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3D printing for the development of implantable devices for cardiovascular disease treatment

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First draft submitted: 22 March 2022; Accepted for publication: 30 June 2022; Published online: 24 August 2022

Keywords: 3D printing • additive manufacturing • bioprinting • cardiovascular disease • stent • vascular graft

Additive manufacturing (also known as 3D printing) has proven to be an effective technology for pharmaceutical and biomedical applications [1,2]. Additive manufacturing is a family of technologies used to prepare 3D objects by adding layers of material in a sequential way [1]. Typically, 3D-printing techniques are classified according to the mechanism followed to add the layers of materials including photopolymerization, sintering or extrusion, among many others [1]. Accordingly, additive manufacturing offers a high degree of flexibility in terms of techniques and materials. In the last decade, there has been growing interest in the use of additive manufacturing for pharmaceutical and medical applications [1,2]. One of the key advantages over conventional methods of manufacturing is that additive manufacturing can be used to prepare dosage forms adapted to patients' needs [3]. In addition to its versatility, another factor that has contributed to the interest of the scientific community in 3D printing in research laboratories is its availability. Over the past decade, the price of certain types of 3D printers (mainly stereolithography and fused deposition modeling) has significantly dropped. Due to these factors, a wide range of dosage forms has been produced using 3D printing, including tablets, capsules and suppositories, among many other examples [4–6]. As a result of extensive work, the first 3D-printed pharmaceutical product (Spritam[®]) approved by the US FDA was introduced to the market in 2016 [7]. In addition to pharmaceutical products, 3D printing has also been used to fabricate medical devices such as implants for drug delivery, orthopedic prostheses, medicated catheters or cardiovascular stents, among many others [8–12]. This editorial is focused on 3D-printed medical devices for the treatment of cardiovascular diseases (CVDs).

CVD is an umbrella term used to define a set of diseases affecting the blood vessels and/or the heart [13]. Currently, CVD is the leading cause of death globally and contributes actively to a reduction in the quality of life of patients suffering from it [13]. A wide variety of therapeutic options are available to treat CVD, including surgical and pharmacological treatments [13]. Surgical procedures often involve the use of medical devices, such as vascular stents or synthetic vascular grafts [2]. As mentioned, the production of such devices can be accomplished using 3D-printing technology [2,14–16]. In this regard, 3D printing offers a high degree of flexibility, as devices can be adapted to the patient's anatomy, wherein the computer design can be attained using medical imaging

techniques such as computed tomography or MRI. The scientific literature includes several examples of 3D-printed implantable devices designed to treat CVD. These can be classified into medical devices (e.g., stents and vascular prostheses) and tissue engineering-based devices. The latter have gained interest in recent years due to the rapid development of 3D bioprinting.

3D-printed implantable devices used to treat cardiovascular diseases

Cardiovascular stents are heavily used to treat coronary artery disease. These devices are implanted in narrowed arteries to expand the lumen to ensure appropriate blood flow [10]. Cardiovascular stents are conventionally made of metal and, in some cases, are coated with different formulations to load drugs onto them [10]. In this way, antiproliferative or antiplatelet drugs can be released into the target site to prevent restenosis or the formation of blood clots [10]. The production of stents using additive manufacturing techniques has been extensively reported. These devices have been produced using a majority of 3D-printing techniques, including high-end equipment such as two-photon polymerization and the more affordable fused deposition modeling printers [10]. Although these devices are mainly produced for research purposes, some studies evaluated the use of 3D printing to produce implantable patient-specific stents in hospitals [17]. This could reduce the supply time from around 150 days to just 20 min. Stents produced via additive manufacturing have been successfully prepared using a wide variety of materials such as poly(caprolactone), poly(propylene), poly(lactic acid) and a variety of photo-crosslinkable resins. Some of these stents have shown comparable mechanical properties to commercially available stents. However, these devices have only been tested *in vitro* or using animal models. Therefore, more research is needed to ensure the safety and efficacy of these devices.

