Ceramics International 44 (2018) 1–9

Contents lists available at ScienceDirect

Ceramics International

journal homepage: www.elsevier.com/locate/ceramint

Review article

The cross-disciplinary emergence of 3D printed bioceramic scaffolds in orthopedic bioengineering

Hossein E. Jazayeri[a,b], Martin Rodriguez-Romero[a], Mehdi Razavi[c], Mohammadreza Tahriri[a], Karan Ganjawalla[d,e], Morteza Rasoulianboroujeni[a], Mohammad H. Malekoshoaraie[f], Kimia Khoshroo[a], Lobat Tayebi[a,*]

[a] Marquette University School of Dentistry, Milwaukee, WI 53233, USA
[b] School of Dental Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA
[c] Department of Radiology, School of Medicine, Stanford University, Palo Alto, CA 94304, USA
[d] Harvard Medical School, Boston, MA 02115, USA
[e] Harvard School of Dental Medicine, Boston, MA 02115, USA
[f] Harvard-MIT Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge, MA 02139, USA

ARTICLE INFO

Keywords:
Bioceramics
3D printing
Scaffolds
Orthopedic
Tissue engineering

ABSTRACT

Over the past several decades, the implementation of bioceramics in orthopedic bioengineering has become increasingly profound. The resemblance of the material to bone histomorphology makes them favorable to use in tissue engineering schemes, in addition to the evidence that they exhibit osteoconductivity and that many manifest the appropriate mechanical strength. Moreover, the strategy to use the 3D bioprinting technique holds the potential to consistently manufacture commercializable scaffolds, tailored for diverse clinical applications with physicochemical property-dependent biodegradation rates, and usher in a new era of effective hard tissue fabrication. This review is the first of its kind in that it has thoroughly compiled the most recent studies on 3D printing of bioceramic scaffolds to treat bone defects and anomalies. Manuscripts were mostly chosen from the last decade, highlighting the novelty of the approach to regenerative orthopedic bioengineering via ceramic-based 3DP technologies. Likewise, in addition to the materials perspective present in the body of this work, tissue engineering scaffold requirements were explained as well as the incorporation of drug delivery schemes for localized drug administration and cargo release rates in pre-clinical studies.

1. Introduction

Three-dimensional printing (3DP) of materials, a method of rapid prototyping technology, has demonstrated outstanding potential over the last decade in scaffold design and production for tissue engineering applications. The earliest method can be accredited to Sachs et al. and their development of early ink-jet freeform printing toward the end of the 20th century [1], and although other types of 3DP have since then emerged, the ink-jet variant demonstrates the highest use. The promise in tailoring the ideal scaffolds by 3DP lies in its user-friendly capabilities which allow for the conversion of CAD data to a rapid and consistent production line of constructs with the desired material, porosity, and dimensions [2,3]. Previously unachievable through time- and cost-efficient means, the method gives rise to defined, interconnected structures that are case-specific for targeted hard tissue defect regeneration. Already, the first clinical trials and case studies demonstrate its resonating success in orthopedic bioengineering. While this process exhibits considerable potential, certain challenges must be addressed in the optimization of patient-specific scaffolds for mainstream acceptance in regenerative medicine. Both the simulation of hard tissue mechanical stiffness and the resolution of printing parameters require further work before regulatory approval by the FDA can be considered [4,5].

Ceramics, in particular, are biomimetic materials with a highly suitable mechanical strength for bone repair [6]. They have been used as bone substitutes due to their mineral resemblance to cortical bone, their biocompatibility and osteoconductivity [7]. The controllable and customizable 3DP application using ceramics has been employed with positive results in regard to optimal mechanical properties and *in vitro* and *in vivo* osteogenic capability [8]. While their popularity as a bone filler for critical orthopedic defects is known to the collective community of bioengineers, material scientists, and clinicians adopting these

* Corresponding author.
E-mail address: lobat.tayebi@marquette.edu (L. Tayebi).

http://dx.doi.org/10.1016/j.ceramint.2017.09.095
Received 21 August 2017; Received in revised form 12 September 2017; Accepted 13 September 2017
Available online 14 September 2017
0272-8842/

new methods, the development of 3-D printing for ceramic scaffold fabrication is a novel concept that has recently been drawing attention [9].

The clinical relevance of this 3DP ceramic scaffold design and implantation encompasses an advantageous technique for rapidly and consistently manufacturing a hard tissue replacement that perfectly resembles the biological framework of natural bone [10]. Because of the fact that patient data can be used in a single step to fabricate the ideal scaffold that fits an individual patient skeletal defect, layer-by-layer sintering serves as a potentially booming discipline for the use of ceramic-based bone substitutes in regenerative medicine [11]. Moreover, using 3DP ceramic scaffolds as drug delivery systems is becoming more widespread as it is pertinent to the field of bioengineering [12].

2. Current Bone Reconstruction

Bony defects typically result from malformations, traumatic injuries, and tumor resections. Biomaterials for reconstruction of bony defects are comprised primarily of osteosynthetic materials, which are placed after osteotomies or traumatic injuries. Other applications involve dental implants for functional augmentations or aesthetic augmentations in the facial region.

The outcomes in bone reconstruction are believed to be dependent on surgical skills, adjacent soft tissue quality, size and location of the bone defect and repair method. Current methods of reconstruction include free and vascularized bone grafts, the use of biomaterials and, more recently, the use of growth factors to induce osteoinduction. The implementation of autologous bone for orthopedic reconstruction may be restricted due to limited amounts of donor bone from harvest sites. Harvested bone may also need to be remodeled into more custom shapes, which may complicate surgery. Furthermore, complications associated with free bone grafts include resorption of the graft and increased mortality associated with the harvest site.

The benefits of alloplastic materials have previously been reported in the literature and have been used alone or in combination with bone transplants or osteoinductive cytokines. The procedure can be used to not only replace missing bone but to also stimulate osteoinduction by acting as a scaffold for bone regrowth. Ideally, implanted materials should be biocompatible with little or no side effects or toxicities. Complications and toxicities of implantable biomaterials used in orthopedic surgery have been previously reported, often resulting in inflammation associated with leukocytosis and fibrosis.

For ostheosynthesis, plates derived from titanium alloys provide major advantages in terms of biocompatibility, stability and individual fitting to the implant bed. The removal of asymptomatic plates and screws after fracture healing is still controversial. However, the risks and costs of secondary surgery for removal face a low rate of complications when the material remains *in situ*. Resorbable osteosynthesis systems have similar mechanical stability and are especially useful in pediatric cases that still encompass orthopedic development.

The huge variety of biomaterials for the reconstruction of bony defects makes it difficult to decide which material is adequate for specific indications and surgical sites. An optimal biomaterial meets every requirement (e.g. biocompatibility, stability, intraoperative fitting, product safety, low costs) but a perfect material meeting all of these criteria does not yet exist. Future developments aim to improve physical and biological properties, especially regarding surface interactions. To date, the progress of tissue engineering applications as they relate to bone regrowth is coming to fruition as many studies are successfully demonstrating the necessary parameters for healing, but until widespread FDA approval and normalization, this highly innovative technique remains in the backseat to traditional orthopedic reconstructive surgery. As such, the use of alternative alloplastic materials provides a viable current option for reconstructive surgery to treat hard tissue injuries and defects.

3. Tissue engineering scaffold requirements

3.1. Porosity

Because trabecular and cortical bone morphology encompasses pore-like structures that support nutrient movement and blood flow, the ideal scaffold must be fabricated with a certain degree of porosity and interconnectivity to similarly allow for the passage of nutrients, osteogenic cells and bioactive molecules that will collectively facilitate mineralization and promote vascularization throughout the structure [13,14]. Studies that involved porous coating of titanium implants also supported both an increase in cortical shear strength and osteogenesis, in addition to direct comparisons between bone ingrowth within porous scaffolds and the lack thereof on solid particles, demonstrate the utter significance of pores in scaffold development [14,15]. Although an ample amount of literature exists on the matter of pore specifications and its role in affecting important factors in regeneration, such as mechanical properties, degradation, and osteogenesis, it is indeed worth mentioning as a requirement for an effective tissue engineering scaffold, especially since it is one of the main advantages in the 3DP approach for scaffold fabrication.

