Engineering 6 (2020) 1222–1231

Contents lists available at ScienceDirect

Engineering

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

Research
Medical Additive Manufacturing—Review

Advances in Medical Applications of Additive Manufacturing

Chunxu Li [a], Dario Pisignano [b,c], Yu Zhao [a,*], Jiajia Xue [d,*]

[a] Department of Orthopaedics, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100730, China
[b] National Enterprise for Nanoscience and Nanotechnology, Nanoscience Institute, National Research Council, Pisa I-56127, Italy
[c] Department of Physics, University of Pisa, Pisa I-56127, Italy
[d] Beijing Laboratory of Biomedical Materials, Beijing University of Chemical Technology, Beijing 100029, China

ARTICLE INFO

Article history:
Received 15 August 2019
Revised 20 December 2019
Accepted 20 February 2020
Available online 15 September 2020

Keywords:
Additive manufacturing
Medical applications
Pharmaceutics
Medical implants
Medical devices

ABSTRACT

In the past few decades, additive manufacturing (AM) has been developed and applied as a cost-effective and versatile technique for the fabrication of geometrically complex objects in the medical industry. In this review, we discuss current advances of AM in medical applications for the generation of pharmaceuticals, medical implants, and medical devices. Oral and transdermal drugs can be fabricated by a variety of AM technologies. Different types of hard and soft clinical implants have also been realized by AM, with the goal of producing tissue-engineered constructs. In addition, medical devices used for diagnostics and treatment of various pathological conditions have been developed. The growing body of research on AM reveals its great potential in medical applications. The goal of this review is to highlight the usefulness and elucidate the current limitations of AM applications in the medical field.

1. Introduction

Additive manufacturing (AM) refers to a set of production technologies applied for the transformation of a three-dimensional (3D) digital model into a 3D physical object through successive material depositions in a layer-by-layer mode [1]. The advent of AM in the 1980s revolutionized the history of manufacturing. In comparison with conventional manufacturing approaches, AM has some obvious advantages. Conventional manufacturing consists of formative (molds) or subtractive (machining) techniques; thus, it requires costly infrastructures and multiple steps, resulting in seriously limited capability in terms of the timely implementation of modifications to the final product [2]. In comparison, due to its designability, AM allows for the fabrication of objects with intricate and complex geometries. For this reason, AM was applied in medical engineering soon after its development, and was rapidly developed to satisfy the needs of patients and clinicians [3,4]. Indeed, AM can be applied to fabricate medical devices used for diagnostics and surgeries, as well as orthoses and prostheses, in developing countries, where expensive devices are too costly [5,6]. The US Food and Drug Administration (FDA) published the first version of guidelines for the application of AM to produce medical devices in 2017 [7]. Anatomical models produced by AM provide benefits for both surgical planning and procedure training, particularly in cases of rare pathologies for which the customization of devices and processes play a critical role [8].

AM techniques have been applied in various areas for biomedical applications. In this article, we focus on the development of AM for the fabrication of drug delivery systems, medical implants, and medical devices—three types of products that are used on a particularly large scale at the clinical level. AM is competitive for the small-scale production of drugs requiring frequent dosage modification and complex geometries. It is advantageous for patient needs as well as for achieving tailored drug release profiles that cannot be easily obtained through conventional mass manufacturing processes [9–14]. AM can also be used to produce customized medical devices, allowing end products to be tailored specifically for the patient and realized at a very low cost. Nowadays, designing and printing personalized implants and prostheses has become the gold-standard method, and is a reliable solution for many patients who require specific constructs. AM has been widely used to fabricate dental parts [15], trauma medical implants, and orthopedic medical devices [16]. Tissue and organ printing is also an emerging area with significantly increasing interest from academia and industry [17]. Surgical applications include anatomical models [18], prostheses and orthoses [19],

* Corresponding authors.
E-mail addresses: zhaoyupumch@163.com (Y. Zhao), jiajiaxue@mail.buct.edu.cn (J. Xue).

https://doi.org/10.1016/j.eng.2020.02.018

and surgical instruments [20]. Anatomical models aid pre-surgical planning and education [21]. Prostheses and orthoses are a broad category that includes implantable materials and external devices. Personalized surgical instruments are necessary to ensure accuracy and improve the efficiency of surgeries [22]. From these points of view, we summarize the applications of AM in the biomedical area in terms of pharmaceuticals, clinical implants, and medical devices. We also discuss and explain the advantages and limitations of AM technology when applied in these contexts. Finally, we discuss the challenges that still exist and provide future directions that may help the development of AM technologies toward large-scale biomedical production.

2. Pharmaceuticals

There are an increasing number of publications concerning the creation of pharmaceutical formulations such as oral (Fig. 1(a) [23]) and transdermal drugs using AM techniques [6]. Technologies of choice in this context include fused deposition modeling (FDM), stereolithography (SLA), binder jetting, powder-bed printing, semi-solid extrusion, and inkjet printing [24]. Although these classes of drugs are still in their infancy, such manufacturing methods offer a few obvious advantages regarding dosage forms and drug formulation. For example, FDM enables the printing of thermolabile active pharmaceutical ingredients (APIs) at a relatively low temperature of 90 °C in comparison with traditional printing and allows a large variety of pharmaceutical-grade polymers to be processed in this way [25]. Inkjet printing has led to the development of a variety of biocompatible bioinks through the use of high-throughput screening methodology to identify 3D printable compounds [26]. AM technology is not only superior to traditional printing technology, but also appropriate for facilitating community pharmacies as well as other health-provision facilities on a small scale, due to its low cost. Recently, sustainable and massive manufacturing of drug-loaded filaments has been made possible [27] while conforming to the good manufacturing practices (GMP) of FDM printers and hot-melt extruders. These works indicate the impending transition from proof-of-concept demonstrations toward real-life applications.

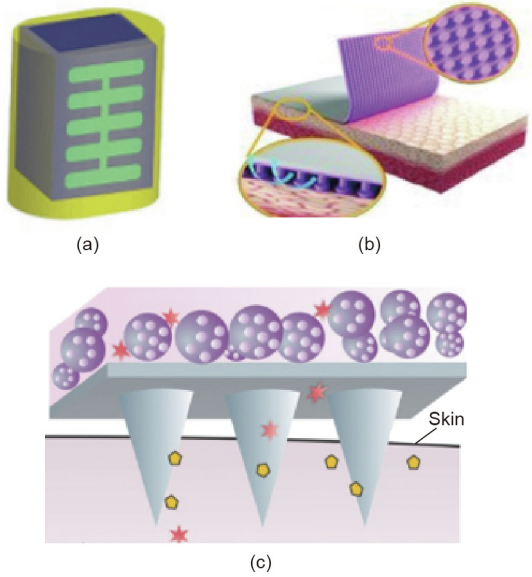

Fig. 1. Applications of AM techniques in pharmaceutics to fabricate different types of drug formulations. (a) Tablets of oral medicines. Reproduced from Ref. [23] with permission of John Wiley & Sons, ©2015. (b) Patches of transdermal drugs. Reproduced from Ref. [43] with permission of John Wiley & Sons, ©2011. (c) Microneedles of transdermal drugs. Reproduced from Ref. [47] with permission of John Wiley & Sons, ©2016.

AM is particularly favorable to promote the drug release of unreleasable soluble compounds. A novel AM technology, which can be categorized as instant powder extrusion, was exemplified by producing itraconazole-loaded printlets as amorphous solid dispersions that could be instantly drawn out of powdered materials. This quick-release technique also obviates the increasingly long-term development time for filament-production-based requirement in FDM [28]. Recent studies have reported on the intensified ability of AM to create lipid-oriented conceptions in order to strengthen the drug release of drugs that are insoluble or nearly insoluble in water [29].

Due to its advantages of accurate and flexible material spatial distribution, AM has gained widespread application in multi-drug combinations. For example, Pereira et al. [30] managed to print a cardiovascular polypill containing four different drug components. In a recent study, Awad et al. [31] announced the successful production of 3D-printed, millimeter-scale pellets (“mini-printlets”) that contain two spatially isolated drugs (paracetamol and ibuprofen). By changing the polymer, the dual mini-printlets can attain customized drug release. A kind of drug achieved immediate release from the matrix, while the second patterns of the drug can gain a long acting effect through the use of ethyl cellulose. In terms of application routes to the body, both oral and transdermal drugs have potential for development via AM technologies.

