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3D printing of bioactive materials for drug delivery applications

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ABSTRACT

Introduction: Three-dimensional (3D) printing, also known as additive manufacturing (AM), is a modern technique/technology, which makes it possible to construct 3D objects from computer-aided design (CAD) digital models. This technology can be used in the progress of drug delivery systems, where porosity has played important role in attaining an acceptable level of biocompatibility and biodegradability with improved therapeutic effects. 3D printing may also provide the user possibility to control the dosage of each ingredient in order to a specific purpose, and makes it probable to improve the formulation of drug delivery systems.

Areas covered: This article covers the 3D printing technologies, bioactive materials including natural and synthetic polymers as well as some ceramics and minerals and their roles in drug delivery systems.

Expert opinion: This technology is feasible to fabricate drug products by incorporating multiple drugs in different parts in such a mode that these drugs can release from the section at a predetermined rate. Furthermore, this 3D printing technology has the potential to transform personalized therapy to various age-groups by design flexibility and precise dosing. In recent years, the potential use of this technology can be realized in a clinical situation where patients will acquire individualized medicine as per their requirement.

1. Introduction

Three-dimensional (3D) printing, also known as additive manufacturing (AM), is a modern technique/technology, which makes it possible to construct 3D objects from computer-aided design (CAD) digital models\textsuperscript{[1–3]} (Supporting Information). As a unique feature of the 3D printing process over conventional techniques like thermoforming and injection molding, it makes it possible to produce products with different sizes or even anomalous shapes having dimensions ranging from some micrometers to centimeters and meters\textsuperscript{[1]}. Nevertheless, each 3D printing technique has its inherent accuracy of printing with advantages or disadvantages, which determines the quality of the resulting products. For instance, the resolution, layer bonding, and surface finish are some of the major challenges associated with 3D micro-scale printing; which sometimes necessitate the use of a post-processing modification such as sintering techniques or incorporation of complementary additives\textsuperscript{[4]}. There have also been attempts to make 3D printing alive by giving the potential for changing its configuration and making it stimuli-responsive, known as 4D printing technology\textsuperscript{[5]}. 3D printing has shown notable potential in the medicine and pharmaceutical industry. Regarding pharmaceutical applications, 3D printing can be served to produce various forms of DDSs\textsuperscript{[6,7]}. The importance of 3D printing in the pharmaceutical industry has boomed by the approval of the first 3D-printed tablet Spritam by the Food and Drug Administration (FDA) for the treatment of seizures\textsuperscript{[8]}. 3D printing facilitates the production of implants or bio-scaffolds with complex geometries under permanent exposure to the tissues and enables repair, regeneration, or replacement of a deactivated tissue/organ. The selection of biomaterial for the fabrication of bio-scaffolds depends on the type and function of the tissue or organ\textsuperscript{[9]}. From an economic point of view, 3D printing is known as an affordable method that eliminates additional production costs like finishing and trimming\textsuperscript{[10]}. It provides more advantages over traditional manufacturing techniques, such as acceleration.
of production, reduction of waste materials, high degree of geometric freedom, and automation of the fabrication process [11]. 3D printing makes possible the regeneration of complex tissues and organs in view of its precise nature as well as the ability of printing geometrically complicated biomaterials [12]. In recent years, a continued attempt has been made to conduct 3D printing of bioactive materials including ceramics [13], polymer composites and nanocomposites [14], battery electrodes [15], and membranes [16]. 3D printing has been progressively applied in the development of DDSs, where porosity and bioactivity have played key roles in achieving an acceptable level of biocompatibility and biodegradability with enhanced therapeutic effects compared to traditional systems. Although the number of reports, review papers, and patents on DDS derived from 3D printed materials follow a sharp ascending trend, there is a lack of a comprehensive and systematic classification, and also the interpretation of the performance of the used biomaterials, devices, and recent achievements. Herein, we review the literature on 3D printing of bioactive and porous materials in drug delivery applications.

2. 3D printing techniques used for drug products

There are several possible ways for 3D printing of materials depending on the application [7,17,18]. For DDSs, useful and innovative printing techniques are usually powder-based printing, powder bed fusion (PBF) such as selective laser melting (SLM), selective laser sintering (SLS), electron beam melting (EBM), extrusion-based printing (EBP) such as fused deposition modeling (FDM), pressure-assisted microsyringe (PAM), photopolymerization-based printing (PBP) such as stereolithography (SLA), digital light processing (DLP), and inkjet printing (IP). Substances fabricated by 3D printing procedures can be of nearly any shape. They are usually formed using digital model data from a 3D, one of the most public file kinds that 3D printers can read. More details of the 3D printing techniques are given in the Supporting Information. Table 1 shows a comparison between the current 3D printing techniques.

3. Types of drug release models used for 3D printing technologies

Drug release is a process by which a drug leaves a dosage form and is exposed to absorption, distribution, metabolism, and excretion (ADME), eventually becoming available for pharmacological activity. Several kinetics models explain drug dissolution from immediate and modified release dosage forms for products from 3D printing technologies. DDSs can control the rate/location of the release of a particular drug. They can

<table>
<thead>
<tr>
<th>Techniques</th>
<th>Polymer used</th>
<th>Advantages</th>
<th>Limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrusion-based printing (EBP)</td>
<td>Fused deposition modeling (FDM)</td>
<td>● Low cost</td>
<td>● Slow speed</td>
</tr>
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<td></td>
<td>Pressure-assisted microsyringe (PAM)</td>
<td>● Simplicity</td>
<td>● Need a post processing</td>
</tr>
<tr>
<td>Photopolymerization-based printing (PBP)</td>
<td>Stereolithography (SLA)</td>
<td>● High accuracy</td>
<td>● Need a post processing</td>
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<tr>
<td></td>
<td>Digital light processing (DLP)</td>
<td>● High resolution</td>
<td>● Drug instability</td>
</tr>
<tr>
<td>Powder bed fusion (PBF)</td>
<td>Selective laser melting (SLM)</td>
<td>● No distinct binder and melt phases</td>
<td>● Limit in range of material</td>
</tr>
<tr>
<td></td>
<td>Selective laser sintering (SLS)</td>
<td>● Easy removal of support powder</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Electron beam melting (EBM)</td>
<td>● Suitable strength</td>
<td></td>
</tr>
<tr>
<td>Inkjet printing (IP)</td>
<td>Continuous inkjet (CIJ)/drop-on-demand (DOD)</td>
<td>● High resolution and precision</td>
<td>● Not suitable for well-controlled composite materials,</td>
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<td></td>
<td>● fast production</td>
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<td>● Requirest postprocessing</td>
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<td>● Lower accuracy than laser sinteringexpensive</td>
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Table 1. Advantages and limitations of various 3D printing techniques.
be classified into two general categories: 1. immediate-release and 2. modified-release.

### 3.1. Immediate-release

Many dosage forms are intended to release the drug immediately after administration. These types of drugs are beneficial if a fast onset of action is needed for therapeutic purposes. For instance, painkiller tablets should disintegrate quickly in GIT to allow a fast uptake into the body. Immediate-release dosage forms usually release the drug in a first-order kinetics profile. This means that the drug releases very quickly at first and then by passing through the mucosal membrane into the body, it can reach the highest plasma level in a relatively short time [19]. Different literatures were published in which modified release solid dosage forms, were fabricated with FDM-3D printing. In these researches, drug release from 3D dosage forms was controlled. Though, it is comparatively problematic to attain an immediate release solid dosage form through FDM-3D printing; since the HME combined FDM procedure contains melting and solidification steps. As a result, the formed solid dosage form, which showed a polymer common structure, becomes hard and rigid. However, immediate release can be extended to dosage forms made by FDM62 3D printing, including the preparation of 3D dosage forms using instant polymers, the construction of special designs such as tablets containing 64 gaps, and the addition of other excipients such as decomposers to Medicinal formulations, especially for commercially uses [20,21].