3.2. Biocompatibility

The integration of ceramic scaffolds into natural bone to enhance the tissue repair process is required for tissue engineering processes. Bonding osteogenesis from calcium phosphate ceramics (CPC), for example, results from the mechanistic release of calcium and phosphate ions and their subsequent coupling [16]. Williams defines the term of biocompatibility as the capability of a material to facilitate natural cellular and molecular activity within a scaffold in the absence of systemic toxicity [17]. Biocompatibility also encompasses osteoconductivity, the promotion of osteoblast adhesion and proliferation, and osteoinductivity, which signifies biomolecular signaling and osteoprogenitor recruitment. Lastly, the ideal biocompatible scaffold supports blood vessel formation within and around its site of implantation [18].

3.3. Biodegradability

A controlled rate of biodegradation over time at the *in vivo* stage while tissue regeneration occurs is essential in proving scaffold suitability for advancement to clinical trials. The biodegradability of a scaffold depends on its material type and application [18]. Bose et al. state that craniomaxillofacial bone scaffolds may demonstrate a bioresorbability rate of 3–6 months while ceramics, in general, exhibit a notably high toughness value and Young's Modulus, which is indicated by a material wear rate of 0.003 mm/year [19,20]. Porous tricalcium phosphate (TCP)-based ceramics display a rate of bioresorption that is similar to neoformation of bone, while other ceramics, such as hydroxyapatite, can potentially be longer-lasting; therefore, different methods of manufacturing and composite ratios need to be measured/employed to yield an optimal biodegradation rate [21,22].

3.4. Mechanical properties

Fabricating a scaffold with mechanical properties consistent with those of the natural environment of bone is essential for clinical success. The stiffness of the scaffold must be such that *in vivo* bone ingrowth proceeds until the newly formed tissue has enough structural integrity to physically support itself [23]. As mentioned, because of the high Young's Modulus of ceramics, in general, they are able to endure a great amount of compression force. Furthermore, because of the fact that 3DP provides users maximal control over macropore size, patient-specific scaffold morphology, and volume consistency in reproduction, the mechanical properties of the ceramic scaffold can be optimized at

Table 1
The main factions of technology and respective processes for bioprinting.

Technology	Process	Post process	Ref.
Stereolithography (SLA)	Layer by layer polymerization of a paste made of photosensitive resin and ceramic by UV/Laser light.	Heat treatment to eliminate the resin and densify the ceramic	[26]
Fused deposition modeling (FDM)	Layer by layer plotting of a paste made of ceramic and binder	Heat treatment to eliminate the binder and densify the ceramic	[27]
Selective Laser Sintering (SLS)	Layer by layer sintering of ceramic particles in a powder bed by laser	Air blasting to remove excess particles	[28]
Laminated object manufacturing (LOM)	Layer by layer fusion of laminates cut to shape with a computer controlled laser using heat and pressure	Machining and drilling	[29]

improved rates, relative to non-3DP methods. As important, due to the developing knowledge of biomaterial composites, the ultimate yield strength and other significant properties of the constructs are improving via the presence of added fillers for optimal tissue repair [24,25]. The most popular technology and processes of printing are shown in the Table 1.

4. Ceramic materials in scaffold fabrication

4.1. Calcium phosphate ceramics

4.1.1. Hydroxyapatite

Within the natural composition of human bone is an inorganic solid, namely carbonate hydroxyapatite (HA), which comprises approximately 65% of total bone mass [30]. Carbonate HA crystals are known to expand along intercellular collagen I networks and contribute to bone ingrowth and osteolysis prevention [31]. For these reasons, HA scaffolds have a history in bone tissue engineering, dental implants, and orthopedic arthroplasties [32–40]. Among the most notable advantages of HA scaffolds are their excellent hard tissue integration capability, innate microporosity for capillary ingrowth, resorption rate, and most recently noted, induction of stem cell differentiation [41]. Moreover, the c-axis oriented crystal growth/degradation is attributed to its unique lattice parameter (a = 0.95 c = 0.68 nm) and hexagonal symmetry. This knowledge then led to the manipulation of scaffold biodegradation rates via alteration of Ca:P molar ratios, where the ratio of stoichiometric HA ($Ca_{10}(PO4)_6(OH)_2$) at 1.67 is the reference point. With low temperature 3DP, the B type HA is commonly synthesized, with carbonates bonded to the PO_4^{3-} sublattice, and is indeed the type found in human bone. As important to degradation control, researchers addressed osteoconduction and *in vivo* interface with osseous tissue through HA composites. Recently, Cox et al. designed a systemic 3DP method for user-specified macropore interconnectivity in HA-polyvinyl alcohol (PVOH) scaffolds [42]. Bulk interconnection (designed at 500 μm macropore sizes) and rough surfacing (microporosity due to HA:PVOH mix) were important factors for osteoconduction since these facilitate scaffold integration *in vivo*, consequent osteocyte migration and vascularization. Although HA composites have diversified, HA remains as the major biomaterial. These include HA-chitosan [43], HA-fibronectin [44], HA-Polycaprolactone [45], and HA-collagen [46,47] constructs for enhanced mechanical strength, osteoinduction, vascularization, and local chondrogenic differentiation. Most notable is the impending clinical implementation of one HA variant. After *in vitro* and *in vivo* trials, Fu et al. led a clinical trial of a coralline HA scaffold implementation in 16 patients who had undergone surgical tumorigenic osseous tissue removal. After only 4 months, astounding results of successful bone regeneration in 15 patients was observed [48]. With such holistic progress, it is rather facile to recognize the approaching clinical translatability of these ceramic variants. As mentioned, 3D printing allows fabricating scaffolds with complex internal structures and high resolution towards patient-specific design. Fig. 1a demonstrates a 3D printed HA scaffold with an internal channel network and Fig. 1b exhibits the granule structures which have remained after sintering [10]. Leukers et al. produced HA scaffolds by 3D printing and seeding MC3T3-E1 cells on the scaffolds. The cells proliferated deep into the structure, forming intercellular contact with HA granules [10]. Preserving cell viability, however, remains to be optimized and will be largely dependent on culture methods, whether static or dynamic, and media content which simulates body fluids.

4.1.2. β-tricalcium phosphate

For over two decades, beta tri-calcium phosphate (β-TCP) scaffolds have earned clinical acceptance as bone graft substitutes in many orthopedic applications [49–55]. Similar to biologic bone mineral precursors, synthesized β-TCP constructs exhibit a Ca:P molar ratio of 1.5 which contributes to its favorable bioresorption rate in comparison to HA variants. Its innate microporosity, due to its stoichiometry, is well known to enhance osteoconductivity [56] in human patients, post-implantation. As is important in all calcium phosphate ceramics, macroporosity manipulation must be balanced to accommodate the need for homogenous bone ingrowth without jeopardizing mechanical strength. Until recent advances in direct 3DP, mechanical strength of these ceramics remained suboptimal once implanted [57]. Tarafder et al. significantly improved maximum compressive strengths to 10.95 ± 1.28 MPa in stereolithographic 3DP TCPs via a 27% porosity coaxial design and subsequent microwave sintering [2]. In later studies, this lab group then used MgO and SrO doping for improved compressive strength, osteogenesis, and mineralization [58] as well as Alendronate seeding for early bone formation in femoral defect models [59]. With microresolution in 3DP as a limiting factor for robust commercialization of TCPs, researchers set to output solutions. Butscher et al. were able to halve the minimum layer thickness from 88 μm to 44 μm and output a surface roughness value of 25 μm via custom moisture application device and de-powdering methods [60,61]. To compare quickened bone formation, Carrel et al. investigated OsteoFlux, Bio-Oss, and Ceros, each of which is a commercially available ceramic. The group was able to demonstrate that 22% + − 2.1 new bone formed in calvaria of sheep only 8 weeks after 3DP TCP-HA blocks (OsteoFlux) were implanted [62], and a fourfold increase in bone formation 3 mm away from site of implantation was noted, when compared to the other ceramics. These observations suggest increased osteoconductivity due to combinations of HA and TCP, which are synonymous with natural bone environments. Research groups have also improved 3DP TCP scaffold fabrication method and purity through the introduction of inorganic binder solutions. Vorndran et al. [63] showed, for the first time, the manufacture of phase pure β-TCP monoliths of defined macroporosity at high resolution by a cement setting reaction through 3D powder printing. As demonstrated in Fig. 2, the samples are obtained comparing three different production regimes, either by (A) using hydroxypropylmethylcellulose modified tricalcium phosphate (TCP, Ca/P = 1.5) powder with water as a binder, (B) by using phosphoric acid as binder with a calcium phosphate powder of a Ca/P ratio of 1.7 and different binder/volume ratios or (C) by printing a tetracalcium phosphate (Ca/P = 2.0)/dicalcium phosphate (Ca/P = 1.0)/tricalcium phosphate powder mixture with citric acid. The production process has been followed by a heat treatment process for all variations to produce phase pure β-TCP (Ca/P = 1.5). In contrast to commonly used polymeric binder systems, printing with phosphoric acid possesses three