2.1. Oral drugs

AM has been applied in pharmaceutics to produce oral drugs with complicated structures and elaborate shapes, which are cost-ineffective or impossible to be achieved through traditional procedures [32]. A wide spectrum of AM techniques can be used to easily manufacture dosage forms with complex geometries, such as microstructured formulations with an internal channel [33], honeycomb [34], network [35], or gyroid forms [9]. The drug release profiles can be tailored by adjusting the morphology and dimension of 3D-printed materials and architectures, such as through composite multilayered or shell–core formulations, to deliver at least one type of API with variable rates due to the designed differences in the specific structure and sequence of layers [36,37]. Furthermore, the creation of complex scaffolds and matrices makes the incorporation of drug-loaded formulations or APIs possible. For example, such a feature might help in the creation of carriers such as capsules with specific compartments, which can incorporate various types of APIs and then release them independently [38]. In addition, this feature can assist in the production of modifiable containers for enclosing drug-loaded alginate beads [39], polymeric nanocapsules [40], or self-nanoemulsifying drug delivery systems [41].

In comparison with traditional injection molding (IM), AM could be better at manufacturing customized capsules in small individualized batches. By 3D printing personalized oral solid dosage forms and multi-particulate systems, the advantages of both these features can be exploited in a synergistic way, providing better dispersion and distribution in the gastrointestinal tract, as well as dose accuracy and convenience. Processing carrier matrices filled with drug-loaded solutions or suspensions is another interesting feature of AM [42]. This approach can guarantee a high dose accuracy and be time effective.

2.2. Transdermal drugs

Applied together with 3D scanning, high-precision AM has been leveraged to manufacture automatically adaptable patches, and has hence been applied in personalized transdermal drugs

(Fig. 1(b) [43]). A study highlighted SLA as a method that outperforms FDM in producing an antiacne device containing salicylic acid, which showed improved thermal stability, drug-loading capacity, and resolution [44]. The device also showed faster drug diffusion in comparison with ethnodrugs, while personalized medicine printing was facilitated by applying a 3D scan of an area to determine the anatomical requirements of the patient [44]. Based on the same concept, the fabrication of a personalized polycaprolactone (PCL) dressing loaded with antimicrobial metals was implemented against scanned templates of a target wound, and demonstrated prolonged release kinetics of the antimicrobials, which is desirable in clinical practice in order to reduce medical intervention to the minimal level [45]. In another study, electrohydrodynamic (EHD) printing was used to fabricate antimicrobial PCL/polyvinylpyrrolidone patches, enabling the release kinetics of loaded tetracycline hydrochloride to be tailored by adjusting the fiber pattern and composition [46].

Transdermal drug delivery has been implemented with microneedles as a minimally invasive approach to improve drug permeation over the skin barrier (Fig. 1(c) [47]). AM techniques have been applied to generate various types of functionalized microneedles. In one study, insulin-xylitol coatings were inkjet printed on SLA-printed pyramid-shaped resin microneedles, which exhibited rapid insulin release while retaining protein integrity [48]. In another study, continuous liquid interface production was applied as an alternative method for coating polyethylene glycol (PEG)-based microneedles with model proteins, and permitted spatial control of the coating pattern [49]. In an attempt to optimize the geometrical properties of the microneedles, chemical etching of the biodegradable poly(lactic acid) (PLA) arrays was adopted as a post-fabrication phase [50]. A microneedle-customized splint was used to achieve personalized drug delivery that was adaptable for the curvature of skin in order to cure trigger finger [51]. A bioinspired needle was designed using AM to mimic the barbs of honeybee stingers with the intention of reducing the extraction and insertion forces during percutaneous application by differentiating the barb design parameters [52].

3. Medical implants

In the field of clinical implanting, there has been a growing development of the shape and function design that allows a considerable degree of matching of foreign objects with internal structures and tissues of the human body, while improving their functions. AM can bridge the difference between biological matter and engineering projects by composing architectures with biocompatibility and bioactivity, which utilize the unique attributes of materials to enhance the combination of tissue regeneration and the implant, along with the surrounding tissues. Current radiological imaging approaches, such as computed tomography (CT), can create an accurate computer-aided design (CAD). Such a design can act as a model for AM, in order to generate implants with an ideal fit to implant-position. Mechanical load bearing is usually provided by hard structures, while biological and chemical functions ranging from muscular contraction to neural processing are mainly provided by soft constructs or structures.

3.1. Hard-structure implants

Accurate control of the internal pore structure of porous architectures can be achieved with AM, which allows complex geometries to be manufactured with repeatability. Among the different approaches, selective laser melting (SLM) can be regarded as a very promising route for the fabrication of medical devices due to its versatility and high accuracy, as well as the good surface finish and structural integrity of the fabricated implants [53]. SLM is an excellent choice for creating the small features (< 500 μm) that are typically present in spinal fusion implant devices.

Hard-structure implants, which play an indispensable part in managing patients undergoing orthopedic injuries, can help with aspects of recovery such as alignment, structural integrity, and motion capability. Most implants are available in standard sizes for fitting patients. However, patients at the extreme edge of anatomical variability, or those with specific disorders, may require customized implants in order to ensure a correct fit [54]. Similar to the processes used in dentistry, CAD models of patients are created based on the patients' anatomical structure, as determined through radiological imaging, making it possible to design and fabricate custom-fit implants with AM. Orthopedic implants require integration with (or the regeneration of) the patients' own bones to create successful tissue support and prevent failed implants. More specifically, customized orthopedic implants seamlessly incorporate the continuous growth of the bone and the designed flexibility in order to prevent stress shielding. Such systems can be fabricated via the selective laser sintering of titanium alloy (Ti–6Al–4V). Cranial reconstruction implants can be made of polyether ether ketone, stainless steel, and titanium, and can be fabricated in advance and then customized on demand for individual patients. In a recent study, Zhang et al. [55] described titanium–copper alloys with a fully equiaxed fine-grained microstructure that displayed promising mechanical properties during AM, in addition to excellent antibacterial properties, good biocompatibility, and corrosion resistance. These materials are interesting for application in the biomedical industry (Fig. 2) [55].

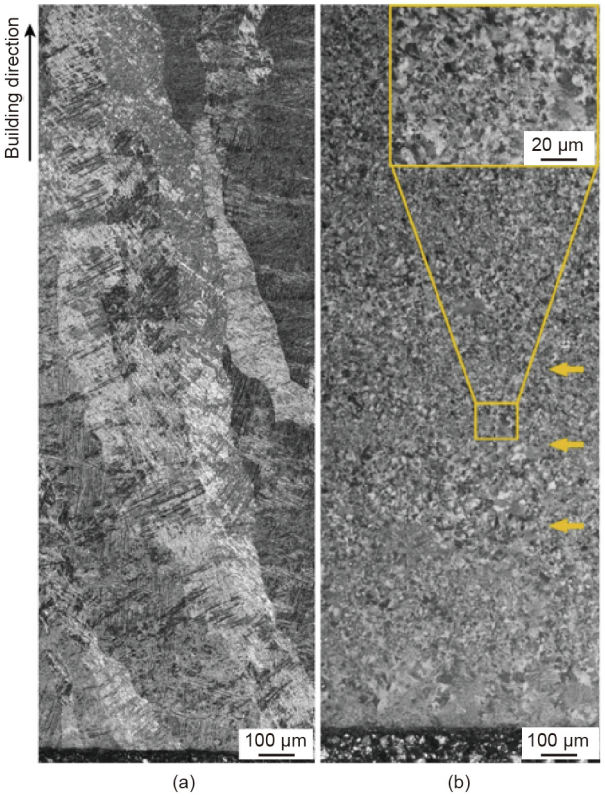

Fig. 2. (a) Optical micrograph of an as-printed Ti–6Al–4V alloy. Coarse columnar grains can be clearly seen; (b) optical microstructures of an as-printed Ti–8.5Cu alloy show fine, fully equiaxed grains along the building direction instead, under the same manufacturing conditions. Layer boundaries are highlighted by arrows. Reproduced from Ref. [55] with permission of Springer Nature, ©2019.

