase: sodium tripolyphosphate and carboxymethylcellulose; Sintering at 1200 °C for 4 h	59/347	-	Great Osteogenesis and osteodifferentiation of cell-seeded composite scaffolds	[109]

[1] Extracellular matrix, [2] Polydeoxyribonucleotide, [3] Recombinant human bone morphogenic protein 2 and [4] alkaline phosphatase

4.1. Mechanical properties

Within the bone healing process, maintaining the strength of the scaffold is of paramount importance to ensure the tissue integrity. Some monophasic apatites like TCP exhibit relatively weak mechanical strength and extreme degradability, losing their load-bearing capability. In this perspective, the addition of a more stable phase like HA and the development of HA/TCP composite scaffolds seem to be helpful [110]. However, their mechanical properties need special considerations due to the inherent brittleness of the constituting ceramics and the destructive impact of pores. Geometrical and phase characteristics are the most critical factors affecting the mechanical properties of 3D porous HA/TCP scaffolds.

Geometrical characteristics are referred to porosity, pore size and struts connection. Mechanical strength is generally deteriorated by increasing porosity. As proof, Macchetta et

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al. [37] reported that by enhancing the CaP powder amount from 10 vol% to 30 vol% in the freeze casting process, the porosity of 75HA/25TCP scaffolds decreases from 72.5% to 31.4%. This gave rise to the improvement of compressive strength from almost 2.3 MPa to the significant value of 36.4 MPa. Porosity can be also controlled by the sintering process. Typically, it has been pointed out that the increase of sintering temperature from 1050 ℃ to 1250 ℃ decreases porosity by 6% in 50HA/50TCP scaffolds due to the promotion of densification, altering the strength from 0.1 MPa to 4.3 MPa [85]. Indeed, by decreasing porosity, stress concentration zones are reduced and the actual surface area to resistant mechanical loads is increased.

Pore and strut connection geometry is another crucial factor influencing the mechanical behaviors of 3D scaffolds. Lim et al. [107] assessed the impact of the pore architecture on the strength of HA/TCP scaffolds processed by 3D printing. They realized that cubic pores provide a lower stress concentration than diamond ones, giving the strength of 6.2 and 2.8-3.6 MPa, respectively. Regarding the specification of the scaffold struts connection, the addition of micro-ribs to the structure of 3D HA/TCP scaffolds manufactured by the direct-ink writing method considerably improved the strength from 28.3 MPa to 45.6 MPa. The micro-ribs also controlled the decline rate of strength due to degradation upon immersion in the physiological environment (Fig. 5) [94]. In conclusion, the control of stress concentration zones is critical to obtain a desirable strength for 3D porous scaffolds.

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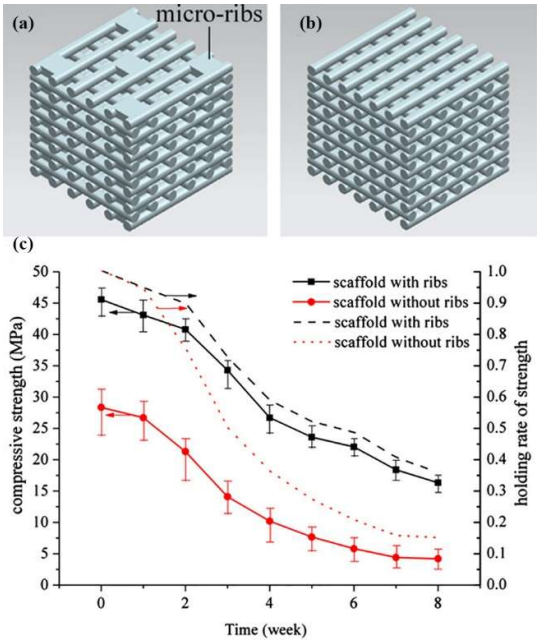

Fig. 5. (a) Scheme of the original scaffold, (b) scheme of the scaffold with micro-ribs and (c) compressive strength of the rib-free and rib-containing HA/TCP 3D-printed scaffolds vs. holding time in the physiological environment, reprinted from Ref. [94].

The addition of TCP to HA and hence the development of HA/TCP composites contribute to two opposite behaviors in mechanical strength; somewhen an improvement [111-113] and sometimes a monotonic decrease [114-116]. The strength deterioration is mainly attributed to the formation of micro-cracks during sintering due to volume changes resulting from the phase transformation between α-TCP and β-TCP [117]. The strengthening effect by TCP is also based on the rule of mixtures. In this perspective, Shuai et al. [83] reported that HA/TCP composite scaffolds with the ratio of 70/30 possess superior mechanical properties compared to HA or TCP monophases, where compressive strength increases from approximately 3.31 MPa and 7.24 MPa for TCP and HA, respectively, to 18.35 MPa for 70HA/30TCP. It is concluded that when the volume fraction of TCP is low, TCP behaves as a

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reinforcing agent in HA as the matrix. However, with the increment of the TCP content, the mechanical properties are deteriorated due to micro-crack formation caused by the thermal expansion coefficient mismatch of HA and TCP.

It has been also pointed out that incorporating HA nanofibers to β-TCP scaffolds noticeably improves the mechanical behaviors of HA/TCP scaffolds [64]. Adding 5 wt% HA nanofibers to TCP increased the compressive strength and toughness by about 6.8 MPa and 0.7 kN/m, respectively. Generally, the enhancement of the mechanical behaviors with the addition of nano-HA to TCP is attributed to three main reasons [30, 64, 118]: (1) strengthening of grain boundaries by the action of residual stresses created by the thermal expansion coefficient mismatch of the phases, (2) crack pinning phenomenon by the compressive residual stresses induced by the inclusions and (3) wavy path of crack propagation due to the interaction of cracks and stress fields around nano-HA [64, 118]. These studies reflected that as well as the relative amount of the CaP phases, the geometry and accommodation of the phases are effective in the mechanical properties of HA/TCP scaffolds.