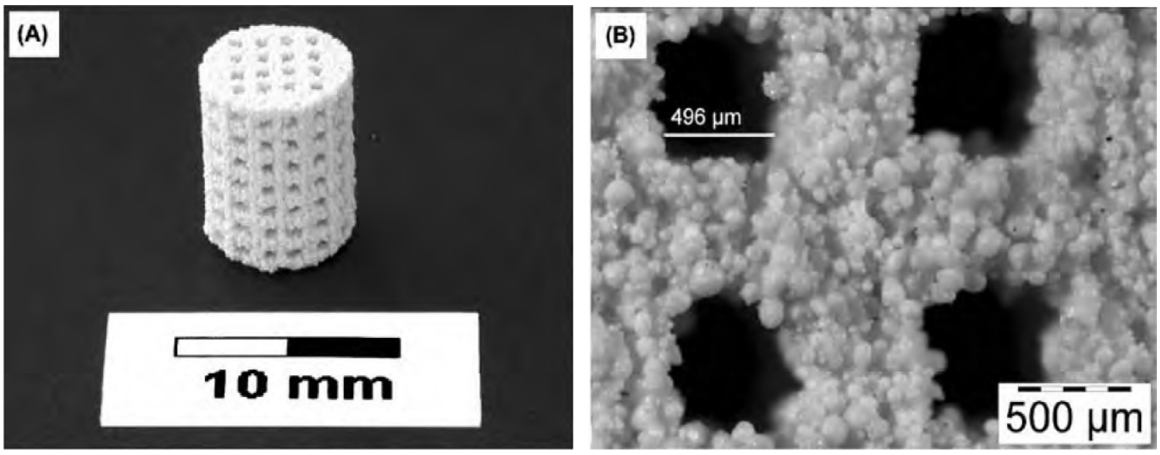

Fig. 1. 3D printed HA scaffold with interconnecting channels. (a) Whole structure, (b) detailed view of the interconnecting channel structure with diameter of about 500 µm [10].

main benefits. First, a higher printing resolution is enabled, thereby improving bone graft design quality. Secondly, a higher mechanical performance is achieved, expanding applications to high-compression bone types. Thirdly, a much faster setting reaction yields the capacity for samples to be removed immediately after printing from the powder bed, strongly reducing the fabrication time in commercialization [63].

4.2. Calcium Phosphate Cements (CPCs)

Calcium Phosphate Cements (CPCs) have been implemented over the last several decades within *in vitro* and *in vivo* studies to show their promise in future clinical orthopedic treatments, including the repair of fractures and defects [64–69]. Although their applications in the three-dimensional printing of scaffolds are still not as widespread as the previous materials mentioned, their advantage in rapid hardening following implantation poises CPCs as early candidates for further scientific investigation in clinical use [70]. In addition to quickened hardening, they are known to exhibit excellent biocompatibility and bioactivity properties despite their limitation in resorption rate control [71]. The low temperature setting characteristic of CPCs enhances their usefulness in orthopedic bioengineering to an even greater degree by serving as an optimal platform for drug loading and delivery [72].

As mentioned in the section pertaining to 3-D scaffold fabrication requirements, this method of innovation ensures reproducibility and provides the user with maximum control over scaffold architecture. Regarding this ceramic variant, 3DP improves CPC *in situ* hardening as a result of the contact between the modified cement liquid and solid phases [73,74]. Gbureck et al. conducted work on 3DP scaffolds composed of CPC and improved the hardening capability of the scaffold by immersing it in dilute phosphoric acid [75]. In another work, he demonstrated the potential of CPCs in supporting bioactive agents by specifically printing bioceramic implants that included angiogenic factors for enhanced tissue healing [76].

4.3. Bioactive glass (BG) and glass-ceramics

The fabrication of scaffolds composed of bioactive glass (BG) and glass-based ceramics has slowly emerged and evolved from prior studies conducted on composite scaffolds containing concentrations of BG [77,78]. More recently, studies have demonstrated that 3DP mesoporous BG (MBG) scaffolds may be candidates for improving bone regeneration due to their demonstrated pro-angiogenic signal induction characterized by the induction of VEGF secretion in multiple cell types [79]. Limiting is that BG scaffolds are inherently brittle and lack the mechanical strength needed to facilitate adequate bone regeneration. Therefore, it has traditionally been more frequent for engineers and materials scientists to combine bioactive glass with another material, such as a polymer, ceramic, or metal, to enhance its properties, both mechanical and biological [79–83]. Noteworthy, Korpela et al. remarks the osteoconductive properties of BG as well as its proven ability to promote recovery following bone trauma and scaffold implantation [84,85]. Typical BG parts fabricated by the present lithography based Additive Manufacturing Technologies are demonstrated in Fig. 3 including a microscopy image of the cylindrical cellular structure (a) and

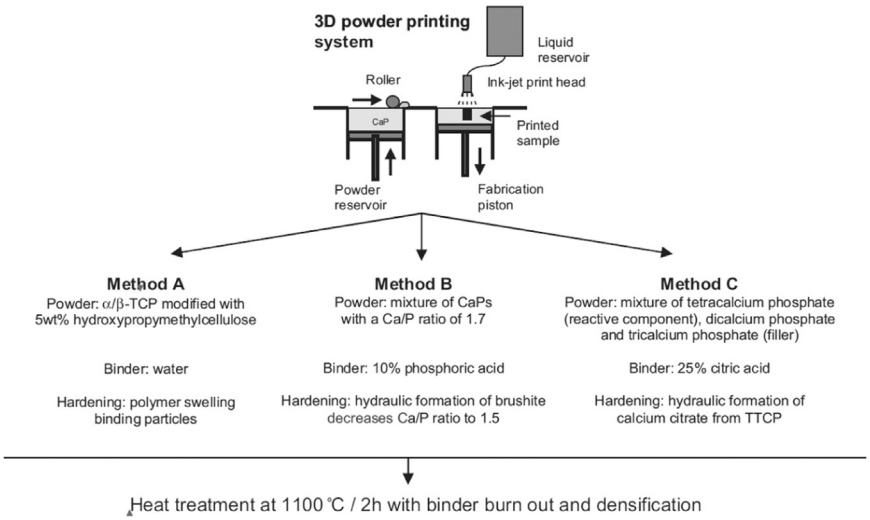

Fig. 2. Schematic illustration of the different preparation regimes for the fabrication of β-TCP by 3D printing [63].

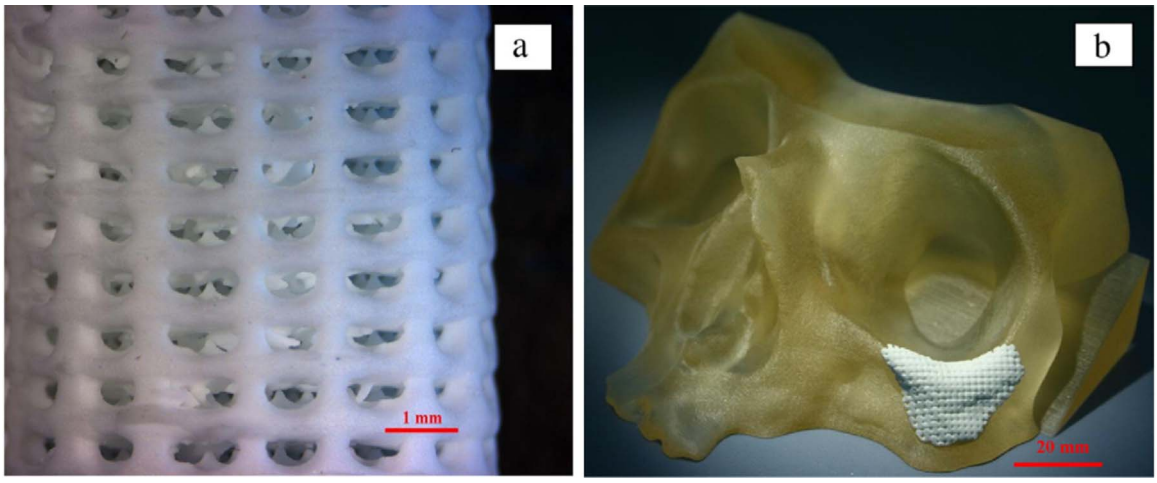

Fig. 3. BG parts fabricated by lithography based additive manufacturing technologies after sintering: (a) cylindrical cellular structure (scaffold) and (b) customized bone implant [86].

the customized BG component for an orthopedic implant in the zygomatic arch (b) [86].