A small number of factors related to an implant's structure and composition can drive its capability to promote bone regeneration. Porosity is a crucial property to ensure the penetration of an implant among tissues and vessel ingrowth [56]. High-resolution AM can be used to create porous implants, with an interwoven bone mesh used to secure the implant into the neighboring bone tissues. Moreover, AM materials with bio-absorbability and osteoinductivity, such as calcium phosphate cement, are effective in decelerating bone growth [57]. Last but not least, implants can concentrate and enhance the effects of drugs and influential growth factors, such as bone morphogenetic protein or vascular endothelial cell growth factor, to ensure local and sustained release at the implantation location. In this way, such implants promote systematic exposure to those compounds [58]. Furthermore, small-scale therapeutics have been called for, putting emphasis on cost-efficiency [59]. Ren et al. [60] reported the use of a general synthetic orthogonal assembly approach to build 3D multilayer-crossed metal oxide nanowire arrays in a controllable manner. This enabled the realization of nanodevices with tailored conductivity, porous structure, and high surface area, which hold promise for application in the repair of spinal cord injury (Fig. 3) [60]. Researchers have also shown the potential of light-curing AM to produce patient-specific dentures with unique antibacterial properties via the inclusion of titanium dioxide (TiO_2) within a polymethyl methacrylate [61].

AM is well-established as a feasible and accurate approach for fabricating durable artificial implants that are comparable to those produced using conventional manufacturing techniques and materials [62]. Close collaboration between implant engineers and surgeons is necessary in order to produce patient-specific implants using AM. In the planning phase of such implants, engineers create a design based on the surgical requirements specified by surgeons, including a porous scaffold for bone ingrowth, the site of bone fixation, optimal alignment of the necessary implants, the bone defects that require reconstruction, and the specific surgical approach. In this way, the desired geometry can be fabricated through AM to provide the required physical and mechanical properties for each surgical application.

3.2. Soft-structure implants

Nowadays, there is an increasing demand for the bioprinting of tissues and organs. Recreating the complex structures of a tissue using cell-compatible materials has been a major challenge. For example, in air-breathing vertebrates, the circulatory and pulmonary systems contain separate networks of channels that intertwine but do not intersect with each other. These architectures are highly complex to mimic, and are especially demanding in terms of microfabrication. AM technologies have been successfully applied to fabricate soft-structure implants for generating tissue constructs, such as heart tissue, kidney, liver, blood vessel, ear, and cartilage. However, further research is still needed in order to decrease the gap between a fully 3D-printed anatomical model and living, biological, soft structures. In fact, most 3D printing materials lack the realism to adequately mimic soft human biological tissue. Thus, postprocessing may be necessary in order to soften structures that have been printed using appropriate precursor materials.

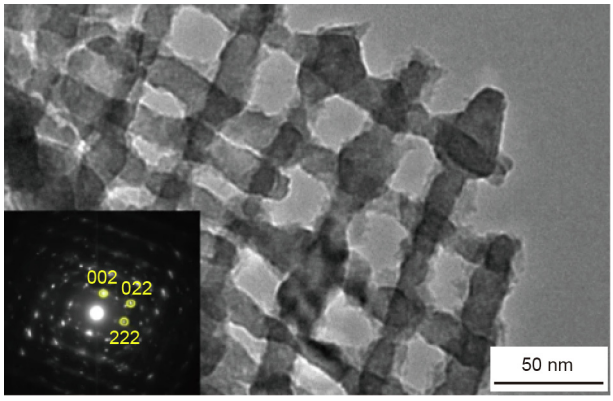

Fig. 3. Transmission electron micrograph of the porous structure formed by interwoven crystalline semiconducting tungsten trioxide (WO_3) nanowires that are "welded" at the crossing points. Reproduced from Ref. [60] with permission of Springer Nature, ©2020.

Grigoryan et al. [63] showed that natural and synthetic food dyes can be used as photoabsorbers to enable the stereolithographic production of hydrogels containing intricate and functional vascular architectures. Using this approach, they demonstrated functional vascular topologies for studies of fluid mixers, valves, and systems for intervascular transport, nutrient delivery, and host engraftment. Kidney organoids derived from human pluripotent stem cells have glomerular- and tubular-like compartments that are largely avascular and immature in static culture. Homan et al. [64] and Johnson et al. [65] demonstrated that vascularized kidney organoids that were cultured under flow expanded their endogenous pool of endothelial progenitor cells and generated vascular networks with perfusable lumens surrounded by mural cells (Fig. 4(a) [64]).

For the treatment of myocardial infarction, 3D printing of mesenchymal stem cells has been shown to be effective in decreasing the scar tissue formation and collagen deposition after infarction [66]. However, the restricted transport of cell-secreting therapeutic cytokines limits the therapeutic efficacy at the implantation site. It has been found that the gel-tissue interface can be effectively removed using a developed cross-linked poly(ethylene glycol) dimethacrylate-based microchanneled hydrogel patch, which can act as a physical barrier to biomolecular transport and thereby assist in the transport of cytokines. In recent years, a considerable amount of research has addressed the dynamic changes in the cell environment, which impact tissue functions. As a result, microfluidics-based cell-culture platforms have been improved to become effective experimental tools for organ bioengineering. The human hepatoma cell line (HepG2), human umbilical vein endothelial cells (HUVECs), and PCL were used to develop a 3D-printed liver-on-a-chip platform [67]. A bioartificial renal tubule device embedding human renal stem/progenitor cells was demonstrated in the context of kidney research [68]. The researchers described the dramatically improved functions of the liver-on-a-chip and heterotypic cell types. Microfluidics have also been used to print a nervous-system-on-a-chip (Figs. 4(b)–(e) [65]), which was depicted by Johnson et al. [65] as a model to investigate a viral infection of the nervous system. The microchannels were manufactured by utilizing micro-extrusion AM to achieve compartmentalized chambers and axonal alignment for cell isolation. Future research on these systems will include the development of new strategies for the treatment of neurological disorders and further investigation of the *in vitro* functionality of personalized 3D-printed models.

Although there have been many successful examples of bioprinting, several problems remain to be solved. The long-term viability of cells is one of the major issues. Another issue involves improving the control of cell proliferation in order to obtain abundant supporting and functional cells and tissue homeostasis. Cell type is of great importance, given that the cells must be able to reconstruct the building blocks of organs with multiple sizes, architectures, and functions. In addition, the tissues applied in AM should be capable of surviving shear stress and pressure during printing, as well as the possible presence of harmful chemical compounds and non-physiological pH values. Apart from the

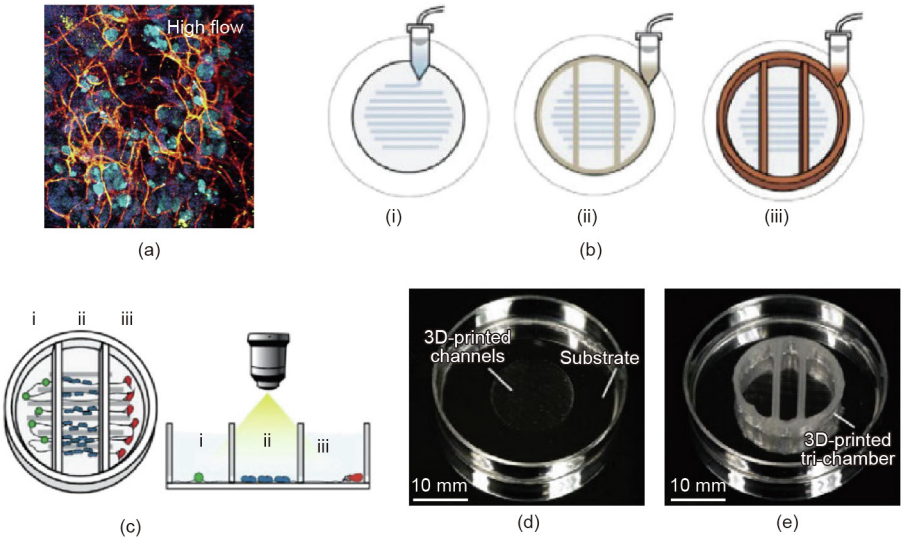

Fig. 4. (a) Developing kidney organoids cultured *in vitro* under high fluid flow exhibit enhanced vascularization during nephrogenesis. (b) 3D printing of a model nervous-system-on-a-chip: (i) channel printing; (ii) seal printing; (iii) chamber printing. (c) Schematic of a 3D-printed nervous-system-on-a-chip with (i) peripheral nervous system neurons, (ii) Schwann cells, and (iii) terminal cell junctions. (d) Circular pattern of silicone microchannels for axonal guidance in a plastic dish. (e) Nervous-system-on-a-chip system. (a) Reproduced from Ref. [64] with permission of Springer Nature, ©2019; (b–e) reproduced from Ref. [65] with permission of the Royal Society of Chemistry, ©2016.

conditions mentioned above, scaffold materials should also satisfy precise standards, such as appropriate structural and mechanical properties, non-toxic byproducts, and biocompatibility, given that cell proliferation, adhesion, and migration will be critically affected by these aspects [69].