4.2. Degradability

Tissue regeneration with the help of biomaterials is a promising approach to boost the body's reparative capacity, which is strongly related to biodegradability. Physicochemical dissolution and phagocytosis by osteoclasts are the two main mechanisms determining the degradation behavior of CaPs [119]. On the significance of biodegradation, it should be noted that this property affects biocompatibility due to interactions between ions released and cells. Typically, regarding Ca ions as one of the most principal components of CaPs, it has been reported that local concentrations higher than 10 mMol can cause cytotoxicity [120]. Additionally, biodegradation is related to bioactivity in terms of both the ion exchange-

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controlled apatite precipitation step and bone formation caused by cellular activities. The equivalency of the degradation and new tissue formation rates is also critical for tissue regeneration.

The optimal degradation rate depends on many factors, such as the dimension and location of the bone defect along with the personal traits of the patient body [121]. Because the bone remolding process is controlled by the mentioned factors and can take a few months to about two years [122]. For instance, the degradation and bone remolding time of at least 9 months for spinal fusion, 3-6 months for craniomaxillofacial applications and up to 24 months for serious bone fractures are well-established [123]. It has been reported that the weight loss of porous HA and TCP after three months in a rabbit's body is 0 and 30%, respectively [124]. Bodde et al. [125] also observed 64% loss of TCP bone grafts between 12-26 weeks of implantation in trabecular defects of a sheep. In another investigation [126], HA exhibited negligible degradation with a surface dissolution rate of 20-30 μm/year. This rapid and slow degradation of TCP and HA, respectively, makes BCPs scaffolds a promising alternative to the monophases. They can be degraded between 3-24 months, which is consistent with the remolding time of different bones [127].

The calcium to phosphate molar ratio (Ca/P) and porosity strongly govern the physicochemical solubility of CaPs. HA (Ca/P = 1.67) possesses a relatively low degradation rate and is typically believed to be non-biodegradable, whereas TCP (Ca/P = 1.50) shows a higher dissolution rate. Thus, HA/TCP composites exhibit a moderate biodegradability, which can be tailored by the ratio of HA/TCP [128]. In this regard, Houmard et al. [82] compared the degradation rate of 20HA/80β-TCP and 60HA/40β-TCP scaffolds by incubating in the simulated body fluid (SBF) and evaluating the weight loss. They observed that the 20HA/80β-TCP scaffold exhibits a higher dissolution rate due to its higher β-TCP content. The same

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conclusion was drawn by Zhao et al. [88]. Additionally, it was found that higher porosity causes higher surface area, environmental exposure and dissolution. The direct relation of the degradation rate with the TCP/HA ratio and surface area is evidently concluded for this type of scaffolds.

4.3. Apatite-formation ability

Biomineralization or apatite-formation ability is a key feature of biomaterials for bioactivity and osteointegration. The apatite-formation ability of 3D porous HA/TCP composite scaffolds is also adjustable by tailoring the HA/TCP ratio and surface area. Fig. 6 typically presents the SEM micrographs of HA, TCP and HA/TCP bone tissue engineering scaffolds after incubating for seven days in the SBF [83]. The HA scaffold indicated no sign of biodegradability and remained flat during immersion. The HA/TCP composite scaffolds exhibited cavities with rough surfaces and apatite particles on their surfaces. With the increment of the TCP/HA ratio, further flake-like apatite was deposited and the depth of the cavities was increased, implying the higher degradation rate and superior apatite-formation ability of the samples [83]. Indeed, the dissolution of CaPs enhances the local concentration of phosphate and calcium ions, providing a supersaturated state and thereby inducing the precipitation of these ions in the form of CaP [129]. In conclusion, the apatite-formation ability is improved by increasing the TCP/HA ratio and surface area.

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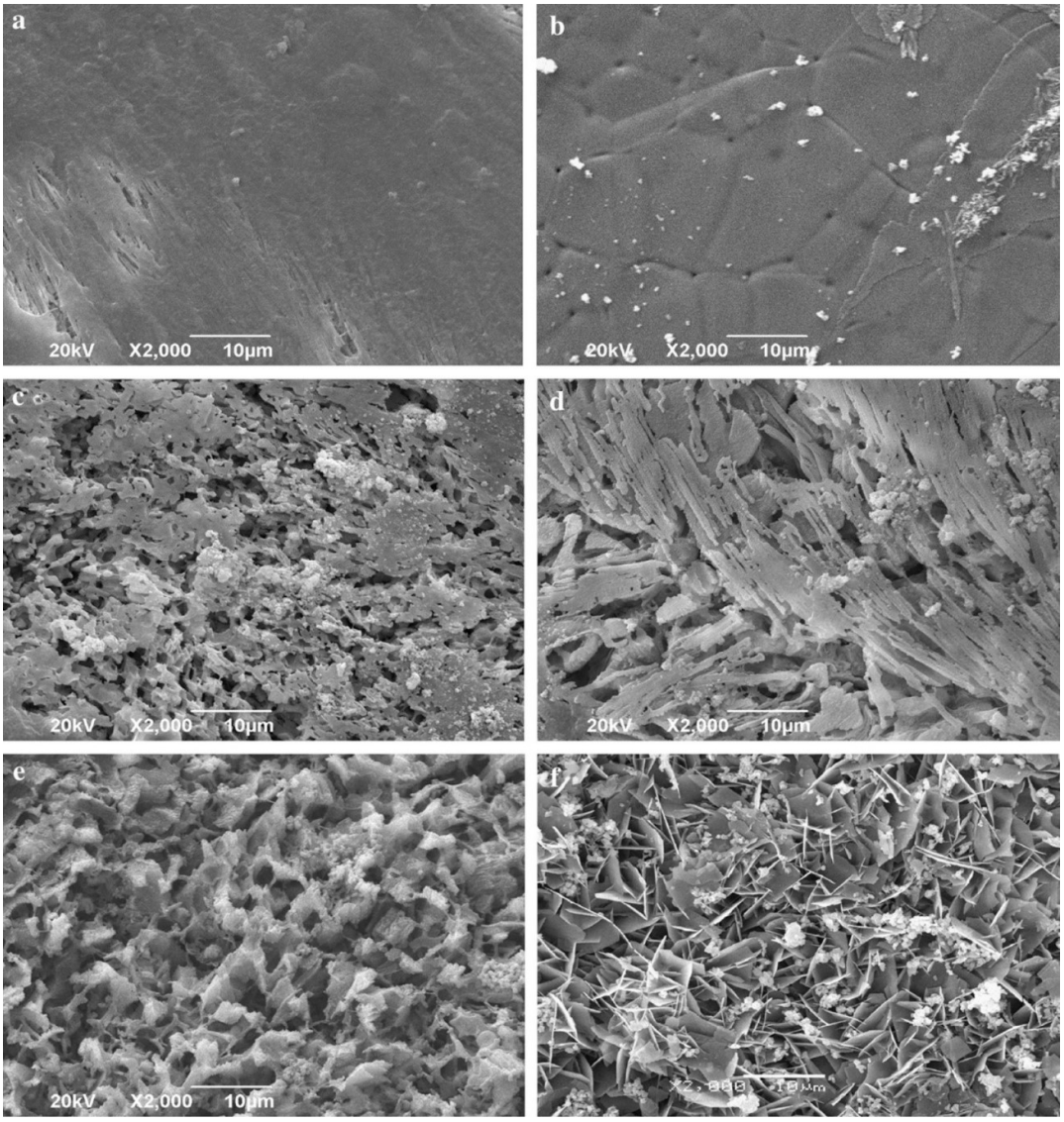