As important, 3DP MBG scaffolds have an excellent apatite mineralization ability and sustained drug delivery properties upon adequate manipulation. Their high mechanical strength, about 200 times that of traditional polyurethane foam templated-MBG scaffolds, demonstrates their clinical translatability potential in high compressive strength applications [87].

Similarly, glass-ceramic scaffolds open new avenues for treatment of load-bearing bone defects in orthopedic, dental and maxillofacial applications. In a recognized study, Roohani-Esfahani et al. [87] produced bioactive glass-ceramic scaffolds called Sr-HT Gahnite with distinctive pore geometries such as rectangular, hexagonal, curved or zigzag at a range of porosities by a direct ink-writing technique (Fig. 4). Scaffolds with hexagonal structure presented a high fatigue resistance (1,000,000 cycles at 1–10 MPa compressive cyclic load), failure reliability and flexural strength (30 MPa). The obtained strength is 150 times greater than values reported for polymeric and composite scaffolds and 5 times greater than reported values for ceramic and glass scaffolds at similar porosity [87].

5. Drug delivery applications

3DP bioceramics are promising drug delivery systems (DDS) due to their rapid, patient-oriented scaffold fabrication for hard tissue replacement/restoration via delivery of relevant therapeutic agents. Most appealing are their adjustable physicochemical parameters, including mesoporosity, cargo release rate via material composition, and combinatorial cargo embedment. Considerably advantageous of this DDS category is the localized administration of biologics, whether growth factors or antitumorigenic recombinants, to diseased tissues via sustained release with minimal immunogenic/cytotoxic response and complete resorption of the delivery vehicle itself. Hence, their therapeutic potential is vast for various osseous tissue regeneration applications, including craniofacial reconstruction, dental hard tissue engineering, post-surgery spinal fusion and osteoporotic fracture remediation/prevention [88–91]. This section discusses the latest approaches to control and sustain release of bioceramic-based drug delivery systems.

Growth hormone (GH) delivery was an early approach to bone regeneration and Guicheux et al. [92] were pioneers in showing that loading a porous biphasic calcium phosphate (BCP) ceramic with only 5 μg of GH yielded a sustained 11 day-release for significant bone formation. Since then, a diverse range of osteocompatible and osteoadhesive materials have been studied including silica-based glasses, chitosan-based tricalcium phosphates, and dynamically-compressed hydroxyapatites [93–95] with respect to their own drug release advantages. Recently, Meininger et al. [96] showed the efficient incorporation of strontium ions unto a magnesium phosphate cement using 3D powder printing. In the study, antiosteoporotic traits, and osteoinductive benefits were highlighted, including the sustained release of Sr^{2+} at 0.02 mg/g per day for enhanced bone formation and resistance to osteoporosis via diminished osteoclast activity. However, a moderate scaffold compressive strength of 40 MPa indicates there is still improvement needed in the development of physiologically-relevant force tolerating phosphate cements.

In retrospection, previous approaches to ceramic fabrication resorted to excessive thermal treatment and often led to drug bioactivity loss. Additionally, using the sol-gel method and supramolecular templating limited controlled mesoporosity [97–100]. In contrast, the diversity of 3DP scaffold-based drug delivery, which includes stereolithography-, deposition-, inkjet-, and selective laser sintering-based drug delivery, has markedly overcome these challenges [101]. The combination of printed macro-pores and intrinsic micro-pores, for example, has paved the way for multi-purpose implantations, including antitumorigenic-osteogenic therapy. With an emphasis on differentiating endogenous bone marrow stromal cells (BMSC) and terminating the typical implant-induced residual osteosarcoma cells (MG-63), Zhang et al. incorporated iron (II, III) oxide nanoparticles unto 3DP beta-tricalcium phosphate (βTCP) scaffolds for bone defect regeneration [102]. Showcasing triangular pore morphology at 300–500 μm per unit and graphene oxide layers enveloping the Fe nanoparticles, the DDS significantly upregulated osteogenic gene expression, BMSC proliferation *in vitro* and caused hyperthermia-based MG-63 targeted cell death in the animal models. Such use of inorganic factors, including copper ions and pore interconnectivity for angiogenesis induction [103,104], are of interest due to their higher stability and lower cost and safety concern relative to transgenic delivery methods.

Of high impact was the Habibovic group study [73] demonstrating ectopic spinal osteoinduction for the first time in an intramuscular implantation of 3D printed brushite and monetite cements. The group showed that paraspinal muscle insertion of dicalcium phosphate dehydrate (DCPD) and dicalcium phosphate anhydrous (DCPA) cements, known for preferred microporosity texture and specific surface areas, yielded significant *in vivo* bone formation along the designed 6-pore channels through the 12-week animal lumbar study. Such was achieved through CAD customization and low-temperature 3DP, important factors for expanding drug delivery applications including anti-inflammatory, antibiotic, and antitumorigenic purposes. For example, Inzana et al. recently showed significantly reduced osteomyelitis occurrences in the context of bone substitute implantation-associated infections by way of vancomycin- and rifampin-laden 3DP tricalcium