### 3.2. Modified-release

The modified-release is applied to define products that change the rate or the time of the release of the drug substance [19]. A modified-release dosage form is designed to deliver the active agent with a delay after its administration or for a prolonged period of time or to a specific location in the body. The reason is to achieve better patient compliance and desired therapeutic effect. FDM 3DP provides the opportunity of constructing oral dosage forms, including complex modified-release products. Modified-release dosage forms are formulations in which the drug-release properties of time and situation are selected to achieve therapeutic purposes not obtainable through common dosage forms. One example is modified-release of drug products such as delayed-release formulations where the drug is released with a delay after its entry [22]. There are various types of modified-release patterns including delayed-release, extended-release, sustained-release, and controlled-release.

#### 3.2.1. Delayed-release

Delayed-release dosage forms are defined as systems that are formulated to release the drug at a time other than immediately. The goal is to target the location of the drug release, e.g. in the small intestine or the colon and not in the stomach [19]. Delayed-release systems are usually applied to protect the drug from disintegration in the low pH media of the stomach or to protect the stomach from irritation through the drug. Therefore, polymers are often used to attain this aim. For example, the tablet or capsule is coated with a suitable polymer [19]. One of the challenges in clinical staff in hospitals is the personalizing gastric-resistant tablets is related with main challenges in order to clinical staff in hospitals. This work helps to construct gastric-resistant 3D printed tablets by FDM 3D printing [23]. The fabrication of an enteric coated tablet using a dual-nozzle single-step FDM printing technology, using PVP and methacrylic acid copolymer for core/shell structures, shows a delayed release of theophylline as a model drug from the enteric system. Here, filaments were compounded by a HME extruder, and CAD software was also used to fabricate a capsule-shaped core with a shell of increasing thicknesses (0.17, 0.3, 0.70, or 0.8 mm). Thus, this type of 3D printing can be used to synthesis of delayed release tablets. Other model drugs frequently accessible as gastric-resistant products were also arranged in this platform.

#### 3.2.2. Extended-release

For immediate-release profiles, frequent dosing with its associated compliance challenge is needed. Through extending the release time of a drug, the frequency of dosing can be decreased. Extended-release dosage forms allow the drug to be released over a prolonged period of time. This is especially important for the treatment of chronic diseases when patients need to take the medication for prolonged periods of time. Extended-release can be achieved by means of sustained- or controlled-release dosage forms [19,24]. The SSE-based 3D printing can be used for the formation of semi-solid tablets under RT conditions, which is caused in flexible dosage forms of theophylline showing extended-release pattern. The theophylline was loaded inside hydrogels formed of hydroxypropyl methylcellulose (HPMC). The results of the dissolution test showed the release of theophylline from 3D printed tablets over 12 hours, and the release profiles of the tablets fit well into the first-order kinetic release models and Korsmeyer-Peppas. As a result, this technique, in addition to being cost-effective and simple, can be used to produce personalized drug compounds [24].

#### 3.2.3. Sustained-release

Sustained release permits release of a particular drug at a programmed rate that leads to drug delivery in order to an extended period of time [25]. This method of drug release is especially helpful for drugs that are metabolized very fast and are eliminated from the body just after administration [26]. Sustained-release profiles can be achieved frequently through the application of appropriate polymers, which are used either to form a matrix in which the drug is dissolved or to coat tablets or capsules. The mixture of HME and FDM 3D printing technology, sustained-release tablets with air chambers that exhibited drug release in order to 24 hours were formed [27]. The 3D printer is capable of producing a capsule that can control the rate of drug release from an internal immediate-release (IR) tablet while floating in gastric fluid. Here, a commercial baclofen IR tablet was placed in the capsule machine. This capsule is capable of sustained drug release while maintaining sufficient buoyancy [28]. By linking a drug delivery systems with common oral formulations, another
formula of new sustained-release formulation could also be established to overcome challenges of common formulations.

3.2.4. Controlled-release

Controlled-release dosage forms also provide a sustained-release profile; nonetheless, in contrast to sustained-release systems, controlled-release forms are developed to constant plasma concentrations, irrespective of the biological environment of the application site [19]. In fact, they control the drug concentration in the circulation, not just the release of the drug from the dosage form, as is in the case of sustained-release forms. We expect lower side effects from a controlled drug delivery system, and taking little pills decreases the risk of forgetting doses. The use of various ratios of cellulose acetate can be used for the construction of the encapsulating shell with the capability to control the amount and the rate of propranolol HCl released from shelf tablet (Indicardin®). Additionally, the profile of the 3D printed controlled-release shell of various sizes influenced the release of propranolol. This assay could be discovered to aid healthcare and customize the drug amount and the release profile of the drugs with minimum side effects [29].

4. 3D printed materials for drug delivery applications

The application of 3D printing in the development of DDSs is a fascinating and evolving issue. Polymers constitute the backbone of the pharmaceutical structures since they can take part in physical stability of incorporated APIs and release rate modulation. Several natural and synthetic polymers of different types have already been examined for the fabrication of various models of DDS. Natural polymers including gelatin, chitosan, and collagen need cross-linkers to become printable; however, the crosslinking agent is quite often cytotoxic [30]. Because of such a limitation, there has been attention toward synthetic polymers for 3D printing.

4.1. Synthetic polymers

4.1.1. Polyvinyl alcohol (PVA)

PVA is known as a biocompatible, thermoplastic, and highly swellable polymer in water [31]. It possesses a Tg of about 85°C with a crystalline melting point ranging from 180°C to 240°C, depending on its degree of hydrolysis [32]. PVA has been used as a drug carrier in different types of medications like tablets, caplets, or capsules, mostly through the FDM technique. It is devoid of toxic effects and considered generally as safe (GRAS) material by FDA [30]. In FDM printing of PVA-loaded solutions, a relatively high temperature, usually above 180°C, is needed to facilitate the extrusion of filaments through a melt extruder. Although using a suitable plasticizer lowers the temperature of the process, the plasticizer and PVA cannot be mixed homogeneously until the temperature is raised up to above 150°C. As a consequence of the high melting temperature of PVA, the semi-crystalline domains remain rigid at temperatures lower than 150°C, due to poor mixing of PVA and the plasticizer. Therefore, the use of PVA for FDM 3D printing is limited to the drugs that may be physico-chemically resistant at high temperatures and do not sublime during the procedure [33]. Goyanes et al. served FDM 3D printing to prepare tablets possessing dissimilar sizes and shapes. Tablets were synthesized with the drug-loaded filament in a water-soluble polymer PVA by a fused-deposition modeling 3D printer. The templates were planned with AutoCAD and transferred as a stereolithography file into MakerWare. The five different plate geometries are shown in Figure 1 (a,b). The printing process had no effect on drug stability. The release of the drug from these tablets depended on the surface-to-volume ratio, which indicated the effect of the geometric shape on the release of the drug [34].