Fig. 6. SEM micrographs of different scaffold specimens after incubating in the SBF: (a) pure HA, (b) HA/TCP (90/10), (c) HA/TCP (70/30), (d) HA/TCP (50/50), (e) HA/TCP (30/70) and (f) pure TCP, reprinted from Ref. [83].

4.4. In vitro cellular activity

Cellular activities, including cell viability, adhesion, proliferation and differentiation, are associated with biocompatibility and tissue reconstruction. The degradation and surface

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(topography and wetting) characteristics of scaffolds essentially determine cell responses. Regardless of these parameters, BCP scaffolds are all biocompatible and able to encourage cell adhesion, differentiation and proliferation behaviors [68, 114]. Concerning the degradation of CaPs accompanied by the release of Ca^{2+} and PO_4^{3-}, the former positively affects the pre-osteoblastic chemotaxis to the bone site and promotes the differentiation and proliferation of osteogenic cells. The latter also influences the behavior of osteogenic cells via the expression of genes like MGP and osteopontin [130, 131]. It has been also depicted that BCP scaffolds exhibit improved cell adhesion, differentiation and proliferation in comparison to pure TCP and HA scaffolds [132]. This can be due to the contribution of degradation products around the BCP scaffolds, forming a micro-environment enriched with Ca^{2+} and PO_4^{3-} compared to HA with low degradability. Also, in the case of TCPs, it can be asserted that the higher degradation rate can lead to the fast destruction of suitable sites for cell adhesion and activity.

One of the main essential parameters affecting cell responses is porosity via controlling the interaction of the biomaterials and cells, in addition to the supply of nutrients and oxygen [58, 133]. In this perspective, Zhao et al. [88] have proved that HA/TCP scaffolds with 50% porosity show better rabbit bone marrow stem cells (BMSCs) attachment and proliferation compared to those with 30% porosity and without pores. Hence, the enhancement of porosity in HA/TCP scaffolds improves cellular activities.

The surface topography of scaffolds has been proved to affect cell activity, especially cell adhesion. In this matter, You et al. [59] concluded the positive impact of micropores and rough topography of HA/TCP scaffolds on the activities of MG63 cells and ALP. Indeed, rough surfaces provide better cellular responses because they can exhibit improved wettability, selective adsorption of proteins and focal contacts with cells [134, 135]. Micropores on the

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surface of scaffolds have a crucial contribution to cell activity as they provide a rougher surface for cells attachment and proliferation.

The phase composition of HA/TCP scaffolds highly impacts the cell behavior of the scaffolds. Zhao et al. [88] studied the phase composition effect of HA/TCP scaffolds on cell attachment. Although the HA/TCP ratio did not affect the morphology and spreading of cells, the scaffolds with the HA/TCP molar ratio of 60/40 displayed the optimal seeding efficiency compared to the other ratios. Shuai et al. [83] also investigated the proliferation of MG63 cells cultured on HA/TCP scaffolds for three days (Fig. 7). Results indicated that the HA/TCP composition considerably affects the cell proliferation, and morphology, where the low cell attachment of HA turns to round-shaped, filopodia extensions upon the 10/90 HA/TCP sample surface. Cells connected to an abundant extracellular matrix with a flattened shape were observable on 30/70 HA/TCP. In the case of 50/50 HA/TCP, matured cells with the formation of white granular apatites were observed, whereas cell adhesion and connectivity decreased in 30/70 HA/TCP and TCP samples due to the fast degradation of TCPs. In another investigation [100], the scaffolds with the HA/TCP molar ratios of 55/45 and 50/50 exhibited higher pre-osteoblastic cell proliferation than the scaffold samples with the HA/TCP molar ratios of 65/35 and 60/40. It is accordingly concluded that despite the unanimity of the literature on the cell cytocompatibility of BCP compositions, different optimal compositions of HA/TCP have been reported to achieve the highest cytocompatibility and cell attachment.