Special attention has been paid to the use of AM in craniofacial reconstructive surgery, since this technology can precisely replicate individual facial features. Cartilage from patients and silicone prostheses can commonly replace regions of the ears that have been damaged by traumatic events or congenital issues. However, such solutions are costly, and patients must usually undergo multiple visits to the hospital. Furthermore, it is difficult to achieve a shape that fits the defect site perfectly without resectioning healthy tissues or using extra fillers. Fortunately, composite structures have been shown to be capable of satisfying expectations in terms of both the geometry and anatomy of the native ear. Scanning printing polishing casting (SPPC) was used to produce artificial ears with low-cost soft tissue [70]. Unkovskiy et al. [71] produced an artificial nose and applied post-process coloring and sealing in addition to silicon-based implants. As a result, the defect of the patient was fitted well. An infant was also implanted with a customized, collapse-resistance PCL-based bioresorbable tracheal splint [72]. AM can be particularly helpful for producing non-standardized implants for pediatric patients. All of the abovementioned studies show that, with the development of AM technology, printed organs are moving toward finer and more complex structures.

Composites that contain multiple types of materials are a promising route toward the production of human tissues using AM techniques, since none of the currently available materials are likely to be able to fully mimic elastic and biological tissues. Multi-material composites may be designed based on the capacity of a selected biological material to replicate the mechanical properties and architecture of native human tissues [73].

4. Medical devices

A medical device is basically a tool used to check and treat patients. Patients have direct contact with such a tool. However, a medical device is not meant to be inside the body throughout the duration of the treatment or examination. Different types of medical devices have been fabricated and developed by AM for both diagnosis and treatment purposes.

4.1. Diagnostic tools

Better evaluation and assessment, and more accurate diagnosis, have been enabled by the application of AM. AM also facilitates the visualization of patient-specific organ anatomy. The amount of information available for preoperative planning has been dramatically increased beyond the features of an individual organ. Therefore, it is believed that surgical planning and education is one of the most important fields for the application of AM technologies. The manufacturing of liver models is one such example. Growing transplantation needs and the limited number of cadaveric livers are stimulating the demand for organs from healthy donors. Zein et al. [74] described transparent models with appropriate color-coded vasculature. Six models of livers from six patients were prepared, and illustrated identical geometrical and anatomical characteristics between the native and printed organs. CT scans were used to visualize the 3D anatomy of the livers, tumors, blood vessels, and organ contours in the patients. Silicone was used to fill and assemble a multilayered structure. Successful subsequent laparoscopic right hemihepatectomies were then undergone by the patients. Another case of preoperative planning based on 3D-printed phantoms occurred in the context of renal malignancy modeling [75]. SLA AM was used to produce five physical phantoms of clear translucent nephrons with red translucent suspected malignancies. The patients then underwent successful partial nephrectomies. It was forecasted that the cost of manufacturing a life-sized liver model with a transparent parenchyma, color-coded vascularization, and tumor sites would be less than 150 USD [76].

To benefit pediatric laparoscopic pyeloplasty, silicon models of the ureter, renal pelvis, and kidney have been improved [77]. This operation is extremely challenging due to the delicate tissues, finer sutures, and smaller workspace it entails. Therefore, it demands strong training. Medical imaging modalities were used to test printed models, such as two-dimensional (2D) and 3D ultrasound

and magnetic resonance imaging (MRI). The production cost was less than 100 USD and required several hours of labor.

In recent years, AM models have been used in the field of cardiology, with a focus on patients with congenital heart disease (Fig. 5(a) [78]). Such pediatric models hold strong educational value. They can present complicated anatomical concepts, such as the spectrum of heterotaxy syndromes, malalignment-type ventricular septal defects, and double-outlet right ventricles. 3D-printed models make the treatment of aortic diseases comparatively easier because they can reproduce the aortic anatomy and diameters exactly. AM has been successfully applied for patients suffering from hypertrophic cardiomyopathy and cardiac tumors; the lesion size serves as the major parameter to determine strategical choices of surgery, such as a heart transplant or a total resection. In this framework, the implementation of 3D models can enable a rapid comprehension of anatomical heart defects, including complicated aspects such as crisscross atrioventricular connections [79].

AM has also been used in the context of the growing number of patients with degenerative issues. A 3D-printed brain system was demonstrated by Marks et al. [80], showing different phases of Alzheimer's disease. This system was used as an educational tool to assist researchers in the understanding of the progressive degenerative changes of the hippocampus and cerebral cortex. Magnetic resonance images of the brains of five patients were captured and printed. The time required to print each model ranged from 15 to 20 h. The authors concluded that the models could not yet be applied for diagnosis, but could be used for the purpose of education.

4.2. Therapeutic tools

Given the clinical applications, we categorize therapeutic instruments into prostheses, orthopedic devices, and surgical tools. Prostheses specifically refer to artificial limbs that are attached to the outside of the body, such as prosthetic hands, arms, and lower limbs. Orthopedic devices are mainly auxiliary tools related to treatment, such as plaster and splints. Surgical tools are used during operations, and include both surgical operation tools whose basic design is based on traditional instruments, such as surgical tweezers, and other tools that are customized for the surgical treatment of specific diseases, such as laparoscopic or endoscopic instruments.

4.2.1. Prostheses

3D structures produced by AM can be carefully designed to achieve high strength-to-weight ratios compared with those of many conventional solid structures. Such structures require less material than a fully solid structure to achieve a similar performance, making them potentially resource efficient. Indeed, reducing the weight is a priority in prosthetic applications. Pham et al. [81] deliberately introduced apparent imperfections into 3D-printed plastic and metal lattices to make them stronger. This strategy mimics on a larger scale the imperfections of structure and composition that can enhance the mechanical performance of normal crystalline materials.

It is a traumatic event to lose a limb, whether from an accident, in combat, or as a result of a calculated decision to address a growing tumor or other deteriorating illness. Amputation can leave a lasting aftermath in a patient's quality of life, and can cause concerned families and friends to suffer as well. In this regard, long-lasting "peg-leg" and "hand-hook" prosthetics, which can meet mechanical demands, can provide adequate recovery of gross motor functions such as standing and walking. However, artificial arms and legs can be improved by means of modern AM fabrication technologies. Based on such technologies, numerous producers of rapid bespoke 3D printing could be established, that

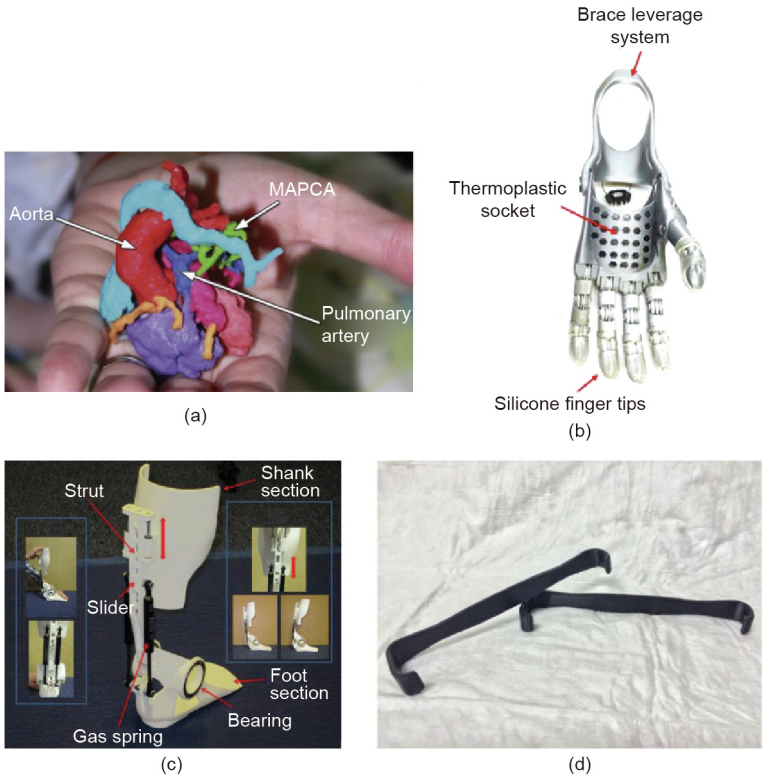

Fig. 5. Medical devices classification. (a) Actual-size 3D model of the heart and great vessels of a 1-day-old male patient with pulmonary atresia, confluent pulmonary branches connected to the pulmonary artery, and multiple aortopulmonary collateral arteries (MAPCAs). Reproduced from Ref. [78] with permission of Elsevier, ©2015. (b) 3D-printed partial hand prosthesis [83]. (c) Adjustable stiffness ankle-foot orthosis [19]. (d) Two printed replicas of PLA surgical prototypes. Reproduced from Ref. [20] with permission of Elsevier, ©2014.

could produce cost-efficient and functional prosthetics for amputees. This development would inevitably affect the future market for orthotics, including both large and mid-sized commercial companies.