Combination therapy, using several drugs in a unit dosage form, is commonly used for the treatment of diseases like infections, diabetes, cancer, and cardiovascular conditions [35]. FDM 3D printing is an attractive method for combination therapy through printing loaded drug filaments, which is called multidrug 3D printing. Goyanes et al. investigated the feasibility of multi-drug incorporation in one formulation by the FDM printing technique [36]. Two different models of capsule-shaped tablets (caplets) were designed containing 9.5% caffeine and 8.2% paracetamol by using PVA filaments (Figure 1(c)). All drug-loaded filaments were successfully extruded at 180°C while preserving the drugs due to their thermodynamic stability. Two types of capsules were printed: first, a multilayer capsule with distinct drug components in each layer, and second, a two-compartment capsule, comprising a caplet enclosed within a bigger caplet (DuoCaplet) with a different type of drug loading. The drug release assay showed the paracetamol and caffeine were released simultaneously regardless of solubility [36]. In multilayer capsules, both paracetamol and caffeine reached 100% release in less than 360 min, while in the DuoCaplet capsules the release was dependent on the external layer dissolution. In other words, the external layer containing the drug (paracetamol or caffeine) was first released followed by complete dissolution to make possible the drug release of internal layer (also paracetamol or caffeine). The amount of drug released from the external layer was reported more than 50% and 80% for paracetamol and caffeine, respectively, suggesting the feasibility of making multi-drug DDSs with modified/controlled release potential.

Hot-melt extrusion (HME) is the procedure of applying pressure and heat to melt a polymer and make it by an orifice. HME is a very appropriate method in order to the development of solid dispersions [37]. HME method is used widely in pharmaceutics, to produce drug-loaded filaments containing high amount of drug [34,36]. To evaluate the effect of the internal micro pores of the 3D-printed materials on the drug release rate of the oral medications, Goyanes et al. fabricated different PVA-based caplets loaded with 8.2% paracetamol or 9.5% caffeine by FDM 3D printing (Figure 1(d)). PVA filaments were cut into small pieces using pelletizer and mixed with the drugs (paracetamol or caffeine) utilizing a mortar and pestle [38].

Oral formulations are usually selected as the preferred way of drug delivery to the systematic circulation. Some of the drugs are
easily absorbed from the gastrointestinal tract (GIT), but some others are quickly eliminated from the systemic circulation because of their short half-lives. Thus, there is an urgent need to design a sustained-controlled release formulation that can gradually release the drug into the GIT and maintain adequate drug concentration in the systemic circulation for a long time [39]. Charoenying et al. reported that it is possible to achieve a sustainable drug release profile by making a GIT-specific DDS with the potential of retaining the drug in the gastric medium. They produced thermal-resistant amoxicillin 250 mg capsule embedded floating PVA-based capsules by FDM 3D printing method or FDM 3D printer (Figure 2) [40]. The floating capsules were thermally cross-linked at different temperatures (120°C, 140°C, and 160°C) and time points (0, 2, and 6 h). The amoxicillin release pattern of non-crosslinked (FPD0) was dependent to the swelling behavior of PVA in the absence of an eruption. Capsule showed 100% release of the amoxicillin within the first 15 min. In contrast, non-cross-linked floating capsules released the amoxicillin with a lag time of 45 min. Such a lag time decreased to 15 min for the cross-linked type FPD4 (both exhibited 100% drug release). Furthermore, in vivo studies showed that the cross-linked capsules could be floated in rabbit stomach for more than 10 h due to their lower density than the gastric fluid. Furthermore, the release profile of different prototype configurations was independent of the initial shape and processing step.

Personalized drug delivery is becoming popular as it can improve drug design in terms of variability of the dosage procedure, the amount and the type of the released drug, and also the effectiveness of treatment. PVA has been used as an extended-release matrix for colon drug delivery. Skowyna et al. fabricated ellipse-shaped tablets to extend the release of prednisolone, using PVA filaments [41]. PVA filaments were incubated within a methanol-based saturated solution containing prednisolone as a solute. Then the drug-loaded filaments were exposed to the glycerol as a plasticizer. Afterward, a series of tablets possessing variable drug contents between 2 and 10 mg were 3D printed by the FDM printer. However, a 24 h drug release analysis showed that the smaller size tablets released the drug faster than other ones. The prednisolone release of above 80% was obtained for samples containing 2–3 mg drug within 12 h. In fact, the smaller the size of the carrier the larger the surface area per g, resulting in a faster diffusion of the drug along with accelerated PVA erosion (Figure 3). More studies are provided in Supporting Information.

4.1.2. Poly (methyl methacrylate) (PMMA)
Poly(methyl methacrylate) (PMMA), known as bone cement, is a non-biodegradable polymeric carrier for bone drug delivery that is an FDA-approved polymer due to its well-known biocompatibility, versatility, and ease of manipulation [42]. PMMA is a synthetic polymer mainly derived from methyl methacrylate monomers using different polymerization methods like

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**Figure 1.** Different-shaped 3D printed tablets with constant (a) surface area, (b) surface area/volume ratio and (c) mass (scale bar in cm) (a, b) [34]. 3D printed caplets from left to right: First, multilayer PVA-based capsule containing 8.2% paracetamol and 9.5% caffeine. Second, DuoCaplet PVA-based capsule containing 9.5% caffeine (outer layer) and 8.2% paracetamol (core layer). Third, DuoCaplet PVA-based capsule containing 8.2% paracetamol (outer layer) and 9.5% caffeine (core layer) (c) [36]. From left to right: First, a size 4 HPMC capsule (VCAPS®M Caprice). Second, PVA-based 3D printed caplet containing 8.2% paracetamol. Third, PVA-based 3D printed caplet containing 9.5% caffeine (d) [38].
photopolymerization. 3D printing is a fast yet precise method for the construction of implantable devices. Implants often have complicated geometries, and they need to be proportionate to each patient depending on the size and shape of the defect. Recent trends in the design and manufacture of implants are based on DDSs capable of being directly embedded in the defect site [43].

Ngo et al. used a mixture of the monomers and oligomers of methacrylic acid esters together with a photoinitiator (known as Clear Resin) to fabricate 3D printed methacrylate-based constructs via SLA technique [44]. This resin was chosen because of its mechanical properties being very similar to those of PMMA. Flurbiprofen drug was incorporated into the constructs under the supercritical CO₂ (scCO₂) as post-processing. The ScCO₂ processing made facile the drug loading into the scaffolds due to its several advantages like usage in low temperature, which is suitable for thermo-sensitive drugs and/or achievement of relatively high drug solubility (Figure 4(a)). The cross-linking polymer network was obtained on the surface of a layer of flexible polydimethylsiloxane (PDMS), using a UV laser. After 3D printing was finished layer-by-layer, the polymer samples were inserted separately inside the reactor chamber. The average drug loading was varied in the range of 12.72–24.08%. Increasing the temperature was accompanied by the increment of the flurbiprofen impregnation into a polymer matrix, thereof the surface roughness increased, but the pressure had less effect on loading capacity and drug solubility, and also the surface roughness.