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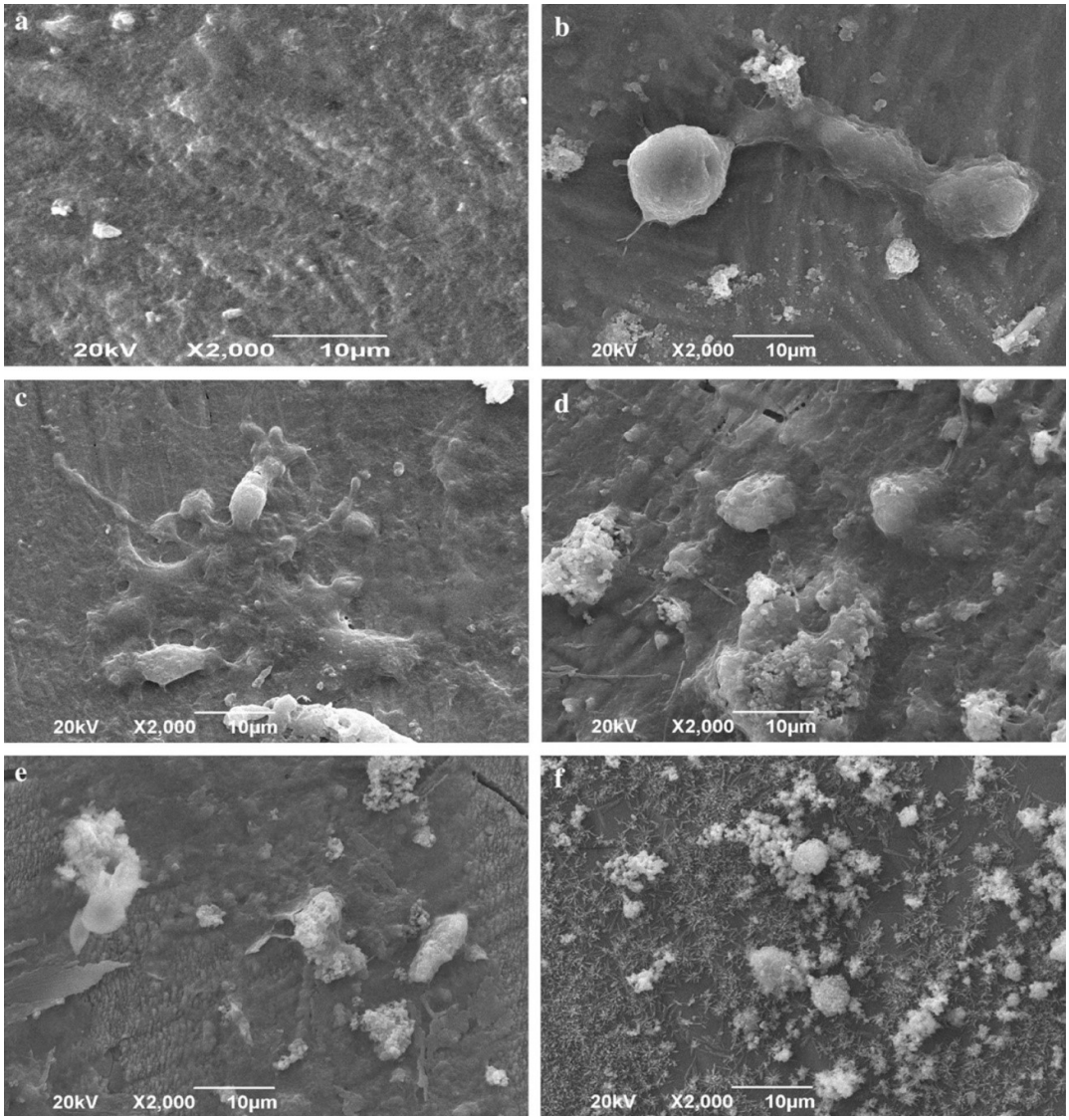

Fig. 7. SEM images of cells on composite scaffolds with various ratios of HA/TCP: (a) pure HA, (b) 90/10, (c) 70/30, (d) 50/50, (e) 30/70 and (f) pure TCP, reprinted from Ref. [83].

As well as the parameters associated with scaffolds, there are testing-related methods affecting the cell adhesion and proliferation response of a given scaffold. Typically, Kim et al. [57] showed if bone mesenchymal stem cells (MSCs) culture on HA/TCP scaffolds is decellularized, the remaining extracellular matrix (ECM) improves the following pre-

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osteoblast (MC3T3-E1) attachment and differentiation, due to mimicking *in vivo* bone physiochemical conditions.

4.5. In vivo osteogenesis ability

The osteogenic capability of bone regenerative 3D scaffolds is one of the features defining the functionality of these substances. The application of 3D porous HA/TCP scaffolds as bone regenerative matrices has been widely investigated. Based on the literature [18, 31, 68], HA/TCP scaffolds are able to promote the bone formation, proving their high bioactivity and osteogenic ability. Typically, it has been reported that 3D-printed BCP scaffolds exhibit a significant vertical bone growth after eight weeks of implantation in a dog mandible, where a uniform distribution of the new bone in density and height along the 3D-printed scaffold was observed [136]. It implies the promising capability of 3D-printed BCP scaffolds to treat bone defects.