Herbert et al. [82] developed a simple prosthetic foot with AM, using an efficient and simple fabrication technology that patients were found to be comfortable with. Zuniga et al. [83] prepared a low-cost 3D-printed hand for children with upper-limb reductions (Fig. 5(b) [83]). Subsequent survey results indicated that the prosthetic hand could have a positive impact on children's quality of life in the context of multiple activities at home and at school.

4.2.2. Orthoses

AM has demonstrated its capability to fabricate custom foot orthoses, ankle-foot orthoses (Fig. 5(c) [19]), and wrist splints [84] with good fit and adequate strength in limited clinical assessments. However, multiple barriers remain to be dealt with to enable the adoption of AM in the field of orthotics. These barriers include: a lack of clinical and design interfaces for an AM system [85]; uneconomic throughput and material cost; and limited material strength [86]. Multiple software platforms are being applied in research to process the 3D geometry of an orthosis. With the goal of realizing these geometries in an effective manner, a software platform has been made specifically for the AM of orthotics. AM can also increase the aestheticism, complexity, and functionality of the realized components, thus overcoming clinical barriers to better efficacy and fit, and enabling a faster delivery time (e.g., same-day visits). Fabrication cost and time are viewed as the two major barriers to the application of AM in orthoses. In fact, AM requires a relatively high initial investment in equipment. As the AM industry and AM technologies improve, however, it is expected that the price of AM equipment will decrease, while the material deposition rate increases. The application of AM techniques can in turn generate better design. For example, sparse structures and the optimization of topology will guarantee that a material is applied in an effective way. Moreover, it is easy to incorporate design tools into the workflow of orthotists. Durability and safety are extremely important in orthoses, which are applied under repeated loading and require both fatigue strength and ultimate strength. Although the majority of studies on the AM of orthoses have been carried out under laboratory conditions, there is need for long-term research to explore achievable durability. For example, thermoplastic materials can be reinforced with carbon fibers [87] in order to obtain more robust and durable components.

4.2.3. Surgical tools

Advancements in radiological imaging have allowed patient-anatomy-based CAD reconstructions to be obtained, which offer patient-specific design and fabrication, as well as customized surgical devices. At present, most surgical equipment is designed to be effective for a wide range of patients, albeit in a largely unspecific way. Nonetheless, unique anatomical features or extremely complicated medical processes can benefit from customized devices that permit a more controlled and simplified operation, which decreases the risk of complications [88]. AM can be used not only to produce efficient devices by quickly transforming a CAD design into usable tools to meet the continuously increasing demands of large-scale organizations such as hospital operating rooms, but also to reduce the cost of tools. A study revealed that 3D-printed retractor based on PLA could perform in comparison with its stainless counterpart, at one tenth of the cost (Fig. 5(d) [20]). As long as the technology can be carried out on a large scale, such systems result in great cost saving. Even in extreme environments such as long-term space missions, 3D-printed surgical tools have proved effective [89]. In fact, the cost-efficiency of 3D-printed surgical devices in low-income countries and organizations makes such devices both feasible and extremely practical.

AM technology has been already used for the creation of personalized surgical operation tools. Navajas and ten Hove [90] reported an example of cooperating with the patient's operation via AM for customizing trocar-cannula fabrication of a transconjunctival vitrectomy, which is a procedure in which the gel-like material of the eye is substituted with saline solution. Under such circumstances, there is no change in the functionality of the trocar-cannula. However, with AM technology, the size of the trocar-cannula can be customized based on the surgical instruments used in this process. Walker et al. [91] developed a similar method for the design of measuring tools to estimate the probe size applied in a lumpectomy, which is a breast cancer removal procedure. The general design of the measuring tools, which have a handle with a sphere on top, is similar to that of a probe. However, with AM, the diameters of the spheres can be adjusted within the range of 1.5–5 cm, as determined by the needs of each patient. In this way, an appropriate probe can be selected while preventing the unnecessary sterilization of probes with the wrong size.

AM can also be applied to fabricate extra parts. Based on a study by Walter et al. [92], a cap can be added over a traditional colonoscope to improve the view of the instrument and to identify the presence of polyps in the colon. AM can be used to customize the size of the cap for various colonoscopies. Ko et al. [93] pointed out that the cap is added to the traditional shape of a gastroscope, and differs depending on the procedure to be implemented. For example, esophageal biopsies have been performed with a cap with a wide end. Steinemann et al. [94] customized a space holder to be inserted in order to expose the esophageal mucosa and assist in a novel laparoscopic surgical procedure aimed at resecting the distal esophageal mucosa.

Using AM, innovative instruments have been designed for treatment or to offer palliative care for various kinds of cancer [95]. A new type of cheap thermo-coagulator was introduced by Chen et al. [96] for the treatment of cervical neoplasia, which is an anomalous growth of cells in the female cervix. Meanwhile, an MRI-compatible device was proposed by Menikou et al. [97], which applied thermal ablation. In a study by Peikari et al. [98], the area of interest was placed in direct contact with a 3D-printed device for a brachytherapy. Dikici et al. [99] proposed a new device to implement a specific gynecological surgery that involved removing the uterus with a laparoscopic approach. Rugg et al. [100] used AM to fabricate a tailored handpiece to hold a scanning fiber endoscope, which is a specific instrument applied to obtain dental images without using X-rays. Traeger et al. [101] proposed a device to implant cell sheets after removing gastrointestinal tumors, which involved AM of the cell-sheet carrier. Last but not least, an individualized robot for minimally invasive surgery (overtube system) was presented by Zizer et al. [102] to make it suitable for a particular surgery during which a gastrointestinal tumor was removed and also performed on the laparoscopic environment to remove small kidney tumors [103].

5. Conclusions and prospects

In this article, we summarized the applications of AM in various biomedical areas. AM is becoming a widely accepted technique in medicine, as it offers patient-specific design, high complexity, on-demand and cost-effective fabrication, and high productivity. As shown in Table 1 [9,19,31–44,53,60,62–64,69,74–82,84–86,88], drugs designed using AM have controlled release kinetics and achieve good efficacy. Medical implants created by AM can improve the safety and accuracy of treatment. Through this advanced technology, preoperative models can help surgeons to

Table 1
Summary of the main characteristics, advantages and limitations, and challenges and future directions of AM technologies in clinical applications of pharmaceuticals, medical implants, and medical devices.

Clinical application	Main characteristics	Advantages	Limitations	Challenges and future directions	References
Oral drug	Produce oral drug with complicated structures and elaborate shapes	Incorporation of drug-loaded formulations or APIs; dose accuracy, convenience, and time-effectiveness	Technical and quality control limitations	Digital health	[9,31–41]
Transdermal drug	Exquisite precision has been leveraged for the manufacturing of automatically adaptable patches	High thermal stability, drug-loading capacity, and resolution; manipulation of the release kinetics of drugs	Technical and quality control limitations	Digital health	[42–44]
Hard-structure implants	Allow accurate control of the internal pore structure of porous architectures, and allow complex geometries to be manufactured with repeatability	Versatility, high precision, accuracy, surface finish, and structural integrity; suited for creating highly porous implants; durable	Implant failure	Enhance biocompatibility and function	[53,60,62]
Soft-structure implants	Recreating human structures within cell-compatible materials	Dramatically improved functions of the cells of organs	Major issues with the long-term viability of the cells and cell proliferation control	Toward finer and more complex structures	[63,64,69]
Diagnostic tools	Visualization of patient-specific organ anatomy	The amount of information has been dramatically increased by preoperative planning beyond the features of individual organs	Long printing time	Shorten printing time; improve the accuracy of diagnosis	[74–80]
Prostheses	Designed to achieve high strength-to-weight ratios	Require less material to achieve similar performance capabilities, potentially resource efficient	Functions and mobility	Long-term limb replacement	[81,82]
Orthoses	Fabricating custom foot orthoses, ankle-foot orthoses, and wrist splints	Good fit and adequate strength	A lack of clinical and design interface; uneconomic throughput and material cost; limited material strength	Durability and safety of orthoses	[19,84–86]
Surgical tools	Designing and fabricating patient-specific, customized surgical instruments	Allow for a more controlled and simplified operative experience; reduce the cost of tools	Modest performance	Improve performance by technological innovation	[88]

plan surgeries, and the generated surgical tools can help to solve certain surgical problems and shorten the operation time. Prostheses and orthoses provide patients with personalized devices to recover certain functions and improve their quality of life.