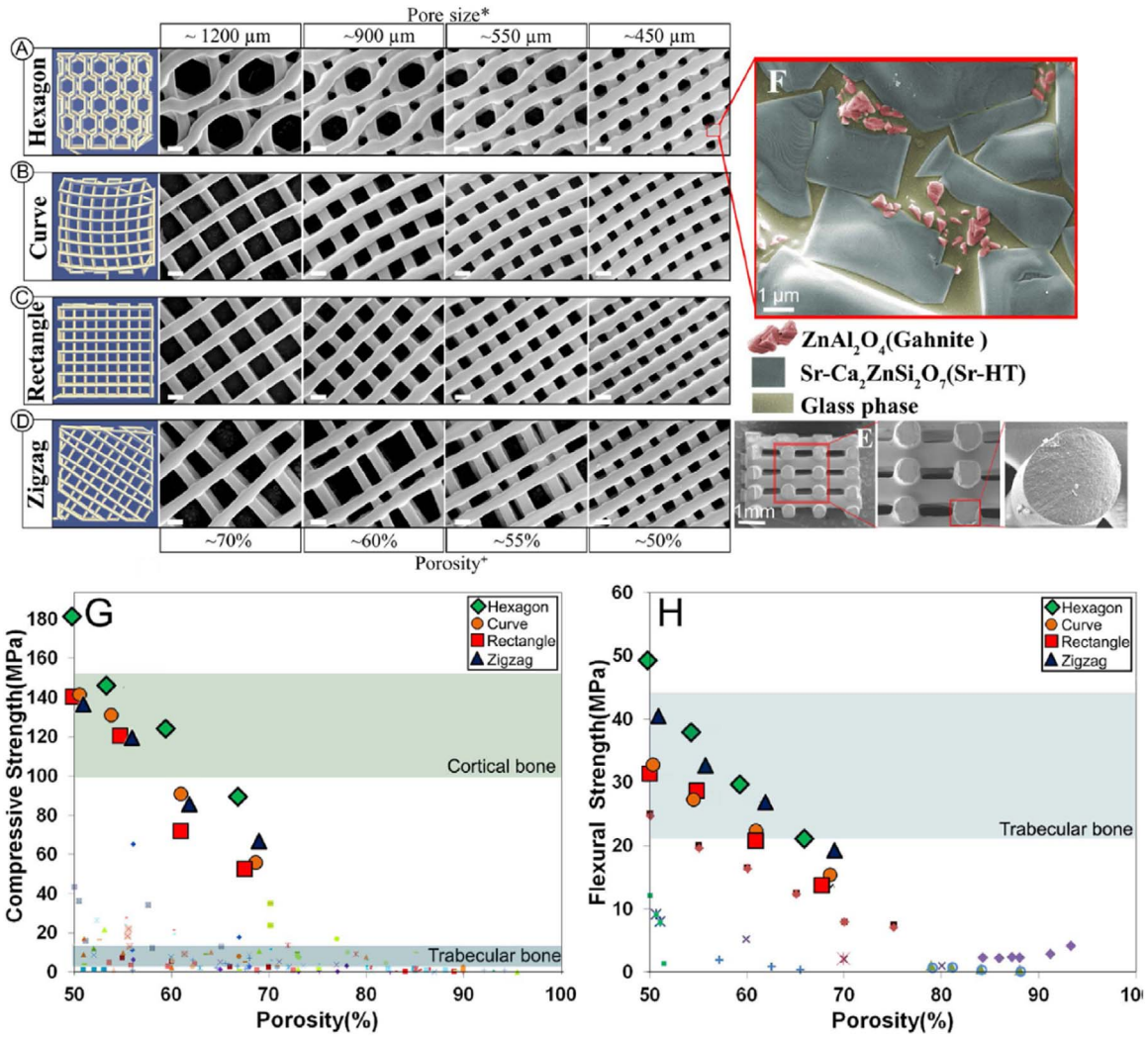

Fig. 4. Computer aided design models (left column) and SEM images of examined scaffolds (scale bars: 500 µm unless stated otherwise). (a) Hexagonal, (b) curved, (c) rectangular and (d) zigzag design, (e) SEM images of fracture surface of a Sr-HT-Gahnite scaffold prepared by direct ink writing, (f) the microstructure of Sr-HT-Gahnite scaffolds, (g) compressive strength of Sr-HT-Gahnite scaffolds with distinct pore geometries vs porosity, and (h) flexural strength of Sr-HT-Gahnite scaffolds with hydroxyapatite and bioactive glass scaffolds [87].

phosphate scaffolds [105].

Considering the future of hard tissue engineering in clinical applications, market costs continue to decrease as DDS become more technologically efficient and resourcefulness of biomaterial usage increases. As discussed, 3D-printed bioceramics have risen as highly promising DDS due to direct/localized drug administration, controllable drug release rates, and non-immunogenic hard tissue regeneration potential, all of which are tunable and patient-design oriented. With such mass production capable foundations, drug delivery enhancements to 3DP bioceramic scaffolds continue to advance rapidly, where theranostic nanoparticles withholding cell targeting, imaging, and stealth properties [106–108] may soon be escorted by these 3DP drug delivery platforms (Fig. 5).

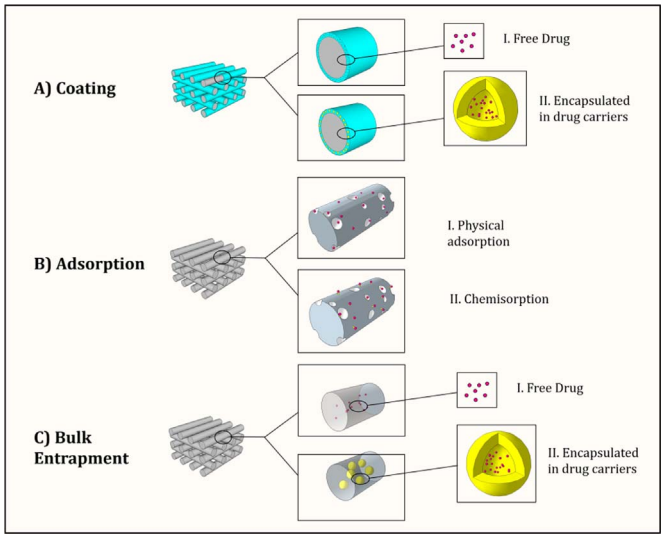

Fig. 5. Schematic of drug delivery system (DDS) synthesis.

6. Conclusions

The combination of advancements in both materials science and bioengineering technology has paved the way for a new generation of therapeutics in clinical regenerative medicine. Most of the information in this review has been gathered from literature spanning only the last decade or so, demonstrating not only the novelty of the idea stressed throughout the article but also the promise shown by *in vitro* and *in vivo* studies that have been producing beneficial ends. Bioceramics have been used in regenerative medicine for their exemplary resemblance to bone tissue in addition to the aforementioned biological and mechanical properties. The recent strides made in the 3DP technique to

efficiently design and manufacture the bioceramic scaffolds, in addition to diversifying its platform by loading the constructs with drugs and growth factors to enhance the regenerative effect, provides tremendous value to both researchers and clinicians alike. It is clear that composite scaffolds will continue to diversify as synthesized by the 3DP strategy with a wide array of therapeutic drugs and bioactive agents. This will only advance orthopedic tissue engineering, and related fields, towards the realization of healing ailment through personalized, patient-tailored medicine.

Acknowledgements

The authors would like to thank Farahnaz Fahimipour and Erfan Dashtimoghadam for their support.