4.1.3. Acrylonitrile butadiene styrene (ABS)
ABS is a thermoplastic copolymer representing outstanding thermal and mechanical behavior together with acceptable chemical resistance [45]. ABS is hard, rigid, intense, and dimensionally stable with a melting temperature of about 200°C [46,47]. On the other hand, the usage of ABS in pharmaceutical systems may be questionable as a consequence of the leaching of the acrylonitrile monomer residue in ABS, because of probable carcinogenic hazards [48]. Carbamazepine (CBZ) is the first antiepileptic drug (AED) proposed for focal seizures that generalized tonic-clonic seizures. The dosage range of CBZ is conventionally suggested between 4 and 12 mg/L [49,50]. The present challenge related to the use of this amount of drug dosage is the initial burst of CBZ release, which results in side effects to the central nervous system (CNS) among which are diplopia, dizziness, nausea headache, and also lightheadedness for about 40% of patients [51]. To overcome this limitation, using zero-order release formulations has been suggested which assists in the reduction of the

Figure 2. Schematic of the 3D-printing, from left to right (a) Sia-Mox® capsule, (b) body part of the floating capsule, (c) cap of the floating capsule, (d) non-crosslinked floating capsule, and (e) enlarged image of the non-crosslinked floating capsule [40].
fluctuation observed in the serum drug amount, which can help reduce side effects.

To achieve this purpose, Lim et al. designed an ABS-based scaffold containing CBZ via FDM 3D printing. The scaffolds were 3D printed varying the hole positions (in the side and top or bottom), the number of holes (4, 8, and 12), and eventually the diameter of holes (1, 1.5, and 2 mm) [52]. The scaffolds were fabricated in the form of cup-shaped bodies possessing a lid on the top to make them sealed after packing the drug inside them. The commercial ABS and 'Tegretol 200' tablets which contained 200 mg CBZ were used as the printing filament and drug model, respectively. All the scaffolds exhibited ascending linear interdependence between the rate of release of CBZ and the average diameter of the holes. More studies are provided in Supporting Information.

4.1.4. Ethyl cellulose (EC)
EC is a water-insoluble thermoplastic polymer with hydrophobic characteristics [53]. It has the potential to improve and modulate the physiological function of drug dosage forms owing to its hydrophobic nature as well as its high swelling capacity. Furthermore, EC possesses properties, such as lack of toxicity, good compressibility, and stability during storage [54]. EC is suitable for the formation of hydrophobic coatings or backing layers. It can also be used as a binder, moisture protector, or as a stabilizing, dispersing, and water-retaining agent to prevent drugs from getting wet and to improve the safe storage of drugs [53]. The rate of drug release, bioactivity, and adsorption severely depends on its water solubility. For example, carbamazepine, a well-known drug applied commonly in the treatment of partial and also tonic clonic seizure disorder can be hardly dissolved in water. Thus, the rate of adsorption of CBZ-incorporated tablets is very slow, suggesting the effect of formulation on the release [55,56].

On the ground of the aforementioned challenge, Borujeni et al. investigated the potential of HME-based 3D printing for manufacturing the drug-encased tablets with zero-order release kinetics [57]. More detail of this study showed in Supporting Information. The dissolution of tablets was evaluated in deionized water, suggesting successful modulation of the release kinetics of CBZ tablets at an optimized EC/HPC ratio (2/1) with nearly 20% release of CBZ within 24 h. It was suggested that the release of CBZ from the printed tablets was independent of the erosion and disintegration phenomenon and it was affected by water diffusion through EC and HPC matrix, ending in the swelling or relaxation of HPC and EC chains.

Pharmaceutical tablets are traditionally manufactured in two classical ways to approach zero-order kinetics. The physical, chemical, and/or geometrical structures of the tablets like multi-layering or coating with a particular material have been manipulated over years to meet such a release profile. Correspondingly, doughnut-shape [58], rectangular [59], parabolic [60], biconvex [61], and core-in-cup [62] shapes are
examined. Among these, tablets prepared from the first family possess cylindrical holes providing an adequate surface area to the drug for a constant release rate. In vitro drug release conducted on 3D printed doughnut-shaped tablets in PBS (pH = 6.8) demonstrated the roles of EC concentrations, tablet diameter, central aperture diameter, and height. A linear release kinetics was achieved by adjusting the aforementioned parameters. The roles of morphology and surface erosion of the outermost and innermost layers on the efficiency of DDSs were also confirmed. The time of drug release was explicitly studied by optimizing the concentration of EC solution and the thickness of disks. 3D printing made possible precise control of diameter and height of annular parts for target release behavior.

4.1.5. Hydroxypropyl methylcellulose (HPMC)

HPMC appears as an ideal candidate macromolecule for developing printable filaments as DDS and DDD. It can be prepared in several grades possessing different molecular weights and substitution degrees of methyl and hydroxyl groups [63,64]. Compared to HPC, HPMC appears in terms of the substitution of the reactive hydroxyl groups present in the glucose structure with the methyl- and hydroxyl-propyl functional groups. HPMC is a hydrophilic, biocompatible, and biodegradable polymer having suitable properties to be used in DDS [65].

Khaled et al. prepared some tablets using EBP printing for mimicking the room temperature drug release profile of commercial guaifenesin bi-layer tablets (GBT) (Figure 5) [66]. It is essential to try to manufacture a specific medication with accurate and personalized treatment dosage (or formula) for every patient exclusively associated with his/her genetic markers. The hydrophilic bilayer tablets composed of hydroxypropyl methylcellulose (HPMC 2208) and poly(acrylic acid) (PAA) were fabricated to meet a sustained-release (SR) layer having hypromellose (HPMC 2910) as a binder and sodium starch glycolate (SSG) and microcrystalline cellulose (MCC) being considered as disintegrants for the sake of immediate release (IR). Finally, they used a desktop extrusion 3D printer to prepare different guaifenesin bilayer tablets (GBT) comprising the guaifenesin as a drug to treatment of respiratory tract infections (Figure 5(a-c)). Drug release studies in simulated gastric fluid (SGF) with pH = 6 exhibited SR for guaifenesin in the course of 12 h study. Approximately, more than 20% of the initial burst release took place from the IR layer in 30 min for guaifenesin, resulting from MCC and SSG inclusion. Since the wettability was improved, the release rate was decreased. In summary, the results demonstrated that both standard commercial tablets and 3D printed tablets exhibited Fickian diffusion drug release, which indicated that the release rate was independent of the guaifenesin concentration within the tablets.
4.1.6. Hydroxypropyl cellulose (HPC)

HPC is a cellulose derivative, wherein three reactive hydroxyls are partially or fully substituted with hydroxypropoxy groups via an ether linkage on each monomer unit. The aliphatic hydroxyl groups in the side chains and the remainder of the hydroxyl groups in the glucose unit are accessible for the formation of hydrogen bonds and hydration leading to the solubility of HPC in water. The existence of such substituent groups in HPC results in high flexibility in this polymer. Consequently, HPC can be hot-melt extruded into flexible and opaque films with bioadhesive characteristics [67,68].

Due to the growing focus on personalized patient treatment in recent years, the need for methods that provide flexibility in the customization of medications with high demand. In this regard, FDM 3D printing has shown the most immediate potential for on-demand dose personalization to be convenient for particular patients’ needs [38]. Relatively, Arafat et al. offered a novel (Gaplet) approach for accelerating drug release from FDM 3D printed cellulose tablets [69]. The approach was based on utilizing FDM’s capability to manufacture relatively complex geometry models that deliver a collapsible tablet structure (Figure 6). Three sets of tablets with different block widths were designed, and each set was printed with increasing inter-block spaces. All tablets were printed with 100% infill. The dissolution study was conducted in 0.1 M HCl (pH = 1.2). It was demonstrated that the wider inter-block space between blocks in the tablets causes less resistance to medium flow through the tablet structure. Hence, inter-block spaces of >1.0 mm were selected to be the optimal distances to provide immediate release profiles (86.7% drug release at 30 min). These results indicated that the incorporation of a multi-block design can be adopted in the delivery systems when high release rate of a drug from polymeric structures is required.