Although AM has been successfully used in many medical applications, there are still issues that need to be addressed, as summarized in Table 1 [9,19,31–44,53,60,62–64,69,74–82,84–86,88]. Optimization of the key processing parameters of AM and the development of a wider selection of biomaterials are necessary in the future.

Acknowledgements

This work is sponsored by the National Key R&D Program of China (2018YFB1105504) and the National Natural Science Foundation of China (81572093). This work is also supported by the funding support from Beijing Laboratory of Biomedical Materials and start-up fund from Beijing University of Chemical Technology.

Compliance with ethics guidelines

Chunxu Li, Dario Pisignano, Yu Zhao, and Jiajia Xue declare that they have no conflict of interest or financial conflicts to disclose.

References

[1] Sames WJ, List FA, Pannala S, Dehoff RR, Babu SS. The metallurgy and processing science of metal additive manufacturing. Int Mater Rev 2016;61(5):315–60.
[2] Zadpoor AA. Design for additive bio-manufacturing: from patient-specific medical devices to rationally designed meta-biomaterials. Int J Mol Sci 2017;18(8):1607.
[3] Hu Q, Sun XZ, Parmenter CDJ, Fay MW, Smith EF, Ranceet GA, et al. Additive manufacture of complex 3D Au-containing nanocomposites by simultaneous two-photon polymerisation and photoreduction. Sci Rep 2017;7:17150.
[4] Mchugh KJ, Nguyen TD, Linehan AR, Yang D, Behrens AM, Rose S, et al. Fabrication of fillable microparticles and other complex 3D microstructures. Science 2017;357(6356):1138–42.
[5] Chen RK, Jin Y, Wensman J, Shih A. Additive manufacturing of custom orthoses and prostheses—a review. Addit Manuf 2016;12:77–89.
[6] Cuellar JS, Smit G, Zadpoor AA, Breedveld P. Ten guidelines for the design of non-assembly mechanisms: the case of 3D-printed prosthetic hands. Proc Inst Mech Eng H 2018;232(9):962–71.
[7] Technical considerations for additive manufactured medical devices—guidance for industry and food and drug administration staff [Internet]. Washington, DC: United States Food and Drug Administration; 2017 Dec 5 [cited 2019 Aug 15]. Available from: https://www.fda.gov/media/97633/download.
[8] Jones DB, Sung R, Weinberg C, Korelitz T, Andrews R. Three-dimensional modeling may improve surgical education and clinical practice. Surg Innov 2016;23(2):189–95.
[9] Fina F, Goyanes A, Madla CM, Awad A, Trenfield SJ, Kuek JM, et al. 3D printing of drug-loaded gyroid lattices using selective laser sintering. Int J Pharm 2018;547(1–2):44–52.
[10] Goyanes A, Scarpa M, Kamlow M, Gaisford S, Basit AW, Orlub M. Patient acceptability of 3D printed medicines. Int J Pharm 2017;530(1–2):71–8.
[11] Feinberg AW, Miller JS. Progress in three-dimensional bioprinting. MRS Bull 2017;42(8):557–62.
[12] Guzzi EA, Tibbitt MW. Additive manufacturing of precision biomaterials. Adv Mater 2019;32(13):1901994.
[13] Guzzi EA, Bovone G, Tibbitt MW. Universal nanocarrier ink platform for biomaterials additive manufacturing. Small 2019;15(1):1905421.
[14] Levato R, Jungst T, Scheuring RG, Blunk T, Groll J, Malda J, et al. From shape to function: the next step in bioprinting. Adv Mater 2020;32(12):1906423.
[15] Gebhardt A, Schmidt FM, Hötter JS, Sokalla W, Sokalla P. Additive manufacturing by selective laser melting the realizer desktop machine and its application for the dental industry. Phys Procedia 2010;5:543–9.
[16] Novakov T, Jackson MJ, Robinson GM, Ahmed W, Phoenix DA. Laser sintering of metallic medical materials—a review. Int J Adv Manuf Technol 2017;93(5–8):2723–52.
[17] Marga F, Jakab K, Khatiwala C, Shepherd B, Dorfman S, Hubbard B, et al. Toward engineering functional organ modules by additive manufacturing. Biofabrication 2012;4(2):022001.

[18] Chae MP, Rozen WM, McMenamin PG, Findlay MW, Spychal RT, Hunter-Smith DJ. Emerging applications of bedside 3D printing in plastic surgery. Front Surg 2015;2:25.

[19] Telfer S, Pallari J, Munguia J, Dalgarno K, McGeough M, Woodburn J. Embracing additive manufacture: implications for foot and ankle orthosis design. BMC Musculoskelet Disord 2012;13:84.

[20] Rankin TM, Giovinco NA, Cucher DJ, Watts G, Hurwitz B, Armstrong DG. Three-dimensional printing surgical instruments: are we there yet? J Surg Res 2014;189(2):193–7.

[21] McGurk M, Amis AA, Potamianos P, Goodger NM. Rapid prototyping techniques for anatomical modelling in medicine. Ann R Coll Surg Engl 1997;79(3):169–74.

[22] Kurenov SN, Ionita C, Sammons D, Demmy TL. Three-dimensional printing to facilitate anatomic study, device development, simulation, and planning in thoracic surgery. J Thorac Cardiovasc Surg 2015;149(4):973–9.

[23] Sun YJ, Soh S. Printing tablets with fully customizable release profiles for personalized medicine. Adv Mater 2015;27(47):7847–53.

[24] Lim SH, Kathuria H, Tan JJY, Kang L. 3D printed drug delivery and testing systems—a passing fad or the future? Adv Drug Deliv Rev 2018;132:139–68.

[25] Kollamaram G, Croker DM, Walker GM, Goyanes A, Basitbc AW, Gaisford S. Low temperature fused deposition modeling (FDM) 3D printing of thermolabile drugs. Int J Pharm 2018;545(1–2):144–52.

[26] Louzao I, Koch B, Taresco V, Ruiz-Cantu L, Irvine DJ, Roberts CJ, et al. Identification of novel "inks" for 3D printing using high-throughput screening: bioresorbable photocurable polymers for controlled drug delivery. ACS Appl Mater Interfaces 2018;10(8):6841–8.

[27] Melocchi A, Parietti F, Maccagnan S, Ortenzi MA, Antenucci S, Briatico-Vangosa F, et al. Industrial development of a 3D-printed nutraceutical delivery platform in the form of a multicompartment HPC capsule. AAPS PharmSciTech 2018;19(8):3343–54.

[28] Goyanes A, Allahham N, Trenfield SJ, Stoyanovd E, Gaisford S, Basit AW. Direct powder extrusion 3D printing: fabrication of drug products using a novel single-step process. Int J Pharm 2019;567:118471.

[29] Vithani K, Goyanes A, Jannin V, Basit AW, Gaisford S, Boyd BJ. An overview of 3D printing technologies for soft materials and potential opportunities for lipid-based drug delivery systems. Pharm Res 2018;36(1):4.

[30] Pereira BC, Isreb A, Forbes RT, Dores F, Habashy R, Petit JB, et al. 'Temporary Plasticiser': a novel solution to fabricate 3D printed patient-centred cardiovascular 'polypill' architectures. Eur J Pharm Biopharm 2019;135:94–103.

[31] Awad A, Fina F, Trenfield SJ, Patel P, Goyanes A, Gaisford S, et al. 3D printed pellets (miniprintlets): a novel, multi-drug, controlled release platform technology. Pharm 2019;11(4):148.

[32] Li Q, Guan X, Cui M, Zhu Z, Chen K, Wen H, et al. Preparation and investigation of novel gastro-floating tablets with 3D extrusion-based printing. Int J Pharm 2018;535(1–2):325–32.