Vascular grafts are tubular prostheses used to redirect blood around a blocked artery within the heart. These grafts can be blood vessels harvested from the patient's leg or can be synthetic prostheses. Vascular grafts have been prepared using 3D printing. Mainly, stereolithography and extrusion-based additive manufacturing technologies have been used to prepare vascular grafts. These grafts are made of biodegradable polymers, such as poly(caprolactone) or poly(propylene fumarate) [14,18,19], or nonbiodegradable polymers, such as thermoplastic polyurethane [15,20]. The resulting prostheses present similar or superior mechanical properties compared with native blood vessels while supporting the growth of endothelial cells [14,18,20]. Additionally, drugs such as dipyridamole or acetylsalicylic acid can be combined with the polymers to obtain vascular grafts capable of preventing platelet adhesion [14,19,20]. Despite some of these devices being successfully tested in animal models showing that 3D-printed grafts maintained functionality for periods of at least 6 months [18], more work is needed before they can be used in clinical trials.

In addition to the production of solid devices like the ones previously described, there is growing interest in developing soft cell-laden materials mimicking biological tissue for 3D printing applications. This is also known as 3D bioprinting. The aim of this technology is to produce implants loaded with cells for tissue regeneration [21]. Cell-based repair and regeneration of healthy vascular cells/tissues is a major focus in regenerative medicine to improve CVD. Stem cell technologies are aiding in the advancement of regenerative medicine by providing patient-derived disease models of vascular cells. Due to the differentiation capabilities of stem cells, reprogramming technologies offer approaches to developing patient-specific disease models [22]. For this purpose, hydrogels such as gelatine or hyaluronic acid are used [21]. They are normally loaded with cells prior to the 3D-printing process, followed by the use of extrusion-based additive manufacturing to add layers of these gels. Due to the flow properties of these materials, in some cases, an extra crosslinking step is needed to maintain the structure of the printed object. In this case, modified polymers with reactive groups (e.g., methacrylate groups) and photoinitiators are required [21]. However, these compounds should be cytocompatible to maintain the integrity of the cells during the printing process. These types of materials can be 3D-printed using photopolymerization-based technologies. To date, a variety of 3D-printed cardiovascular tissues such as blood vessels and myocardium have been manufactured yielding tissues capable of cell adhesion, proliferation, differentiation and even cell migration. Nevertheless, this technology is still in development and more work is needed before fully functional 3D-printed tissues can be produced.

Future perspective

3D printing is a disruptive manufacturing technology that has shown great potential in several industries. Healthcare applications of this technology are being extensively studied by researchers and companies. Due to these substantial efforts, the FDA has approved several 3D-printed pharmaceutical and medical devices in recent years, such as Spiritam, a rapidly dissolving levetiracetam tablet and FLX™ implants to support the spine. One of the key benefits of 3D printing is its ability to be applied at the point of care, allowing the development of personalized implants and

therapies. Pioneering works in this area have been reported for the production of customized oral dosage forms and cranial plates in hospitals and clinics. In addition to these applications, there is a clear interest in the development of bespoke devices for the treatment of CVD, as well as cell-loaded implants for tissue regeneration. The use of a personalized approach allows for site-specific drug delivery with proper adhesion while reducing adverse events and achieving efficient treatment. This is particularly important in CVD, as a large number of the drugs used for the treatment of CVD, such as digoxin or warfarin among many others, have a narrow therapeutic index (i.e., a small range between the effective and toxic dose), making it crucial to control the drug dose based on the patient's genetic makeup and disease condition.

Despite the promising clinical applications of 3D printing, there remain some regulatory issues relating to quality control and quality assurance of 3D-printed devices that must be addressed before their adoption. Additionally, some of the materials used for 3D-printing applications are not FDA approved, limiting the applicability of some of these technologies. Another concern with the development of implantable devices is their sterility, wherein they must be prepared under aseptic conditions or sterilized prior to their implantation. Accordingly, more studies on the effect of sterilization conditions on 3D-printed materials are needed. The FDA is working closely with researchers and, accordingly, has provided some guidance for the development of medical devices using 3D-printing technologies. In a similar manner, the Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom will be modifying regulations to include tissue-engineered products and 3D printing at the point of care. This is just the beginning, as the conversation between regulatory agencies and different pharmaceutical stakeholders is taking place to address challenges and concerns relating to innovative pharmaceutical approaches. Accordingly, it is likely that more 3D-printed medical device products will be released to the market in the next few years.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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