The degradation, surface and cell response characteristics of scaffolds are considered as parameters governing the osteogenic potential of HA/TCP scaffolds. Also, the pore structure is an essential factor of 3D scaffolds for the bone regeneration purpose. New blood vessels similar to pores supply oxygen, nutrients and metabolic wastes removal. Furthermore, they provide the bone structure with some hormones, growth factors and neurotransmitters expressed from other tissues, urging the cellular activity related to the bone formation [137, 138]. Farahpour et al. [139] compared 3D HA/TCP scaffolds with 5, 10 and 20% porosity by the radiological evaluation of the scaffolds implanted in male white rabbits. All of the samples showed the osteoconduction and osteoinduction ability, where the sample with 20% porosity provided the highest bone regeneration ability. In another study [140], the effect of the pore size (0.8, 1.2 and 1.6 mm) on the bone formation ability of BCP scaffolds was compared at the

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fixed porosity of 70%. It was concluded that the BCP scaffold with 0.8 mm pore size demonstrated superior osteogenesis ability due to the higher reactivity. That is, higher porosity and smaller pore size (higher surface area) provide improved osteogenesis ability via controlling cell activities and vascularization.

The degradation rate of CaPs plays a dual impact on the osteogenic behavior of 3D scaffolds. On the one hand, a high degradation rate has shown to be helpful since MSCs differentiation and mineralization are promoted by phosphate and calcium ions (osteoinduction). On the other hand, a relatively stable surface is crucial for the deposition of new bone from the osteoconduction viewpoint [141, 142]. Consequently, 3D porous HA/TCP scaffolds remarkably possess a higher osteogenic ability compared to HA and TCP monophases due to their intermediate degradation rate. Arinzeh et al. [143] investigated the influence of the HA/TCP ratio (100/0, 76/24, 63/37, 56/44, 20/80, and 0/100) on the bone formation using 3D scaffolds. The biological assay results corroborated that the HA/TCP ratio of 20/80 exhibits the highest new bone-formation ability (Fig. 8) [143]. In conclusion, optimizing the HA/TCP ratio is critical to obtain the highest bone formation owing to the balance between the bioresorbability of TCP and the bioactivity of HA.

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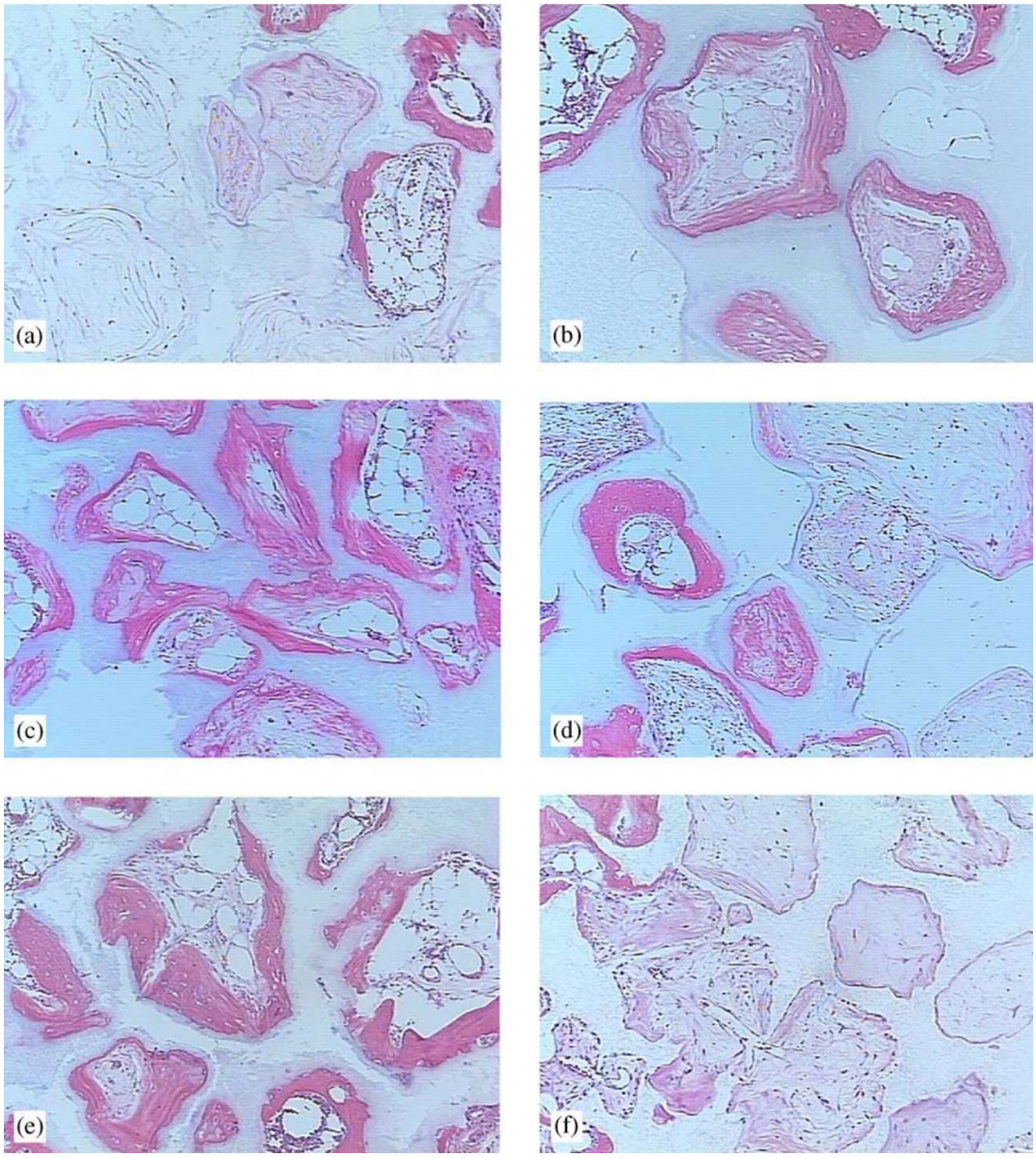

Fig. 8. Historical representative of composite scaffolds with various HA/TCP ratios: (a) pure HA, (b) 76/24, (c) 63/37, (d) 56/44, (e) 20/80 and (f) pure TCP. New bones are stained with pink, CaPs are white, loose connective tissues are light pink and cells are colored with dark pink, reprinted from Ref. [143].