4.1.7. Hydroxypropyl methylcellulose acetate succinate (HPMCAS)

HPMCAS has a cellulose backbone with a substitution of methoxy, hydroxypropoxy, succinyl, and acetyl groups [63]. Six grades of HPMCAS are commercially available. The F (fine) and G (granular) grades are different in particle sizes, while the L, M, and H grades differ only in their pH solubility. The pH solubility for the L, M, and H grades are at pH ≥5.5, 6.0, and 6.5, respectively. Hence, the release of drug in GIT can be regulated by selecting a suitable grade of HPMCAS. HPMCAS has excellent extrudability, but poor printability due to the high brittleness of the filament.

For this purpose, Scoutaris et al. used FDM 3D printing technology coupled with HME to prepare pediatric ‘candy-like’ formulations in the form of different shapes such as bottle, heart, lion, and bear for 2–11 years old children [70]. The tablets were produced in such a way to imitate ‘sweet-like’ chewable medications. The aim of this work was to improve the compliance of children to the prescribed
medication. Tablets were fabricated using HPMCAS as a polymeric matrix that was loaded with indomethacin (IND). IND is an anti-inflammatory drug that is commonly used for the reduction of pain, fever, inflammation, and stiffness. More detail of this study showed in Supporting Information. All printed samples indicated excellent taste masking with no bitterness and no aftertaste at all. It has been already determined that the masking effect is related to the drug–polymer interactions through H-bonding [71]. Furthermore, the release profiles of all printed objects (in PBS with pH = 6.5) were very similar and independent of the printed designs. Each printed form showed >80% drug release within the first 60 min. The rapid IND release was associated with the high solubility of HPMCAS in pH >6.0 and molecularly dispersion of IND within the printed tablets. More studies of the FDM 3D printing technique using HPMCAS in printlet fabrication in Supporting Information are provided.

4.1.8. Eudragit

Eudragit polymers are a group of polymethacrylate with pharmaceutical applications. They are nontoxic, non-biodegradable, and non-absorbable. All Eudragit polymers have thermoplastic properties with low Tg (between 9°C and 150°C), high thermostability, and high miscibility with excipients and APIs [72]. Therefore, they are suitable for the HME process [73].

For over 50 years, coumarins have been the most suggested oral anticoagulants [74]. Limited doses of warfarin tablets are available in the market and dose modification usually requires splitting or cutting of high-dose tablets and/or multiple-tablet consumption, which could lead to changes in drug content [75,76]. Consequently, a dynamic system that can provide accurate delivery of warfarin dose is extremely important. Arafat et al. assessed the suitability of FDM 3D printing to fabricate purposely designed solid dosage forms and deliver tailored precision doses of warfarin using an in vitro model [74]. To achieve this purpose, rat-tailored 3D printed warfarin ovoid-shaped were generated and administered to rats to obtain their pharmacokinetic parameters.

Solid dosage forms composed of Eudragit Ethyl citrate (TEC);tri-calcium phosphate (TCP);sodium warfarin (46.75:3.25:49:1) were printed at a temperature printing of 135°C. TEC was used in the formulation as a plasticizer to reduce the Tg temperature of filaments to 34°C from 54°C. In order to establish the potential of the approach to control the low dose of the drug for clinical usage, a series of tablets with increasing volumes were manufactured, while the ratios between dimensions remained constant (Figure 7). All tablets displayed a release pattern of >80% dissolution in SGF within 45 min irrespective of their individual sizes. On the other hand, in vivo studies demonstrated that 3D printed tablets were proportionally effective as their comparative solution dosage form.

One suggested solution for dose individualization is the on-demand manufacturing of solid dosage forms by using benchtop 3D printers (5). This approach is specifically appropriate for the fabrication of enteric dosage forms. Okwuosa et al. presented a different approach for the manufacturing of enteric-coated tablets by means of a dual-nozzle single-step FDM 3D printing process [23]. The gastric-resistant tablets were created, using PVP and Eudragit L100-55 for core and shell structures, respectively. For the preparation of the API-loaded filaments, an optimized mixture of the polymer (PVP), filler (talc) or tribasic phosphate sodium (TBP), plasticizer (TEC), and API (theophylline) was adopted. In vitro dissolution tests showed that 0.17 mm and 0.35 mm shell thickness led to an early release of the drug in the acidic medium (pH = 1.2). In contrast, thicker shells could provide superior control of drug release, i.e., <3% of drug released after 120 min in an acidic medium. This was contributed to the formation of 3–5 layers. Results demonstrated that by reducing the resolution of the 3D printing, which means the reduction of layers to fabricate the shell, relatively slower response to pH change could be obtained in comparison to high resolution.

One of the problems faced by personalized medicine is recommending commercially drug combinations [77]. It is important to substitute standardized dose tablet regimes with a dynamic-dose dispenser, which allows quick and efficient manufacturing for individual patient’s needs. For this

![Figure 6. (a) 3D model images. (b) images of tablet designs with 1 mm block and increasing inter-block spacing: 0.0, 0.2, 0.4, 0.6, 0.8, 1.0 and 1.2 mm [69].](image-url)
purpose, an easy and safe adjustable dispensing station must be provided. Obviously, such criteria cannot be carried out by conventional tableting procedures.

In this regard, Pietrzak et al. provided a mini-dispensing dose controlling station using the FDM 3D printing method [78] (Figure 8). Theophylline was selected as a thermostable model drug, which is commercially used as an extended-release formulation with a dose range of 60–300 mg. They evaluated the potential of exploiting FDM printing to achieve a controlled dose of theophylline by using immediate and extended-release polymers (Eudragit RL100 and RS100).

4.1.9. Poly (Ethylene glycol) (PEG) and polyethylene glycol diacrylate (PEGDA)

Crosslinkable photopolymers have been suggested as ideal feeding materials to overcome the challenges of printing solid dosage forms containing thermo-sensitive drug substances [79]. Because of no contribution of heat and ease of preparation procedure, photo-polymerization-based methods such as DLP and SLA techniques have attracted much interest for the fabrication of oral solid dosage forms.

Kadrya et al. applied a DLP printer to fabricate tablets, using PEGDA and PEGDMA as photoreactive polymers, 2-Hydroxy-4’-(2-hydroxyethoxy)-2-methylpropiophenone as photoinitiator, and theophylline as a model drug with the concentration of [80] PEGDA 20% (v/v), PEGDMA 20% (v/v), 0.5% (w/v) 2-Hydroxy-4’-(2-hydroxyethoxy)-2-methylpropiophenone, and 1% (w/w) theophylline [80]. All tablets were printed at room temperature. Three different groups of tablets were fabricated for each photopolymer: non-perforated tablets and tablets with two or six perforations (Figure 9). Tablets containing two and six perforations were prepared to increase the surface area and thus enhance the release rate. The results of dissolution tests that were carried out in PBS media demonstrated that the intact non-perforated tablets of PEGDMA could provide maximum release in 6 h and 65% of the drug was released during an hour. In contrast, intact tablets prepared using PEGDA exhibited the same release patterns, but drug release was maximized after 8 h. Tablets prepared of either polymer with two holes showed the same release profiles; ~98% drug was released within 3 h. However, PEGDMA-tablets with six holes showed 100% drug release in 1.5 h, while PEGDA-tablets containing 6 holes had 97% drug release in 3 h. PEGDMA-tablets with 6 holes provided much faster and pronounced drug release than PEGDA-tablets, suggesting that PEGDMA would be better suitable for immediate release tablets.