References

[1] E. Sachs, M. Cima, P. Williams, D. Brancazio, J. Cornie, 3-Dimensional printing – rapid tooling and prototypes directly from a Cad model, J. Eng. Ind.-Trans. ASME 114 (4) (1992) 481–488.
[2] S. Tarafder, V.K. Balla, N.M. Davies, A. Bandyopadhyay, S. Bose, Microwave-sintered 3D printed tricalcium phosphate scaffolds for bone tissue engineering, J. Tissue Eng. Regen. Med. 7 (8) (2013) 631–641.
[3] M. Yazdimamaghani, M. Razavi, D. Vashaee, L. Tayebi, Development and degradation behavior of magnesium scaffolds coated with polycaprolactone for bone tissue engineering, Mater. Lett. 132 (2014) 106–110.
[4] A. Khalyfa, S. Vogt, J. Weisser, G. Grimm, A. Rechtenbach, W. Meyer, M. Schnabelrauch, Development of a new calcium phosphate powder-binder system for the 3D printing of patient specific implants, J. Mater. Sci. Mater. Med. 18 (5) (2007) 909–916.
[5] B. Derby, Printing and prototyping of tissues and scaffolds, Science 338 (6109) (2012) 921–926.
[6] J.R. Jones, L.L. Hench, Regeneration of trabecular bone using porous ceramics, Curr. Opin. Solid State Mater. Sci. 7 (4–5) (2003) 301–307.
[7] M. Schieker, H. Seitz, I. Drosse, S. Seitz, W. Mutschler, Biomaterials as scaffold for bone tissue engineering, Eur. J. Trauma 32 (2) (2006) 114–124.
[8] C. Wu, W. Fan, Y. Zhou, Y. Luo, M. Gelinsky, J. Chang, Y. Xiao, 3D-printing of highly uniform CaSiO 3 ceramic scaffolds: preparation, characterization and in vivo osteogenesis, J. Mater. Chem. 22 (24) (2012) 12288–12295.
[9] C. Wilson, J. De Bruijn, C. Van Blitterswijk, A. Verbout, W. Dhert, Design and fabrication of standardized hydroxyapatite scaffolds with a defined macro--architecture by rapid prototyping for bone-tissue-engineering research, J. Biomed. Mater. Res. Part A 68 (1) (2004) 123–132.
[10] B. Leukers, H. Gülkan, S.H. Irsen, S. Milz, C. Tille, M. Schieker, H. Seitz, Hydroxyapatite scaffolds for bone tissue engineering made by 3D printing, J. Mater. Sci.: Mater. Med. 16 (12) (2005) 1121–1124.
[11] P.H. Warnke, H. Seitz, F. Warnke, S.T. Becker, S. Sivananthan, E. Sherry, Q. Liu, J. Wiltfang, T. Douglas, Ceramic scaffolds produced by computer-assisted 3D printing and sintering: characterization and biocompatibility investigations, J. Biomed. Mater. Res. Part B: Appl. Biomater. 93 (1) (2010) 212–217.
[12] U. Gbureck, E. Vorndran, F.A. Müller, J.E. Barralet, Low temperature direct 3D printed bioceramics and biocomposites as drug release matrices, J. Control. Release 122 (2) (2007) 173–180.
[13] V. Karageorgiou, D. Kaplan, Porosity of 3D biomaterial scaffolds and osteogenesis, Biomaterials 26 (27) (2005) 5474–5491.
[14] Y. Kuboki, H. Takita, D. Kobayashi, E. Tsuruga, M. Inoue, M. Murata, N. Nagai, Y. Dohi, H. Ohgushi, BMP-induced osteogenesis on the surface of hydroxyapatite with geometrically feasible and nonfeasible structures: topology of osteogenesis, J. Biomed. Mater. Res. 39 (2) (1998) 190–199.
[15] M. Svehla, P. Morberg, B. Zicat, W. Bruce, D. Sonnabend, W.R. Walsh, Morphometric and mechanical evaluation of titanium implant integration: comparison of five surface structures, J. Biomed. Mater. Res. 51 (1) (2000) 15–22.
[16] P. Lichte, H. Pape, T. Pufe, P. Kobbe, H. Fischer, Scaffolds for bone healing: concepts, materials and evidence, Injury 42 (6) (2011) 569–573.
[17] D.F. Williams, On the mechanisms of biocompatibility, Biomaterials 29 (20) (2008) 2941–2953.
[18] M.J. Olszta, X. Cheng, S.S. Jee, R. Kumar, Y.-Y. Kim, M.J. Kaufman, E.P. Douglas, L.B. Gower, Bone structure and formation: a new perspective, Mater. Sci. Eng.: R: Rep. 58 (3) (2007) 77–116.
[19] S. Bose, M. Roy, A. Bandyopadhyay, Recent advances in bone tissue engineering scaffolds, Trends Biotechnol. 30 (10) (2012) 546–554.
[20] Y.C. Liu, J. Lim, S.H. Teoh, Review: development of clinically relevant scaffolds for vascularised bone tissue engineering, Biotechnol. Adv. 31 (5) (2013) 688–705.
[21] P.V. Giannoudis, H. Dinopoulos, E. Tsiridis, Bone substitutes: an update, Injury 36 (3) (2005) S20–S27.
[22] M.P. McAndrew, P.W. Gorman, T.A. Lange, Tricalcium phosphate as a bone graft substitute in trauma: preliminary report, J. Orthop. Trauma 2 (4) (1988) 333–339.
[23] D.W. Hutmacher, Scaffolds in tissue engineering bone and cartilage, Biomaterials 21 (24) (2000) 2529–2543.
[24] A.J. Ambard, L. Mueninghoff, Calcium phosphate cement: review of mechanical and biological properties, J. Prosthodont. 15 (5) (2006) 321–328.
[25] A.J. Ambard, L. Mueninghoff, Calcium phosphate cement: review of mechanical and biological properties, J. Prosthodont.: Off. J. Am. Coll. Prosthodont. 15 (5) (2006) 321–328.
[26] F.P. Melchels, J. Feijen, D.W. Grijpma, A review on stereolithography and its applications in biomedical engineering, Biomaterials 31 (24) (2010) 6121–6130.
[27] A. Khalyfa, S. Vogt, J. Weisser, G. Grimm, A. Rechtenbach, W. Meyer, M. Schnabelrauch, Development of a new calcium phosphate powder-binder system for the 3D printing of patient specific implants, J. Mater. Sci.: Mater. Med. 18 (5) (2007) 909–916.
[28] C. Shuai, P. Li, J. Liu, S. Peng, Optimization of TCP/HAP ratio for better properties of calcium phosphate scaffold via selective laser sintering, Mater. Charact. 77 (2013) 23–31.
[29] S. Yang, K.-F. Leong, Z. Du, C.-K. Chua, The design of scaffolds for use in tissue engineering. Part II. Rapid prototyping techniques, Tissue Eng. 8 (1) (2002) 1–11.
[30] B. Clarke, Normal bone anatomy and physiology, Clin. J. Am. Soc. Nephrol. 3 (Suppl 3) (2008) S131–S139.
[31] H. Oonishi, Orthopaedic applications of hydroxyapatite, Biomaterials 12 (2) (1991) 171–178.
[32] H. Eslami, M. Solati-Hashjin, M. Tahriri, The comparison of powder characteristics and physicochemical, mechanical and biological properties between nanostructure ceramics of hydroxyapatite and fluoridated hydroxyapatite, Mater. Sci. Eng.: C 29 (4) (2009) 1387–1398.
[33] M. Tahriri, M. Solati-Hashjin, H. Eslami, Synthesis and characterization of hydroxyapatite nanocrystals via chemical precipitation technique, Iran. J. Pharm. Sci. 4 (2) (2008) 127–134.
[34] H. Eslami, M. Solati-Hashjin, M. Tahriri, Synthesis and characterization of nanocrystalline fluorinated hydroxyapatite powder by modified wet-chemical process, J. Ceram. Process. Res. 9 (2008) 224–229.
[35] K. Fatehi, F. Moztarzadeh, M. Solati-Hashjin, M. Tahriri, M. Rezvannia, R. Ravarian, In vitro biomimetic deposition of apatite on alkaline and heat treated Ti6A14V alloy surface, Bull. Mater. Sci. 31 (2) (2008) 101–108.
[36] H. Eslami, M. Solati-Hashjin, M. Tahriri, F. Bakhshi, Synthesis and characterization of nanocrystalline hydroxyapatite obtained by the wet chemical technique, Mater. Sci. Pol. 28 (1) (2010) 5–13.
[37] M. Tahriri, F. Moztarzadeh, Preparation, characterization, and in vitro biological evaluation of PLGA/nano-fluorohydroxyapatite (FHA) microsphere-sintered scaffolds for biomedical applications, Appl. Biochem. Biotechnol. 172 (5) (2014) 2465–2479.
[38] D. Bizari, F. Moztarzadeh, M. Rabiee, M. Tahriri, F. Banafatizadeh, A. Ansari, K. Khoshroo, Development of biphasic hydroxyapatite/dicalcium phosphate dihydrate (DCPD) bone graft using polyurethane foam template: in vitro and in vivo study, Adv. Appl. Ceram. 110 (7) (2011) 417–425.
[39] F. Heidari, M. Razavi, M. Ghaedi, M. Forooghi, M. Tahriri, L. Tayebi, Investigation of mechanical properties of natural hydroxyapatite samples prepared by cold isostatic pressing method, J. Alloy. Compd. 693 (2017) 1150–1156.
[40] R. Masaeli, T.S.J. Kashi, R. Dinarvand, V. Rakhshan, H. Shahoon, B. Hooshmand, F.M. Abbas, M. Raz, A. Rajabnejad, H. Eslami, Efficacy of the biomaterials 3 wt %-nanostrontium-hydroxyapatite-enhanced calcium phosphate cement (nanoSr-CPC) and nanoSr-CPC-incorporated simvastatin-loaded poly (lactic-co-glycolic-acid) microspheres in osteogenesis improvement: an explorative multi-phase experimental in vitro/vivo study, Mater. Sci. Eng.: C 69 (2016) 171–183.
[41] J. Michel, M. Penna, J. Kochen, H. Cheung, Recent advances in hydroxyapatite scaffolds containing mesenchymal stem cells, Stem Cells Int. 2015 (2015) 305217.
[42] S.C. Cox, J.A. Thornby, G.J. Gibbons, M.A. Williams, K.K. Mallick, 3D printing of porous hydroxyapatite scaffolds intended for use in bone tissue engineering applications, Mater. Sci. Eng. C Mater. Biol. Appl. 47 (2015) 237–247.
[43] B.S. Kim, J.S. Kim, Y.S. Chung, Y.W. Sin, K.H. Ryu, J. Lee, H.K. You, Growth and osteogenic differentiation of alveolar human bone marrow-derived mesenchymal stem cells on chitosan/hydroxyapatite composite fabric, J. Biomed. Mater. Res. A 101 (6) (2013) 1550–1558.
[44] C. Gardin, E. Bressan, L. Ferroni, E. Nalesso, V. Vindigni, E. Stellini, P. Pinton, S. Sivolella, B. Zavan, In vitro concurrent endothelial and osteogenic commitment of adipose-derived stem cells and their genomical analyses through comparative genomic hybridization array: novel strategies to increase the successful engraftment of tissue-engineered bone grafts, Stem Cells Dev. 21 (5) (2012) 767–777.
[45] Y. Xia, P. Zhou, X. Cheng, Y. Xie, C. Liang, C. Li, S. Xu, Selective laser sintering fabrication of nano-hydroxyapatite/poly-epsilon-caprolactone scaffolds for bone tissue engineering applications, Int. J. Nanomed. 8 (2013) 4197–4213.
[46] J. Zhou, C. Xu, G. Wu, X. Cao, L. Zhang, Z. Zhai, Z. Zheng, X. Chen, Y. Wang, In vitro generation of osteochondral differentiation of human marrow mesenchymal stem cells in novel collagen-hydroxyapatite layered scaffolds, Acta Biomater. 7 (11) (2011) 3999–4006.
[47] M.M. Villa, L. Wang, J. Huang, D.W. Rowe, M. Wei, Bone tissue engineering with a collagen-hydroxyapatite scaffold and culture expanded bone marrow stromal cells, J. Biomed. Mater. Res. B Appl. Biomater. 103 (2) (2015) 243–253.
[48] K. Fu, Q. Xu, J. Czernuszka, J.T. Triffitt, Z. Xia, Characterization of a biodegradable coralline hydroxyapatite/calcium carbonate composite and its clinical implementation, Biomed. Mater. 8 (6) (2013) 065007.
[49] M.R. Urist, A. Lietze, E. Dawson, Beta-tricalcium phosphate delivery system for bone morphogenetic protein, Clin. Orthop. Relat. Res. (187) (1984) 277–280.
[50] H.H. Horch, R. Sader, C. Pautke, A. Neff, H. Deppe, A. Kolk, Synthetic, pure-phase beta-tricalcium phosphate ceramic granules (Cerasorb) for bone regeneration in the reconstructive surgery of the jaws, Int. J. Oral Maxillofac. Surg. 35 (8) (2006) 708–713.
[51] A. Ogose, T. Hotta, H. Kawashima, N. Kondo, W. Gu, T. Kamura, N. Endo,