Concerning pre-seeding cells and growth factors, Yang et al. [144] investigated the osteogenesis ability of MSCs-seeded HA/TCP scaffolds, showing newly formed bones at

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peripheries and within macropores after eight weeks of implantation in nude mouses. In addition to bone materialization, new blood vessels were formed in bone-formation areas haphazardly. In another study, Zhang et al. [145] assessed the bone-formation ability of HA/TCP scaffolds after per-seeding four types of bone marrow and dental pulp cells. Within ten weeks, only the samples seeded with rat BMSCs offered the new bone formation, mostly on lateral parts with bone-like structures in the center of the scaffolds. This study reflected the high dependency of the bone formation promoted by pre-seeding on the donor and how the cells were provided, either directly from the donor or repeated passaging. Also, Lim et al. [31] cultured recombinant human bone morphogenic protein 2 on HA/TCP scaffolds and an improved bone-formation ability was detected compared with the non-treated scaffolds. Thus, pre-seeding cells and growth factors on 3D porous HA/TCP scaffolds could effectively improve their osteoconductivity and osteoinductivity response.

5. Applications of 3D porous HA/TCP composite scaffolds

3D porous BCP scaffolds are able to fill bone defects and facilitate the bone repair/reconstruction process effectively, so that they have been widely investigated in clinical regenerative applications. Also, 3D porous HA/TCP composite scaffolds have been employed as drug/growth factor delivery platforms to facilitate the healing process.

5.1. Bone regeneration

It has been reported [146] that craniofacial bones having a complicated 3D geometry can be replaced by 3D-printed CaPs like BCPs. The treatment of the maxillary sinus of humans by these scaffolds has been also reported to result in 28% new bone formation after 6 months [147]. Also, there are several reports on applications of BCP scaffolds for bone therapy in

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animals, such as mouse (ectopic model) [28], sheep (calvarial defects) [148], rabbit (calvarial defects) [31], pig (calvarial defects) [102], rat (calvarial defects) [104], rabbits (medial femoral condyle) [68], dog mandible (medial femoral condyle) [149] and small animals (femoral epiphysis) [29]. This success rate of BCP scaffolds suggests their great potential for further bone regeneration applications in other sites and vertebrates. Typically, BCPs can be used instead of HA and TCP scaffolds which are comprehensively employed in various areas, such as maxilla, mandible, alveolar bone, calvarium, long bones and dentine applications since BCPs show a higher ability of bone formation compared to single-phase CaPs.

Table 4 summarizes the clinical bone formation ability of 3D porous HA/TCP scaffolds after implantation in different surgery sites of the human body. In this regard, Iezzi et al. [150] investigated sinus augmentation procedures using BCP, where almost 30 % newly formed bone was observed after 6 months of implantation. In another report [151], BCP implants for maxillary sinus augmentation showcased 29% new bone formation after 6 months. Mangano et al. [152] also assessed the bone formation ability of BCP scaffolds in maxillary alveolar ridge after 7 years, where 59% new bone formation was observed. Giuliani et al. [153] compared granular and 3D porous BCP scaffolds implanted for sinus augmentation in 6 and 9 months. The porous scaffolds exhibited superior new bone formation ability at both periods of time compared to the granular ones, where the porous scaffold was capable of mimicking the healthy native bone in a more effective manner.

Table 4. Clinical bone formation ability of 3D porous BCP scaffolds after implantation in different implantation sites of the human body

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HA/TCP ratio	Porosity (%)	Implantation site/procedures	Implantation duration (months)	Newly formed bone (%)	Residual materials (%)	References
60/40	-	Sinus augmentation	6	30	28	[150]
30/70	64	Maxillary sinus augmentation	6	29	26	[151]
30/70	-	Maxillary sinus augmentation	6	30	29	[154]
30/70	60	Maxillary alveolar ridge	84	59	26	[152]
60/40	-	Alveolar ridge preservation	6	29	22	[155]
30/70	-	Sinus augmentation	6 9	26 33	33 29	[153]

5.2. Drug/growth factor delivery

BCP scaffolds can be successfully impregnated with drugs or growth factors to further improve their functionality for bone reconstruction or endow additional properties, such as antibacterial ability to the scaffolds. This application of HA/TCP scaffolds relies on the controllability of their degradation rate and accordingly the carried agent release [156].

Concerning drug delivery applications, Park et al. [157] fabricated alendronate-loaded BCP scaffolds with enhanced bone formation *in vitro* and *in vivo* for rat tibia defects. Also, Kim et al. [158] indicated the improved ability of alendronate-loaded BCP scaffolds to increase ALP activity and upregulate osteogenesis-related gene expressions. In another approach, Lin et al. [159] impregnated BCP scaffolds with doxycycline (Dox) encapsulated PLGA-

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Methoxypolyethylene glycols (PLGA-mPEG) microspheres to ensure the sustained release of Dox. The prepared scaffolds exhibited an enhanced BMSCs activity. However, *in vivo* tests are still required to investigate the osteogenesis ability of this scaffold. Berberine-loaded BCP scaffolds were also fabricated by Sun et al. [97] resulting in low cytotoxicity and enhanced MC3T3 cell activity. Also, by increasing the concentration of the antibacterial drug, the resistance against bacteria growth increased.