4.2. Natural polymers

4.2.1. Gelatin

Gelatin is a natural protein derived from animals’ connective tissues, mainly skin and bones, which is considered a greatly valuable candidate in order to medical uses according to several advantages such as being commercially available at low cost, biocompatibility and biodegradability, FDA approval,
Figure 8. Schematic image of the synthesis of 3D-printed theophylline tablet. (a) The mixture of drug and polymer to the synthesis of theophylline loaded filaments, (b and c) computer software is used to design tablet, (d) the theophylline loaded Eudragit RL filament is applied as a feed to FDM 3D printer, (e) 3D printed Eudragit RL tablets fabricated by printing resolution [78].

Figure 9. (a). Design of 3D printed theophylline tablets, (b and c) Images of the top and tilted views of 3D printed tablets without perforation and those with two or six holes, (d) Images of opaque PEGDA and transparent PEGDMA printed tablet [80].
and more importantly, it is less antigenic than collagen, non-carcinogenic and present the arginine-glycine-aspartic (RGD) motifs, which are known to be crucial for promoting cell adhesion. Gelatin comprises different functional groups for chemical/physical modifications through crosslinking. Chemical crosslinking methods typically employ chemicals such as aspartic, aldehydes, and glutamic acids [81], whereas physical crosslinking methods employ drying, heating, and irradiation processes [82]. In addition, gelatin can be used to design vehicles, such as encapsulating agents, scaffolds, and tablet binders, for the delivery of drugs and bioactive molecules, including anti-inflammatory drugs, antibacterial agents, nucleic acids, and growth factors [83]. In drug delivery systems, medications are entrapped within a gelatin matrix from which they are released in diffusion – and/or erosion-controlled manners. According to the low mechanical strength and stability of gelatin, the pharmacological drawbacks of conventional gelatin drug delivery vehicles result in nonspecific distribution, high side effects, and toxicity.

Etxabide et al. fabricated 3D printed gelatin scaffolds as carriers of dexamethasone sodium phosphate (DSP), a hydrophilic glucocorticosteroid drug with potent anti-inflammatory, with the aim of reducing DSP toxic side-effects caused through long-term or extensive use of the drug [84]. A solution containing 10% w/v gelatin, 10 wt% glycerol (on gelatin dry basis), and 4 mg/mL DSP was prepared as the ink. An extrusion-based printing containing a pneumatic driven dispersing system was used to print scaffolds with grid-like patterns with and without DSP. Heat-treated scaffolds were marked as HT, while HT samples containing DSP were marked as HT-DSP. The color of heat-treatment samples changed to yellowish according to the chemical reaction (Figure 10(a)). Interestingly, the addition of DSP slightly affected the crosslinking extension, and the reaction remarkably improved scaffolds’ water resistance by decreasing buffer absorption capacity values from ~515% to 360%. In addition, the solubilization percentage was decreased from 45 min with 75% of solubilization to more than 1 week with about 50% of solubilization. The in vitro DSP release behavior of scaffolds showed a burst release (40% in 30 min) followed through a slower sustained release (more than 80% in 90 min) with eventually resuming a plateau.

4.2.2. Chitosan

Chitosan is a linear polysaccharide with a random arrangement of β-(1–4)-linked d-glucosamine and N-acetyl-d-glucosamine, which is generally derived from the shells of shrimp and other sea crustaceans. 3D printing of chitosan hydrogels has attracted wide attention because of their excellent biocompatibility, zero toxicity, biodegradability, antibacterial activities, and low cost. Moreover, the recently reported 3D-printed chitosan scaffolds lack enough strength and are involved in toxic and organic solvents, thus their use is limited in tissue engineering and drug delivery applications [85]. Hafezi et al. manufactured film-based dressings made from chitosan for potential wound healing applications by a 3D printing technique [86] (Figure 10(b)). To prepare the 3D printed films, chitosan powder and plasticizer (glycerol or PEG) were dissolved in acetic acid to make a chitosan solution. Subsequently, 5 ml of genipin solution as a crosslinking agent was mixed with the chitosan solution to allow complete crosslinking between genipin and chitosan. The final gel was used for the 3D printing of biofilms. The tensile characteristics of chitosan films in the presence of plasticizer (glycerol or PEG) indicated that chitosan-genipin-PEG600 3D printed biofilms with the ratio of 1:1 polymer to plasticizer were appropriate for drug release evaluation due to their higher flexibility. Furthermore, human skin fibroblast cells were seeded on the printed structures to evaluate the cytotoxicity of the films through MTT assay tests. The results of in vitro drug release profile in PBS from chitosan-genipin-PEG600 showed about 67% of drug release within the first hour and 62.72% after 2 hours. The MTT assay also demonstrated that more than 90% of cells were viable after 48 hours confirming the nontoxic nature of the 3D printed chitosan-genipin-PEG600 films.

4.3. Other biomaterials

4.3.1. Bioceramics

Bioceramics are a class of biomaterials with biological functions, which frequently used for the repair and reconstruction of bone and dental defects [87]. Calcium phosphate-based cements (CPCs), hydroxyapatite (HA), and alpha-tricalcium phosphate (α-TCP) together with β-tricalcium phosphate (β-TCP) and biphasic calcium phosphate (BCP) (a mixture of HA with α-TCP and silica-based bioactive glasses) can be named as the most representative bioceramics with high capacity for bone drug delivery.

BJ printing at low temperature (below 37°C) is used to create a calcium phosphate (CaP) scaffold as a matrix for controlled delivery of heat-labile bioactive molecules like growth factors or antibiotics. Furthermore, low temperatures allow better distribution of the drug within the complex printed geometries [88], but sometimes it would be possible to see adsorption of the growth factors or drugs on the surface of the 3D printed CaP scaffolds in the course of processing [89]. Both the quantity of the released drug and the rate of release are governed by the loading protocol and CaP phase. However, burst release may take place for the drug within 1 to 2 h. With the aid of 3D printing, it is possible to homogeneously load the drug in situ benefiting from site-specific localization of drugs, leading to improved sustainability. For example, Inzana et al. used 3D printing to load vancomycin (5%) and rifampin (0.5%) within CaP scaffolds to substitute bone tissue [90]. The existence of PLGA coating initially resulted in the sustained release of rifampin within 2 weeks in vitro. For fabrication of drug/growth factor-incorporated scaffolds under low temperature or mild post-processing conditions, material extrusion is more versatile than the BJ. For this purpose, mineralized slurry or paste compositions are suitable substances as they can be extruded easily at physiological temperature. The optimization of the rheological properties of the slurries composed of different components is important in the 3D printing technique. On the other hand, by mixing the bioceramics with biodegradable polymers, the mechanical strength of the printed materials would be improved [91]. Additionally, the insertion of drugs...
into such composites enhances their potential in osteomyelitis treatment [92], and it is greatly advantageous to act on the surrounding tissues with an appropriate concentration level and for a desired period. Martínez-Vázquez et al. fabricated rapid prototype composite scaffolds with gelatin and silicon-doped hydroxyapatite (HASi) at room temperature, based on the material extrusion method. Gelatin, known as a green macromolecule obtained from collagen is the main protein of bone structure. Moreover, HASi is among the most promising bioceramics with acceptable bioactivity function. HASi/gelatine was used to make slurries with a weight ratio of 9.0 and then loaded with 2.0 wt.% of vancomycin before the extrusion of the structures [93]. At the end of the printing, the scaffolds were cross-linked with glutaraldehyde (GA)