[33] Arafat B, Wojsz M, Isreb A, Forbes RT, Isreb M, Ahmed W, et al. Tablet fragmentation without a disintegrant: a novel design approach for accelerating disintegration and drug release from 3D printed cellulosic tablets. Eur J Pharm Sci 2018;118:191–9.

[34] Kyobula M, Adedeji A, Alexander MR, Saleh E, Wildman R, Ashcroft I, et al. 3D inkjet printing of tablets exploiting bespoke complex geometries for controlled and tuneable drug release. J Control Release 2017;261:207–15.

[35] Verstraete G, Samaro A, Grymonpré W, Vanhoorne V, Van Snick B, Booneet MN, et al. 3D printing of high drug loaded dosage forms using thermoplastic polyurethanes. Int J Pharm 2018;536(1):318–25.

[36] Tagami T, Nagata N, Hayashi N, Ogawa E, Fukushige K, Sakai N, et al. Defined drug release from 3D-printed composite tablets consisting of drugloaded polyvinylalcohol and a water-soluble or water-insoluble polymer filler. Int J Pharm 2018;543(1–2):361–7.

[37] Haring AP, Tong Y, Halper J, Johnson BN. Programming of multicomponent temporal release profiles in 3D printed polypills via core-shell, multilayer, and gradient concentration profiles. Adv Healthc Mater 2018;7(16):1800213.

[38] Maroni A, Melocchi A, Parietti F, Foppoli A, Zema L, Gazzaniga A. 3D printed multi-compartment capsular devices for two-pulse oral drug delivery. J Control Release 2017;268:10–8.

[39] Gioumouxouzis CI, Chatzitaki AT, Karavasili C, Katsamenis OL, Tzetzis D, Mystiridou E, et al. Controlled release of 5-fluorouracil from alginate beads encapsulated in 3D printed pH-responsive solid dosage forms. AAPS PharmSciTech 2018;19(8):3362–75.

[40] Beck RCR, Chaves PS, Goyanes A, Vukosavljevic B, Buanz A, Windbergs M, et al. 3D printed tablets loaded with polymeric nanocapsules: an innovative approach to produce customized drug delivery systems. Int J Pharm 2017;528(1–2):268–79.

[41] Markl D, Zeitler JA, Rasch C, Michaelsen MH, Müllertz A, Rantanen J, et al. Analysis of 3D prints by X-ray computed microtomography and terahertz pulsed imaging. Pharm Res 2017;34(5):1037–52.

[42] Okwuosa TC, Soares C, Gollwitzer V, Habashy R, Timmins P, Alhnan MA. On demand manufacturing of patient-specific liquid capsules via coordinated 3D printing and liquid dispensing. Eur J Pharm Sci 2018;118:134–43.

[43] Kwak MK, Jeong HE, Suh KY. Rational design and enhanced biocompatibility of a dry adhesive medical skin patch. Adv Mater 2011;23(34):3949–53.

[44] Goyanes A, Det-Amornrat U, Wang J, Basit AW, Gaisford S. 3D scanning and 3D printing as innovative technologies for fabricating personalized topical drug delivery systems. J Control Release 2016;234:41–8.

[45] Muwaffak Z, Goyanes A, Clark V, Basit AW, Hiltona ST, Gaisford S. Patient-specific 3D scanned and 3D printed antimicrobial polycaprolactone wound dressings. Int J Pharm 2017;527(1–2):161–70.

[46] Wang JC, Zheng H, Chang MW, Ahmad Z, Li JS. Preparation of active 3D film patches via aligned fiber electrohydrodynamic (EHD) printing. Sci Rep 2017;7:43924.

[47] Ye Y, Yu J, Wang C, Nguyen NY, Walker GM, Buse JB, et al. Microneedles integrated with pancreatic cells and synthetic glucose-signal amplifiers for smart insulin delivery. Adv Mater 2016;28(16):3115–21.

[48] Pere CPP, Economidou SN, Lall G, Ziraud C, Boateng JS, Alexander BD, et al. 3D printed microneedles for insulin skin delivery. Int J Pharm 2018;544(2):425–32.

[49] Caudill CL, Perry JL, Tian S, Luft JC, DeSimone JM. Spatially controlled coating of continuous liquid interface production microneedles for transdermal protein delivery. J Control Release 2018;284:122–32.

[50] Luzuriaga MA, Berry DR, Reagan JC, Smaldone RA, Gassensmith JJ. Biodegradable 3D printed polymer microneedles for transdermal drug delivery. Lab Chip 2018;18(8):1223–30.

[51] Lim SH, Ng JY, Kang L. Three-dimensional printing of a microneedle array on personalized curved surfaces for dual-pronged treatment of trigger finger. Biofabrication 2017;9(1):015010.

[52] Sahlabadi M, Hutapea P. Novel design of honeybee-inspired needles for percutaneous procedure. Bioinspir Biomim 2018;13(3):036013.

[53] Yan C, Hao L, Hussein A, Young P. Ti–6Al–4V triply periodic minimal surface structures for bone implants fabricated via selective laser melting. J Mech Behav Biomed Mater 2015;51:61–73.

[54] Haglin JM, Eltorai AEM, Gil JA, Marcaccio SE, Botero-Hincapie J, Daniels AH. Patient-specific orthopaedic implants. Orthop Surg 2016;8(4):417–24.

[55] Zhang D, Qiu D, Gibson MA, Zheng Y, Fraser HL, StJohn DH, et al. Additive manufacturing of ultrafine-grained high-strength titanium alloys. Nature 2019;576(7785):91–5.

[56] Chang B, Song W, Han T, Yan J, Li F, Zhao L, et al. Influence of pore size of porous titanium fabricated by vacuum diffusion bonding of titanium meshes on cell penetration and bone ingrowth. Acta Biomater 2016;33:311–21.

[57] Barba A, Diez-Escudero A, Maazouz Y, Rappe K, Espanol M, Montufar EB, et al. Osteoinduction by foamed and 3D-printed calcium phosphate scaffolds: effect of nanostructure and pore architecture. ACS Appl Mater Interfaces 2017;9(48):41722–36.

[58] Bijukumar DR, McGeehan C, Mathew MT. Regenerative medicine strategies in biomedical implants. Curr Osteoporos Rep 2018;16(3):236–45.

[59] Cipitria A, Reichert JC, Epari DR, Saifzadeh S, Berner A, Schell H, et al. Polycaprolactone scaffold and reduced rhBMP-7 dose for the regeneration of critical-sized defects in sheep tibiae. Biomaterials 2013;34(38):9960–8.

[60] Ren Y, Zou Y, Liu Y, Zhou X, Ma J, Zhao D, et al. Synthesis of orthogonally assembled 3D cross-stacked metal oxide semiconducting nanowires. Nat Mater 2020;19:203–11.

[61] Chen SG, Yang J, Jia YG, Lu B, Ren L. TiO_2 and PEEK reinforced 3D printing PMMA composite resin for dental denture base applications. Nanomaterials 2019;9(7):1049.

[62] Tahayeri A, Morgan M, Fugolin AP, Bompolaki D, Athirasala A, Pfeifer CS, et al. 3D printed versus conventionally cured provisional crown and bridge dental materials. Dent Mater 2018;34(2):192–200.

[63] Grigoryan B, Paulsen SJ, Corbett DC, Sazer DW, Fortin CL, Zaita AJ, et al. Multivascular networks and functional intravascular topologies within biocompatible hydrogels. Science 2019;364(6439):458–64.

[64] Homan KA, Gupta N, Kroll KT, Kolesky DB, Skylar-Scott M, Miyoshi T, et al. Flow-enhanced vascularization and maturation of kidney organoids *in vitro*. Nat Methods 2019;16(3):255–62.

[65] Johnson BN, Lancaster KZ, Hogue IB, Meng F, Kong YL, Enquist LW, et al. 3D printed nervous system on a chip. Lab Chip 2016;16(8):1393–400.

[66] Melhem MR, Park J, Knapp L, Reinkensmeyer L, Cvetkovic C, Flewellyn J, et al. 3D printed stem-cell-laden, microchanneled hydrogel patch for the enhanced release of cell-secreting factors and treatment of myocardial infarctions. ACS Biomater Sci Eng 2017;3(9):1980–7.

[67] Lee H, Cho DW. One-step fabrication of an organ-on-a-chip with spatial heterogeneity using a 3D bioprinting technology. Lab Chip 2016;16(14):2618–25.