In addition to drugs, other biological agents like growth factors, proteins, DNA or hormones can be carried and locally released by BCP scaffolds. Guicheux et al. [160] investigated BCP scaffolds loaded with human growth hormone (hGH) implanted in rabbits, leading to 65% enhancement in bone formation compared to the samples without the hormones. Roldan et al. [161] also examined the osteogenesis ability of BCP scaffolds loaded with bone morphogenetic protein (BMP-7) combined with MSCs or vascular endothelial growth factor (VEGF). Both the samples exhibited newly formed bones at mice ectopic sites. Johnson et al. [102] compared BCP scaffolds loaded with dental pulp neural crest MSCs (DPNCCs) and bone marrow aspirate (BMA) in the calvarial bone of swines. The results showcased that while both the samples support new bone formation, the BMA-loaded scaffolds have more trabecular bone structure. In another report, Strobel et al. [162] focused on seeding primary osteoblasts (OB) and/or loading BMP-2 into BCP scaffolds. The implantation of the scaffolds into male rats demonstrated that while the singular use of OB or BMP-2 could enhance bone formation, their simultaneous employment can enhance bone formation synergistically. The information about some of the BCP scaffolds employed for carrying agents is listed in Table 5.

Table 5. BCP scaffolds utilized for delivery purposes and their performance

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HA/TCP ratio	Porosity (%) /Pore Size (µm)	Carried agent	Results	Reference
60/40	-/100-300	Alendronate	Sustained release for 28 days, enhanced cell growth and upregulation of osteogenesis-related gene expression	[158]
40/60	90.8-92.3/300-600	Dox loaded (PLGA-mPEG) microspheres	Sustained release for 2 months, enhanced cell activity	[159]
60/40	92-94/360-440 and 900-1150	BMP-7 and MSCs/ BMP-7 and VEGF	Observation of newly formed bone	[161]
60/40	50/565	hGH	Dose-dependent increase of bone growth	[160]
-	-/100-300	Alendronate	Sustained release, enhanced ALP activity and gene expression *in vitro* and callus formation *in vivo*	[157]
60/40	80/200-400	PDRN/ rhBMP-2	Increase in bone formation	[31]
50/50	-/150-600	Berberine	Antibacterial property, enhanced cell activity	[97]
60/40	75/100-500	bone marrow and dental pulp stromal cells derived from rat or human	Cell growth and ECM mineralization *in vitro* and mature bone formation for rat BMSCs *in vivo*	[145]
50/50	-/4000	BMA or DPNCCs	Calvarial bone regeneration similar to native bone	[102]

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50/50	65.3/100-600	Primary osteoblast and BMP-2	Synergistic enhancement of bone formation, mRNA expression of bone-specific genes	[162]

6. Approaches to enhance the biofunctionality of 3D porous HA/TCP composite scaffolds

As discussed above, the mechanical, degradation, biomineralization, biocompatibility and osteogenesis behaviors of 3D porous HA/TCP scaffolds can be adjusted by parameters like the HA/TCP ratio and geometrical architecture. However, their mechanical and biological properties still require further enhancements. Particularly, their relatively low mechanical strength and antibacterial properties can cause serious problems during the bone healing process. In this regard, some extrinsic modifications on the structure of scaffolds, including using polymeric additives, dopants and coatings, have shown to be beneficial to enhance their bioperformance.

6.1. Polymeric additives

Sintering may result in some undesired properties in BCP porous scaffolds, such as brittleness caused by unsuitable transformations and the decrement of biological activities. Furthermore, sintering at elevated temperatures prevents the possibility of loading biological agents or drugs into scaffolds. The minor use of polymeric additives is an effective way to overcome the mentioned problems with sintering, while providing adequate mechanical properties. In this perspective, Sun et al. [97] constructed a drug-loaded 3D-printed scaffold modified with sodium alginate. A ceramic slurry as the ink of 3D printing was prepared by mixing calcium phosphate powders (BCP, β-TCP:HA=1:1 in wt%), sodium alginate, berberine

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(drug) and deionized water. After printing, the scaffolds were immersed into 30% calcium chloride solution for cross-linking. Then, the cross-linked scaffolds were freeze-dried to create spatial voids. The drug release was controlled by modulating the printing inks and the porosity of the scaffolds. The drug-loaded BCP scaffold exhibited excellent antibacterial and bone regeneration activities.

In another investigation [87], PVA and phosphoric acid in different concentrations were used instead of a sintering process to fabricate HA/TCP composite scaffolds. It was realized that the PVA binder exhibits no chemical reaction with bioceramic particles. On the contrary, the binding mechanism in the scaffolds processed by phosphoric acid was chemical, resulting in better mechanical interactions and properties. In this investigation, the compressive strength of the porous 3D-printed scaffolds with PVA was 1.34 MPa, whereas this value reached 2.6 MPa by utilizing phosphoric acid as the binder. It is accordingly concluded that the use of polymeric additives excuses high-temperature sintering, offering biological factor loading and delivery.

6.2. Doping

Doping is one of the most routine approaches to alter properties of ceramics, including CaPs. In this respect, Marques et al. [163] compared the mechanical properties and biocompatibility of un-doped BCP and 7Sr3Ag-doped BCP scaffolds fabricated by the robocasting technique. They observed that the mechanical strength increases from 7.0 MPa to 40.0 MPa by doping with 7Sr3Ag powder as a result of the more solids loading in the ceramic ink. The BCP-7Sr3Ag scaffold stimulated osteoblasts and was proven to have antibacterial properties due to the presence of Ag.

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Sr both stimulates osteogenesis by encouraging the formation of the β-catenin protein and inhibits the bone bioresorption [164]. Sr substitution in HA has accordingly shown promise in enhancing osteoblast proliferation, bioresobability and new bone formation [165]. Mohapatra et al. [58] pointed out that the volume fraction of macropores, water uptake capacity and cell viability are notably increased by adding more Sr-HA contents to BCP scaffolds.

Magnesium (Mg) is indispensable to human metabolism and exhibits osteogenesis activity [166]. Mg-substituted HA and β-TCP facilitate osteoblast adhesion and proliferation [167]. It has been reported that doping of 10 mol% Mg to BCP scaffolds increases the strength from 0.3 MPa to 2.1 MPa owing to improved densification [168]. This alteration was owing to the increased thermal stability of β-TCP, which prevents its transformation to an unfavorable α-TCP phase during sintering. In conclusion, the mechanical, degradation, apatite-formation ability, cell interaction and osteogenesis behaviors of HA/TCP scaffolds can be modified through doping with trace ions, especially the constituent ions of natural bone.