Comparison of hydroxyapatite and beta tricalcium phosphate as bone substitutes after excision of bone tumors, J. Biomed. Mater. Res. B Appl. Biomater. 72 (1) (2005) 94–101.
[52] W.R. Walsh, F. Vizesi, D. Michael, J. Auld, A. Langdown, R. Oliver, Y. Yu, H. Irie, W. Bruce, Beta-TCP bone graft substitutes in a bilateral rabbit tibial defect model, Biomaterials 29 (3) (2008) 266–271.
[53] R.W. Bucholz, Nonallograft osteoconductive bone graft substitutes, Clin. Orthop. Relat. Res. (395) (2002) 44–52.
[54] I.R. Zerbo, A.L. Bronckers, G.L. de Lange, G.J. van Beek, E.H. Burger, Histology of human alveolar bone regeneration with a porous tricalcium phosphate. A report of two cases, Clin. Oral Implants Res. 12 (4) (2001) 379–384.
[55] A. Khojasteh, F. Fahimipour, M.B. Eslaminejad, M. Jafarian, S. Jahangir, F. Bastami, M. Tahriri, A. Karkhaneh, L. Tayebi, Development of PLGA-coated β-TCP scaffolds containing VEGF for bone tissue engineering, Mater. Sci. Eng.: C 69 (2016) 780–788.
[56] A. Ogose, N. Kondo, H. Umezu, T. Hotta, H. Kawashima, K. Tokunaga, T. Ito, N. Kudo, M. Hoshino, W. Gu, N. Endo, Histological assessment in grafts of highly purified beta-tricalcium phosphate (OSferion) in human bones, Biomaterials 27 (8) (2006) 1542–1549.
[57] A. Butscher, M. Bohner, S. Hofmann, L. Gauckler, R. Muller, Structural and material approaches to bone tissue engineering in powder-based three-dimensional printing, Acta Biomater. 7 (3) (2011) 907–920.
[58] S. Tarafder, W.S. Dernell, A. Bandyopadhyay, S. Bose, SrO- and MgO-doped microwave sintered 3D printed tricalcium phosphate scaffolds: mechanical properties and in vivo osteogenesis in a rabbit model, J. Biomed. Mater. Res. B Appl. Biomater. 103 (3) (2015) 679–690.
[59] S. Tarafder, S. Bose, Polycaprolactone-coated 3D printed tricalcium phosphate scaffolds for bone tissue engineering: in vitro alendronate release behavior and local delivery effect on in vivo osteogenesis, ACS Appl. Mater. Interfaces 6 (13) (2014) 9955–9965.
[60] A. Butscher, M. Bohner, N. Doebelin, L. Galea, O. Loeffel, R. Muller, Moisture based three-dimensional printing of calcium phosphate structures for scaffold engineering, Acta Biomater. 9 (2) (2013) 5369–5378.
[61] A. Butscher, M. Bohner, N. Doebelin, S. Hofmann, R. Muller, New depowdering-friendly designs for three-dimensional printing of calcium phosphate bone substitutes, Acta Biomater. 9 (11) (2013) 9149–9158.
[62] J.P. Carrel, A. Wiskott, M. Moussa, P. Rieder, S. Scherrer, S. Durual, A 3D printed TCP/HA structure as a new osteoconductive scaffold for vertical bone augmentation, Clin. Oral Implants Res. 27 (1) (2016) 55–62.
[63] E. Vorndran, M. Klarner, U. Klammert, L.M. Grover, S. Patel, J.E. Barralet, U. Gbureck, 3D powder printing of β-tricalcium phosphate ceramics using different strategies, Adv. Eng. Mater. 10 (12) (2008) B67–B71.
[64] E. Sanzana, M. Navarro, F. Macule, S. Suso, J. Planell, M. Ginebra, Of the in vivo behavior of calcium phosphate cements and glasses as bone substitutes, Acta Biomater. 4 (6) (2008) 1924–1933.
[65] M. Haghbin-Nazarpak, F. Moztarzadeh, M. Solati-Hashjin, A.R. Mirhabibi, M. Tahriri, Preparation, characterization and gentamicin sulfate release investigation of biphasic injectable calcium phosphate bone cement, Ceram.–Silik. 54 (4) (2010) 334–340.
[66] K. Khoshroo, T. Almela, M. Tahriri, F. Fahimipour, Z. Metalwala, K. Moharamzadeh, L. Tayebi, 3D-printing of porous calcium phosphate cements for bone tissue engineering, Dent. Mater. 32 (2016) e56–e57.
[67] A.S. Khorasani, H. Nuranian, A.A. Yuzbashi, S. Moghaddas, M. Raz, M. Tahriri, The Effects of Nanoparticles of Silica and Alumina on Flow Ability and Compressive Strength of Cementitious Composites, Key Engineering Materials, Trans Tech Publications, 2015, pp. 119–127.
[68] M. Rezvannia, F. Moztarzadeh, M. Tahriri, Formation of hydroxyapatite nanoneedles on the surface of a novel calcium phosphate/blood plasma proteins biocement in simulated body fluid (SBF), J. Ceram. Process. Res. 10 (5) (2009) 669–673.
[69] M. Haghbin-Nazarpak, F. Moztarzadeh, M. Solati-Hashjin, M. Tahriri, K. Khoshroo, Injectable and bioresorbable calcium phosphate delivery system with gentamicin sulphate for treatment of bone diseases: in vitro study, Adv. Appl. Ceram. 110 (8) (2011) 482–489.
[70] M.P. Ginebra, M. Espanol, E.B. Montufar, R.A. Perez, G. Mestres, New processing approaches in calcium phosphate cements and their applications in regenerative medicine, Acta Biomater. 6 (8) (2010) 2863–2873.
[71] M. Bohner, U. Gbureck, J.E. Barralet, Technological issues for the development of more efficient calcium phosphate bone cements: a critical assessment, Biomaterials 26 (33) (2005) 6423–6429.
[72] M.P. Ginebra, T. Traykova, J.A. Planell, Calcium phosphate cements as bone drug delivery systems: a review, J. Control. Release: Off. J. Control. Release Soc. 113 (2) (2006) 102–110.
[73] P. Habibovic, U. Gbureck, C.J. Doillon, D.C. Bassett, C.A. van Blitterswijk, J.E. Barralet, Osteoconduction and osteoinduction of low-temperature 3D printed bioceramic implants, Biomaterials 29 (7) (2008) 944–953.
[74] U. Klammert, T. Reuther, C. Jahn, B. Kraski, A.C. Kubler, U. Gbureck, Cytocompatibility of brushite and monetite cell culture scaffolds made by three-dimensional powder printing, Acta Biomater. 5 (2) (2009) 727–734.
[75] U. Gbureck, T. Hozel, U. Klammert, K. Wurzler, F.A. Muller, J.E. Barralet, Resorbable dicalcium phosphate bone substitutes prepared by 3D powder printing, Adv. Funct. Mater. 17 (18) (2007) 3940–3945.
[76] U. Gbureck, T. Holzel, C.J. Doillon, F.A. Muller, J.E. Barralet, Direct printing of bioceramic implants with spatially localized angiogenic factors, Adv. Mater. 19 (6) (2007) 795 (-+).
[77] Q. Fu, E. Saiz, M.N. Rahaman, A.P. Tomsia, Bioactive glass scaffolds for bone tissue engineering: state of the art and future perspectives, Mater. Sci. Eng. C Mater. Biol. Appl. 31 (7) (2011) 1245–1256.
[78] J. Russias, E. Saiz, S. Deville, K. Gryn, G. Liu, R. Nalla, A.P. Tomsia, Fabrication and in vitro characterization of three-dimensional organic/inorganic scaffolds by robocasting, J. Biomed. Mater. Res. Part A 83 (2) (2007) 434–445.
[79] C. Wu, Y. Luo, G. Cuniberti, Y. Xiao, M. Gelinsky, Three-dimensional printing of hierarchical and tough mesoporous bioactive glass scaffolds with a controllable pore architecture, excellent mechanical strength and mineralization ability, Acta Biomater. 7 (6) (2011) 2644–2650.