[68] Sciancalepore AG, Sallustio F, Girardo S, Passione LG, Camposeo A, Mele E, et al. A bioartificial renal tubule device embedding human renal stem/progenitor cells. PLoS ONE 2014;9(1):e87496.

[69] Cui H, Nowicki M, Fisher JP, Zhang LG. 3D bioprinting for organ regeneration. Adv Healthc Mater 2017;6(1):1601118.

[70] He Y, Xue G, Fu J. Fabrication of low cost soft tissue prostheses with the desktop 3D printer. Sci Rep 2014;4:6973.

[71] Unkovskiy A, Spintzyk S, Brom J, Huettig F, Keutel C. Direct 3D printing of silicone facial prostheses: a preliminary experience in digital workflow. J Prosthet Dent 2018;120(2):303–8.

[72] Zopf DA, Hollister SJ, Nelson ME, Ohye RG, Green GE. Bioresorbable airway splint created with a three-dimensional printer. N Engl J Med 2013;368(21):2043–5.

[73] Qiu K, Haghiashtiani G, McAlpine MC. 3D printed organ models for surgical applications. Annu Rev Anal Chem 2018;11(1):287–306.

[74] Zein NN, Hanouneh IA, Bishop PD, Samaan M, Eghtesad B, Quintini C, et al. Three-dimensional print of a liver for preoperative planning in living donor liver transplantation. Liver Transpl 2013;19(12):1304–10.

[75] Silberstein JL, Maddox MM, Dorsey P, Feibus A, Thomas R, Lee BR. Physical models of renal malignancies using standard cross-sectional imaging and 3-dimensional printers: a pilot study. Urology 2014;84(2):268–73.
[76] Witowski JS, Pedziwiatr M, Major P, Budzyński A. Cost-effective, personalized, 3D-printed liver model for preoperative planning before laparoscopic liver hemihepatectomy for colorectal cancer metastases. Int J Comput Assist Radiol Surg 2017;12(12):2047–54.
[77] Cheung CL, Looi T, Lendvay TS, Drake JM, Farhat WA. Use of 3-dimensional printing technology and silicone modeling in surgical simulation: development and face validation in pediatric laparoscopic pyeloplasty. J Surg Educ 2014;71(5):762–7.
[78] Ryan JR, Moe TG, Richardson R, Frakes DH, Nigro JJ, Pophal S. A novel approach to neonatal management of tetralogy of fallot, with pulmonary atresia, and multiple aortopulmonary collaterals. JACC Cardiovasc Imaging 2015;8(1):103–4.
[79] Valverde I. Three-dimensional printed cardiac models: applications in the field of medical education, cardiovascular surgery, and structural heart interventions. Rev Esp Cardiol 2017;70(4):282–91.
[80] Marks M, Alexander A, Matsumoto J, Matsumoto J, Morris J, Petersen R, et al. Creating three dimensional models of Alzheimer's disease. 3D Print Med 2017;3(13):1–11.
[81] Pham MS, Liu C, Todd I, Lertthanasarn J. Damage-tolerant architected materials inspired by crystal microstructure. Nature 2019;565 (7739):305–11.
[82] Herbert N, Simpson D, Spence WD, Ion W. A preliminary investigation into the development of 3D printing of prosthetic sockets. J Rehabil Res Dev 2005;42(2):141–6.
[83] Zuniga JM, Dimitrios K, Peck JL, Srivastava R, Pierce JE, Dudley DR, et al. Coactivation index of children with congenital upper limb reduction deficiencies before and after using a wrist-driven 3D printed partial hand prosthesis. J Neuroeng Rehabil 2018;15:48.
[84] Paterson AM, Bibb R, Campbell RI, Bingham G. Comparing additive manufacturing technologies for customised wrist splints. Rapid Prototyp J 2015;21(3):230–43.
[85] Rogers B, Bosker GW, Crawford RH, Faustini MC, Neptune RR, Walden G, et al. Advanced trans-tibial socket fabrication using selective laser sintering. Prosthet Orthot Int 2007;31(1):88–100.
[86] Hsu LH, Huang GF, Lu CT, Hong TY, Liu SH. The development of a rapid prototyping prosthetic socket coated with a resin layer for transtibial amputees. Prosthet Orthot Int 2010;34(1):37–45.
[87] Christ S, Schnabel M, Vorndran E, Groll J, Gbureck U. Fiber reinforcement during 3D printing. Mater Lett 2015;139:165–8.
[88] Liu K, Zhang Q, Li X, Zhao C, Quan X, Zhao R, et al. Preliminary application of a multi-level 3D printing drill guide template for pedicle screw placement in severe and rigid scoliosis. Eur Spine J 2017;26(6):1684–9.
[89] Wong JY, Pfahnl AC. 3D printing of surgical instruments for long-duration space missions. Aviat Space Environ Med 2014;85(7):758–63.
[90] Navajas EV, ten Hove M. Three-dimensional printing of a transconjunctival vitrectomy trocar-cannula system. Ophthalmologica 2017;237(2):119–22.
[91] Walker JG, Licqurish S, Chiang PPC, Pirotta M, Emery JD. Cancer risk assessment tools in primary care: a systematic review of randomized controlled. Ann Fam Med 2015;13(5):480–9.
[92] Walter BM, Hann A, Frank R, Meining A. A 3D-printed cap with sideoptics for colonoscopy: a randomized *ex vivo* study. Endoscopy 2017;49(8):808–12.
[93] Ko WJ, Song GW, Hong SP, Kwon C, Hahm KB, Cho JY. Novel 3D-printing technique for caps to enable tailored therapeutic endoscopy. Dig Endosc 2016;28(2):131–8.
[94] Steinemann DC, Müller PC, Apitz M, Nickel F, Kenngott HG, Müller-Stich BP, et al. An *ad hoc* three dimensionally printed tool facilitates intraesophageal suturing in experimental surgery. J Surg Res 2018;223:87–93.
[95] Epaminonda E, Drakos T, Kalogirou C, Theodoulou M, Yiallouras C, Damianou C. MRI guided focused ultrasound robotic system for the treatment of gynaecological tumors. Int J Med Robot Comput Assist Surg 2016;12 (1):46–52.
[96] Chen J, Pickett T, Langell A, Trane A, Charlesworth B, Loken K, et al. Industry-academic partnerships: an approach to accelerate innovation. J Surg Res 2016;205(1):228–33.
[97] Menikou G, Yiallouras C, Yiannakou M, Damianou C. MRI-guided focused ultrasound robotic system for the treatment of bone cancer. Int J Med Robot Comput Assist Surg 2017;13(1):e1753.
[98] Peikari M, Chen TK, Burdette EC, Fichtinger G. Section-thickness profiling for brachytherapy ultrasound guidance. In: Proceedings of the Conference on Medical Imaging 2011: Visualization, Image-Guided Procedures, and Modeling; 2011 Feb 13–15; Lake Buena Vista, FL, USA; 2011.
[99] Dikici S, Dikici BA, Eser H, Gezgin E, Başer Ö, Şahin S, et al. Development of a 2-DOF uterine manipulator with LED illumination system as a new transvaginal uterus amputation device for gynecological surgeries. Minim Invasive Ther Allied Technol 2018;27(3):177–85.
[100] Rugg AL, Nelson LY, Timoshchuk MAI, Seibel EJ. Design and fabrication of a disposable dental handpiece for clinical use of a new laser-based therapy-monitoring system. J Med Device 2016;10(1):011005.
[101] Traeger MF, Roppenecker DB, Leininger MR, Schnoes F, Lueth TC. Design of a spine-inspired kinematic for the guidance of flexible instruments in minimally invasive surgery. In: Proceedings of the IEEE/RSJ International Conference on Intelligent Robots and Systems; 2014 Sep 14–18; Chicago, IL, USA; 2014.
[102] Zizer E, Roppenecker D, Helmes F, Hafner S, Krieger Y, Lüth T, et al. A new 3D-printed overtube system for endoscopic submucosal dissection: first results of a randomized study in a porcine model. Endoscopy 2016;48(8):762–5.
[103] Krieger YS, Roppenecker DB, Stolzenburg JU, Lueth TC. First step towards an automated designed multi-arm snake-like robot for minimally invasive surgery. In: Proceedings of the 6th IEEE International Conference on Biomedical Robotics and Biomechatronics (BioRob); 2016 Jun 26–29; Singapore; 2016.