6.3. Coating

Coating as a surface modification technique has been widely applied on tissue engineering scaffolds to enhance their performance. Different coatings have been applied on 3D porous HA/TCP scaffolds to improve 1) cell adhesion, differentiation and proliferation, 2) controlled release of drugs and oxygen and 3) mechanical properties.

Sustained release of oxygen from biomaterials can be a remarkable way to enhance tissue endurance and decrement of necrosis since oxygen plays a principal role in some vital cell functions like the differentiation and proliferation of stem cells, angiogenic gene expression and collagen synthesis [169, 170]. In this regard, calcium peroxide (CPO)-encapsulated polycaprolactone (PCL) was coated over HA/TCP scaffolds to augment the oxygen level to the

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engineered tissue [171]. The osteoblast viability and proliferation were significantly improved in 3% CPO/PCL-coated scaffolds due to oxygen released by the subsequent decomposition of H_2O_2. In a similar study [172], robocast BCP scaffolds coated with CPO-encapsulated PCL exhibited significant antibacterial activity owing to the sustained release of oxygen, which could effectively inhibit the growth of S. aureus bacteria.

It is generally believed that two types of pore structures, including micropore (<100 μm) and macropore (100-800 μm), are required for bone regeneration. The former promotes cell attachment, while the latter eases vascularization and bone growth [173]. According to Ref. [174], applying nano-HA coating on BCP scaffolds through the dip-coating process increases the surface area of the BCP scaffolds by generating a nanostructured surface with a multitude of nano-to-micro pore size (<10 μm), resulting in a substantial improvement in the biomineralization and functionality of the BCP scaffolds.

The use of polymer-based coatings is also promising for 3D porous HA/TCP scaffolds. Miao et al. [175] coated a 3D porous HA/TCP scaffold with PLGA and observed a considerable increase in mechanical strength. The strength and modulus were altered from 0.06 MPa and 2.58 MPa for the bare scaffold to 0.66 MPa and 16.85 MPa for the coated scaffold, respectively. This behavior was attributed to the infiltration of open micropores or/and cracks in the walls of the scaffolds.

Roohani et al. [60] evaluated the influence of a nanocomposite PCL-HA coating on the behaviors of HA/β-TCP scaffolds. The strength reached 2.1 MPa after coating, twenty-one times higher than the strength of the uncoated BCP scaffold. This implies the remarkable reinforcing effect of the nanocomposite coating layer with great interfacial bonding between PCL and HA, which withstood the deformation. An excellent induction of ALP activity and osteogenic gene expression was also observed for the coated scaffold.

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It has been pointed out that HA/β-TCP 3D-printed scaffolds after collagen coating demonstrate an excellent osteogenic efficiency and enhance cell attachment with the help of the collagen coating [109]. Collagen is one of the constituents of bone tissues and contains ECM molecules like fibronectin and integrin, which boosts cell attachment. In this study, buccal fat pad stem cells (BFPSCs) and human-induced pluripotent stem cells (hiPSCs) were chosen to investigate the osteogenic ability of the scaffolds manufactured by 3D printing, where 3D scaffolds seeded with hiPSCs and BFPSCs exhibited well-spread and attached cells. The shape of hiPSCs changed to a rounded shape similar to osteoblasts and osteocytes, whereas BFPSCs turned to a thickened and extended cell layer shape, implying the faster differentiation process by hiPSCs and the generation of a cell-scaffold construct. Eventually, coating is recognized as the most effective approach to alter the biological and biomechanical properties of HA/TCP scaffolds by manipulating the surface of the scaffolds.

7. Conclusion and future prospects

3D porous HA/TCP composite scaffolds are worthy alternatives to monophasic CaPs, but special considerations are required to achieve their maximum biocapacity. Among different scaffolding techniques, 3D printing is the most proper choice for their fabrication due to its remarkable capability in developing scaffolds with complex geometries and sophisticated pore structures. Among 3D printing techniques, the direct-ink writing method demonstrates excellent capabilities to manufacture 3D scaffolds with a magnificent resolution and pore structures to be employed as a delivery system for therapeutic genes and drugs. 3D porous HA/TCP composite scaffolds exhibit an adjustable biodegradation rate by the HA/TCP ratio at an inverse relation, which is promising for designing patient-specific scaffolds. However, the HA/TCP ratio plays a dual role in the biomechanical behavior of these scaffolds. On the one

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hand, an unsuitable HA/TCP ratio can cause crack formation and propagation during sintering. On the other hand, an apt HA/TCP ratio can generate a reinforcement effect in these composite scaffolds. Furthermore, this ratio plays a critical role in osteogenic ability through affecting the bioresorbability and bioactivity of HA/TCP composite scaffolds. Therefore, precise control over the HA/TCP ratio is required for an acceptable bioperformance. Indeed, the optimum ratio depends on many factors like the dimension and location of the bone defect as well as the personal traits of the patient body. It should be noted that the performance of HA/TCP scaffolds can be improved by some modification methods like polymeric additives, doping and coating. Among them, coating is the most effective approach to alter the biological and biomechanical properties of HA/TCP scaffolds.

The development of scaffolds with different properties in their interior and exterior frameworks by 3D printing techniques, trying to mimic the bone structure, seems to be a novel way to regenerate bone. In addition, the rapid production and development of patient-specific 3D porous HA/TCP scaffolds with the help of the 3D printing technology can tackle problems like the unmatched biodegradation rate of scaffolds with bone growth rate. Other areas that need further investigations are loading of drugs and other biological agents after scaffolding or in the coating process.

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