[80] M. Mozafari, E. Salahinejad, V. Shabafrooz, M. Yazdimamaghani, D. Vashaee, L. Tayebi, Multilayer bioactive glass/zirconium titanate thin films in bone tissue engineering and regenerative dentistry, Int. J. Nanomed. 8 (2013) 1665–1672.
[81] M. Yazdimamaghani, D. Vashaee, S. Assefa, K.J. Walker, S.V. Madihally, G.A. Kohler, L. Tayebi, Hybrid macroporous gelatin/bioactive-glass/nanosilver scaffolds with controlled degradation behavior and antimicrobial activity for bone tissue engineering, J. Biomed. Nanotechnol. 10 (6) (2014) 911–931.
[82] M. Yazdimamaghani, M. Razavi, D. Vashaee, L. Tayebi, Surface modification of biodegradable porous Mg bone scaffold using polycaprolactone/bioactive glass composite, Mater. Sci. Eng. C Mater. Biol. Appl. 49 (2015) 436–444.
[83] R. Ravarian, F. Moztarzadeh, M.S. Hashjin, S. Rabiee, P. Khoshakhlagh, M. Tahriri, Synthesis, characterization and bioactivity investigation of bioglass/hydroxyapatite composite, Ceram. Int. 36 (1) (2010) 291–297.
[84] J. Korpela, A. Kokkari, H. Korhonen, M. Malin, T. Närhi, J. Seppälä, Biodegradable and bioactive porous scaffold structures prepared using fused deposition modeling, J. Biomed. Mater. Res. Part B: Appl. Biomater. 101 (4) (2013) 610–619.
[85] A. Yazdanpanah, R. Kamalian, F. Moztarzadeh, M. Mozafari, R. Ravarian, L. Tayebi, Enhancement of fracture toughness in bioactive glass-based nanocomposites with nanocrystalline forsterite as advanced biomaterials for bone tissue engineering applications, Ceram. Int. 38 (6) (2012) 5007–5014.
[86] P. Tesavibul, R. Felzmann, S. Gruber, R. Liska, I. Thompson, A.R. Boccaccini, J. Stampfl, Processing of 45S5 Bioglass® by lithography-based additive manufacturing, Mater. Lett. 74 (2012) 81–84.
[87] S.-I. Roohani-Esfahani, P. Newman, H. Zreiqat, Design and fabrication of 3D printed scaffolds with a mechanical strength comparable to cortical bone to repair large bone defects, Sci. Rep. 6 (2016) 19468.
[88] S.V. Dorozhkin, Biocomposites and hybrid biomaterials based on calcium orthophosphates, Biomatter 1 (1) (2011) 3–56.
[89] A. Khojasteh, F. Fahimipour, M.B. Eslaminejad, M. Jafarian, S. Jahangir, F. Bastami, M. Tahriri, A. Karkhaneh, L. Tayebi, Development of PLGA-coated β-TCP scaffolds containing VEGF for bone tissue engineering, Mater. Sci. Eng.: C (2016) 780–788.
[90] H.E. Jazayeri, M.D. Fahmy, M. Razavi, B.E. Stein, A. Nowman, R.M. Masri, L. Tayebi, Dental applications of natural-origin polymers in hard and soft tissue engineering, J. Prosthodont. 25 (6) (2016) 510–517.
[91] M.D. Fahmy, H.E. Jazayeri, M. Razavi, R. Masri, L. Tayebi, Three-dimensional bioprinting materials with potential application in preprosthetic surgery, J. Prosthodont. 25 (4) (2016) 310–318.
[92] J. Guicheux, O. Gauthier, E. Aguado, D. Heymann, P. Pilet, S. Couillaud, A. Faivre, G. Daculsi, Growth hormone-loaded macroporous calcium phosphate ceramic: in vitro biopharmaceutical characterization and preliminary in vivo study, J. Biomed. Mater. Res. 40 (4) (1998) 560–566.
[93] Y.M. Lee, Y.J. Park, S.J. Lee, Y. Ku, S.B. Han, P.R. Klokkevold, C.P. Chung, The bone regenerative effect of platelet-derived growth factor-BB delivered with a chitosan/tricalcium phosphate sponge carrier, J. Periodontol. 71 (3) (2000) 418–424.
[94] S. Kimakhe, S. Bohic, C. Larrose, A. Reynaud, P. Pilet, B. Giumelli, D. Heymann, G. Daculsi, Biological activities of sustained polymyxin B release from calcium phosphate biomaterial prepared by dynamic compaction: an in vitro study, J. Biomed. Mater. Res. 47 (1) (1999) 18–27.
[95] W. Xia, J. Chang, Well-ordered mesoporous bioactive glasses (MBG): a promising bioactive drug delivery system, J. Control. Release 110 (3) (2006) 522–530.
[96] S. Meininger, S. Mandal, A. Kumar, J. Groll, B. Basu, U. Gbureck, Strength reliability and in vitro degradation of three-dimensional powder printed strontium-substituted magnesium phosphate scaffolds, Acta Biomater. 31 (2016) 401–411.
[97] M. Vallet-Regi, F. Balas, D. Arcos, Mesoporous materials for drug delivery, Angew. Chem. Int. Ed. Engl. 46 (40) (2007) 7548–7558.
[98] J.M. Bouler, M. Trecant, J. Delecrin, J. Royer, N. Passuti, G. Daculsi, Macroporous biphasic calcium phosphate ceramics: influence of five synthesis parameters on compressive strength, J. Biomed. Mater. Res. 32 (4) (1996) 603–609.
[99] S.H. Li, J.R. De Wijn, P. Layrolle, K. de Groot, Synthesis of macroporous hydroxyapatite scaffolds for bone tissue engineering, J. Biomed. Mater. Res. 61 (1) (2002) 109–120.
[100] N. Tamai, A. Myoui, T. Tomita, T. Nakase, J. Tanaka, T. Ochi, H. Yoshikawa, Novel hydroxyapatite ceramics with an interconnective porous structure exhibit superior osteoconduction in vivo, J. Biomed. Mater. Res. 59 (1) (2002) 110–117.
[101] J.W. Lee, D.W. Cho, 3D printing technology over a drug delivery for tissue engineering, Curr. Pharm. Des. 21 (12) (2015) 1606–1617.
[102] Y. Zhang, D. Zhai, M. Xu, Q. Yao, J. Chang, C. Wu, 3D-printed bioceramic scaffolds with a Fe3O4/graphene oxide nanocomposite interface for hyperthermia therapy of bone tumor cells, J. Mater. Chem. B 4 (17) (2016) 2874–2886.
[103] J. Barralet, U. Gbureck, P. Habibovic, E. Vorndran, C. Gerard, C.J. Doillon, Angiogenesis in calcium phosphate scaffolds by inorganic copper ion release, Tissue Eng. Part A 15 (7) (2009) 1601–1609.
[104] X. Xiao, W. Wang, D. Liu, H. Zhang, P. Gao, L. Geng, Y. Yuan, J. Lu, Z. Wang, The promotion of angiogenesis induced by three-dimensional porous beta-tricalcium phosphate scaffold with different interconnection sizes via activation of PI3K/Akt

pathways, Sci. Rep. 5 (2015) 9409.
[105] J.A. Inzana, R.P. Trombetta, E.M. Schwarz, S.L. Kates, H.A. Awad, 3D printed bioceramics for dual antibiotic delivery to treat implant-associated bone infection, Eur. Cell Mater. 30 (2015) 232–247.
[106] Y. Kim, B. Lee Chung, M. Ma, W.J. Mulder, Z.A. Fayad, O.C. Farokhzad, R. Langer, Mass production and size control of lipid-polymer hybrid nanoparticles through controlled microvortices, Nano Lett. 12 (7) (2012) 3587–3591.
[107] S.M. Janib, A.S. Moses, J.A. MacKay, Imaging and drug delivery using theranostic nanoparticles, Adv. Drug Deliv. Rev. 62 (11) (2010) 1052–1063.
[108] A. Baeza, M. Colilla, M. Vallet-Regi, Advances in mesoporous silica nanoparticles for targeted stimuli-responsive drug delivery, Expert Opin. Drug Deliv. 12 (2) (2015) 319–337.