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**Figure 10.** (a) 3D printer with extrusion-based print-head (a), non-heated (NH), heat-treated (HT) and HT with dexamethasone sodium phosphate (HT-DSP) scaffolds (b) [84]. (b) Schematic of film-based dressings prepared from chitosan for potential wound healing applications by 3D printing technique (a); CH-GE and CH-GE-PEG600 3D printed film (b); MTT assay for the CH-GE-PEG3D printed films with Triton-X – 100 and control (c) [86].
(0.25 wt.%/vol) solution. The scaffolds behaved as hydrogels but exhibited compressive characteristics similar to that of the trabecular bone of the same density. They were suggested to be favorable structures capable of withstanding mechanical stresses in a range that can be hold out during the surgery. Regarding the cross-linking, it was demonstrated that the dissemination of antibiotics from the scaffolds was proportional to the time of GA exposure. The scaffolds exhibited a first-order drug release diffusion kinetics, even though their sustained-release was limited to about 10 h in vitro.

Bioactive glasses (BGs) are a class of surface reactive glass-ceramic biomaterials and comprise the bioactive glass, Bioglass®. Among the properties of these biomaterials is their biocompatibility and bioactivity, which has led to their use as an implant device in the human body to repair as well as replace damaged bones [94–96]. The synthesis of mesoporous bioactive glasses (MBGs) in bio-sciences managed to the form of a novel class of nanostructured materials with applications in drug delivery systems, bone-bonding ability, and tissue engineering [95]. 3D printing technology permits a relatively effective manufacture of BG scaffolds with various patterns considered through a widespread variability of pore sizes and shapes. In fact, MBG scaffolds with porosity grade or high porosity have significant potential in order to interfacial tissue engineering, for instance, the interface among trabecular and cancellous bone can be represented to some magnitude as changed density and porosity values can be easily obtained by the printing of a proper design. Some of the literatures showing the drug delivery capability of 3D-printed MBG scaffolds for the burst release of a model drug (DEX) inside the first 48 h, which is predominantly showed in order to providing therapeutic activity in acute inflammatory phase. In vivo experiment in rat model also established the reduction of the drug after 2-week implantation [97]. More examples of these materials showed in Supporting Information, Table 2 shows the various types of drugs that the bioactive material is suitable for loading of them for drug delivery systems.

5. 3D printing products and commercial future

The future outlook of 3D printing technology is anticipated to rely on its capability to offer 3DP processes, which can fabricate on-demand personalized doses in regionalized situations. It is estimated that the restoration of common pharmaceutical manufacturer to more flexible 3D printed products will be immediately with more formulations in the market. Lastly, the commercial products of 3DP technology will be reliant on the ability of translation of exclusive dosage geometries as per patient needs and the cost. The first 3D printed commercial FDA-approved tablet ‘Spritam®’ has been established through using the solid deposition method [101,102]. This tablet is a greatly porous scaffold allowing rapid disintegration in the patient’s mouth with a slight amount of water. The 3D tablet proposes the benefit of decreasing the time in order to the action because a great formation of the drug is accessible in order to absorption through the oral mucosa into the circulation. Thus, this type of formulation can open a novel manner in planning dosage forms in order to patients who brawl to swallow a tablet. 3D printing is a extremely flexible procedure that permits you to design the size of the tablets to precisely control the dosage [103]. These technologies showed tempt into the market place in the form of tablets, nanosuspensions, or hydrogels [104]. Different types of pharmaceutical preparations developed with 3D printing are shown in Table 3. Presently, commercial 3D printers do not take through Good Manufacturing Practice requests. Thus, adaptable their apply to create solid oral dosage in clinical uses, remains an unmet need. Consequently, the requirement in order to quality control by process analytical technologies (PAT), near-infrared (NIR) spectroscopy, and colorimetry, is important for monitoring drug activity [105].

6. Conclusion

3D printing in drug formulation is becoming a new method for various patients since it gets the manufacturing close to them and proposes individualization of therapy. In fact, current progresses in technology and enhanced studies in this

<table>
<thead>
<tr>
<th>Materials</th>
<th>Drug</th>
<th>Application</th>
<th>Ref</th>
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</thead>
<tbody>
<tr>
<td>PVA</td>
<td>Caffeine, Paracetamol, Amoxicillin, Allopurinol, Dronedarone, Prednisolone</td>
<td>Physicochemically resistant at high temperatures [34,38,40,56]</td>
<td></td>
</tr>
<tr>
<td>PMMA, PEGDA</td>
<td>Flurbiprofen, theophylline</td>
<td>Thermo-sensitive drugs Floating drug delivery systems [44]</td>
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<tr>
<td>HPC</td>
<td>CIN</td>
<td>Drugs with low bioavailability Release of drug in GIT [69]</td>
<td></td>
</tr>
<tr>
<td>EC</td>
<td>Diclofenac sodium</td>
<td>Drugs with low bioavailability Release of drug in GIT [69]</td>
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<tr>
<td>HPMCAS</td>
<td>Indomethacin</td>
<td>Drugs with low bioavailability Release of drug in GIT [69]</td>
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<tr>
<td>Eudragit</td>
<td>Budesonide, theophylline</td>
<td>Gastro-resistant drugs [26]</td>
<td></td>
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<tr>
<td>PVA</td>
<td>Amoxicillin</td>
<td>Oral formulations Expandable gastroenteric devices [40]</td>
<td></td>
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<tr>
<td>PVA</td>
<td>Allopurinol</td>
<td>Oral formulations Expandable gastroenteric devices [40]</td>
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<tr>
<td>PVA</td>
<td>Prednisolone</td>
<td>Colon drug delivery [99]</td>
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<tr>
<td>EC</td>
<td>Acetaminophen</td>
<td>Multi-layered drug delivery [100]</td>
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<tr>
<td>CaP</td>
<td>rhBMP-2</td>
<td>Growth factor delivery [64]</td>
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Table 3. Different types of pharmaceutical preparations developed with 3D printing.
field can promise more safe and effective treatment. 3D printing can give the worker the possibility to control over the dosage of each ingredient for a specific purpose, and makes it possible to optimize the formulation of DDSs, which is not simply possible by the conventional manufacturing methods. Albeit this technology is still in its early stages, it looks to be an innovative tool that proposes more flexibility in drug fabrication and is probable to convert drug delivery systems to various levels, in the future.

7. Expert opinion on perspectives and challenges

3D printing has been under development over the last decade, and several promising DDD and DDS have been manufactured. Overall, the use of 3D printing makes it possible to control the overloading capacity (the higher the better) and release kinetics (zero-order with constant rate is the goal). In other words, by regulating the rate and the locus of the drug in the 3D printed scaffolds can regulate drug delivery systems in response to a determined to each individual. Nevertheless, the number of factors controlling the loading capacity and release kinetics in 3D printed DDD and DDS makes the multi-stage optimization of responses. From a material point of view, selecting a specific polymer with desired biodegradability, thermal stability, mechanical strength, and hydrophilic nature remarkably governs the final shape of the DDSs as well as the amount of drug encapsulated, and its release. From a processing perspective, 3D printing makes possible the regeneration of tissues such as skin and bone, but the long-term delivery of APIs for the treatment of chronic skin or bone infections is difficult. Natural polymers are a good choice in the case of tissue reconstruction; however, they have lower mechanical stability. Each printing method is suitable for a specific goal and should employ a particular polymer. For instance, BJ printing can expand pharmaceutical products with highly controlled microstructures, which appeared distinctly useful for controlled drug delivery purposes. SLM printing is another suitable technique for engineering porous biodegradable microstructures with controlled-release of drug delivery capability, but it is more rapid in comparison to BJ method. On the other hand, in the laser-based printing methods, at least one component should be capable of absorbing the beam energy at the appropriate wavelength of the process. This constraint limits the number of polymers as a candidate for pharmaceutical purposes. In the case of FDM printing, it is important to select thermoplastic polymers due to the high temperature of the printing process. Some further difficulties are arising from the inability of bioprinting of some drugs or our poor knowledge about the physicochemical characteristics of drug–polymer interactions.

Though there are many benefits aligned with 3D printing for manufacturing DDSs, a number of serious challenges of this method should be considered for the commercialization of such technologies. For instance, the manufacture of dosage forms by 3D printing is pertinent to proper optimization of the performance of the software, the properties of the raw materials, and machine parameters. FDM and powder-grounded printing make use of a spraying nozzle to deposit the dosage forms layer by layer, with serious difficulty to flow the ink or powder between two consecutive printing shots [111]. Regarding the mechanical resistance of the printed materials, the former technique appears promising, whereas the latter has low resistance. To improve powder-based 3D printing, numerous serious challenges should be overcome, such as inappropriate feeding of ink, nozzle clogging, the free movement of binder, and elution. Moreover, powder-based printing is very hazardous with high health risks to the user, necessitating precise [112]. SLA can hardly be used, because it is slow, and the number of available biocompatible and nontoxic photopolymerizable UV-curable materials is limited.

Despite the aforementioned challenges, the future ahead of using 3D printing for the development of DDD and DDS is bright. SLM makes possible the development of tailored DDSs with precise porosity and thereof optimized drug release kinetics. Researchers are focused on the optimization of this technique, by reducing the powder wastes remaining after SLM printing. They will also eliminate the unavailability of pharmaceutical excipients and APIs. For PAM printing, the cross-linking mechanism and shear-thinning properties should be matched, highlighting the role of rheology. Regarding PAM 3D printing, feeding and spraying problems are to a large extent resolved. However, cross-linking takes place in the time span of 3D printing, such that online monitoring of this technique will be improved before long. We believe that a conclusion workflow which integrates attentions from target product, drug formulation, procedure engineering, controlling and supply chain management is essential to select appropriate uses and to evade the pitfall of the thinking.

**Abbreviation**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>DDSs</td>
<td>Drug delivery systems</td>
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<tr>
<td>AM</td>
<td>Additive manufacturing</td>
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<tr>
<td>CAD</td>
<td>Computer-aided design</td>
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<td>FDA</td>
<td>Food and Drug Administration’s</td>
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<td>SLA</td>
<td>Stereolithography</td>
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<td>SLM</td>
<td>Selective laser melting</td>
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<td>DLP</td>
<td>Digital light processing</td>
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<td>CIU</td>
<td>Continuous inkjet</td>
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<td>DOD</td>
<td>Drop-on-demand</td>
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<td>BJ</td>
<td>Binder jetting</td>
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<tr>
<td>PBF</td>
<td>Powder bed fusion</td>
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<td>Tg</td>
<td>Transition temperature</td>
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<tr>
<td>FDM</td>
<td>Fused deposition modeling</td>
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<tr>
<td>PAM</td>
<td>Pressure-assisted microsyringe</td>
</tr>
<tr>
<td>PBP</td>
<td>Photopolymerization-based printing</td>
</tr>
<tr>
<td>API</td>
<td>Active pharmaceutical ingredient</td>
</tr>
<tr>
<td>DMD</td>
<td>Digital micro-mirror device</td>
</tr>
<tr>
<td>PVA</td>
<td>Polivinyl alcohol</td>
</tr>
<tr>
<td>GIT</td>
<td>Gastrointestinal tract</td>
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<tr>
<td>SGF</td>
<td>Simulated gastric fluid</td>
</tr>
<tr>
<td>EGD</td>
<td>Expandable gastroenteric devices</td>
</tr>
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<td>CPCs</td>
<td>Calcium phosphate-based cements</td>
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<td>Hydroxyapatite</td>
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<td>Biphasic calcium phosphate</td>
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<td>CaP</td>
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<td>PLGA</td>
<td>Poly(lactic-co-glycolic acid)</td>
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<tr>
<td>HV</td>
<td>Hydroxyaleral</td>
</tr>
</tbody>
</table>

(Continued)
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PHBV Poly(hydroxybutyrate-co-hydroxyvalerate)
ALP Alkaline phosphatase
OCN Osteocalcin
PMMA Poly(methyl methacrylate)
PDMS Polydimethylsiloxane
PEGDA Polyethylene glycol diacrylate
MW Molecular weight
BSA Bovine serum albumin
DPBS Dulbecco’s Phosphate Buffered Saline
CNS Central nervous system
SOD Sodium dodecyl sulfate
MCC Mucociliary clearance
MEC Custom-made expansion chamber
HBSS Hank’s balanced salt solution
CBZ Carbamazepine
EC Ethyl cellulose
HPC Hydroxypropyl cellulose
TEC Triethyl citrate
DDD Drug delivery device
HPMC Hydroxypropyl methylcellulose
PAA poly (acrylic acid)
SR Sustained release
SSG Sodium starch glycolate
MCC Microcrystalline cellulose
IR Immediate release
SGF Simulated gastric fluid
SFF Solid free-form fabrication
PEH Pseudophedrine hydrochloride
HPMC Hydroxypropyl cellulose
USP United States Pharmacopeia
HPMCAS Hydroxypropylmethylcellulose acetate succinate
IND Indomethacin
TEC Triethyl citrate
TCP Tri-calcium phosphate
IBD Inflammatory bowel disease
SIM Simvastatin
LDL Lipoproteins
SIM Simvastatin
EDAC N-(3-dimethylaminopropyl)-N’-ethylcarbodiimide hydrochloride crystalline
BSP Bone sialoprotein
RUNX2 Run-related transcription factor 2
OPN Osteopontin
IVR Intravaginal ring
IUS Intrauterine system
NF Nitrofurantoin
PTX Paclitaxel
DMAc N,N-dimethylacetamide
hTMSCs Human nasal inferior turbinate-derived mesenchymal stromal cells
4-ASA 4-Aminosalicylic acid
IUS Intrauterine system
SR Subcutaneous rod
HME Hot melt extrusion
RGD Arginine-glycine-aspartic acid
DSP Dexamethasone sodium phosphate
EDC Carbodiimide
FS Fluorescein sodium
FTIR Fourier-transform infrared spectroscopy
DSC Differential scanning calorimetry
XRD X-ray diffraction
TGA Thermogravimetric analysis
MEC Minimal effective concentration

Declaration of interest

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.


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**Showed the importance of a new oral drug delivery system in order to gastroretentive controlled drug release by 3D printer.** This capsular system can control drug release from the tablet while floating in the gastric fluid.

67. • Showed the production of complex formulations printed into bilayer tablets using an cost-effective desktop 3D printer.
76. • In vivo study showed the flexibility of FDM 3D printers to form solid dosage types to suit the anatomy of an animal subject.
83. • Tablets prepared of polymer with 2 holes exhibited the efficient release rate; <80% of drug within 3 h.


