Annals of 3D Printed Medicine 4 (2021) 100037

Contents lists available at ScienceDirect

Annals of 3D Printed Medicine

journal homepage: www.elsevier.com

Research paper

3D Printing in medicine: Technology overview and drug delivery applications

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ARTICLE INFO

Article History:
Received 30 October 2021
Accepted 16 November 2021
Available online 18 November 2021

Keywords:
3D printing
Layer-by-layer
Pharmaceuticals
Personalized medicine
Customized dose
Drug delivery

ABSTRACT

The concept of tailored medicine for individual patients have been around for a while but recently earned much attention. Great interest is given to 3D printing technology due to its immense application potential in the pharmaceutical industry and other health care sectors. 3D printing technology involves Layer-by-layer fabrication of 3Dgra objects from digital designs. This review gives a detailed yet much-focused discussion about 3D printing technology, the outline of 3D printing-based drug delivery technology its application in the pharmaceutical product development process. Based on the method of material layering, 3D printers are generally inkjet, extrusion, or laser-based systems. This review discusses the different types of 3D printers and their applications in different areas of drug delivery. A selection of recent researches carried out in the field of pharmaceutical 3D printing for drug delivery applications is also included. In addition to the promising opportunities, the review discusses the technical and regulatory challenges that slow down the implementation of such technology in the pharmaceutical and health care sector and the suggested measures to overcome such challenges.

1. Introduction

Since the FDA approval of the 3D-printed drug Spritam® (levetiracetam) in 2015, the interest in this technology has increased substantially among researchers and pharmaceutical companies [1]. The method of Spritam® fabrication has given the formulation the ultrafast disintegration property which is difficult to produce using the conventional technologies of tablet manufacturing. The use of binder jetting printing to produce Spritam® allows the high porosity of the tablet which results in the fast dissolving of the drug. Since then, researchers have begun to explore the advantages of the other 3D printing technologies to produce formulations that were difficult to produce by the conventional methods. Also, with the increased interest in personalized medicine, this technology has become a promising solution for the production of small quantities of medicines at the appropriate dose and drug release.

The 3D printing technique is an additive manufacturing method that is based on the principle of deposition/solidification of successive layers to form the digitally designed 3D shape. There are three main systems of 3D printing that have been explored for their ability to produce pharmaceutical formulations and they are laser-based writing systems, printing-based inkjet systems, and nozzle-based deposition systems [2]. These three systems will be discussed in detail in this review. Briefly, The laser-based writing system is based on directing the laser on the layer to be solidified of the photosensitive liquid resin and the process is repeated to solidify multiple layers to build the 3D structure. While inkjet printing works on jetting the liquid that contains the medicine and additives on a predetermined area to make a layer, and by repeating the process, successive layers are formed that build the 3D shape [3]. Two types of inkjet technology are available, continuous inkjet printing (CIJ) that works by a continuous jetting of droplets, and drop-on-demand (DOD) that works by jetting droplets in response to a trigger signal. The layers printed using this technology have a very small thickness, which gives a high-resolution print but consumes a long time. The nozzle-based system depends on the extrusion of pharmaceutical substances from a narrow nozzle either by pressure, called Pressure AssistedMicrosyringe (PAM)also called semisolid extrusion(SSE), or

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https://doi.org/10.1016/j.stlm.2021.100037

by melting the material filaments, called Fused Deposition Modeling (FDM) [1–5,7–10].

The advancement and flexibility of 3D printing made it possible to prepare pharmaceutical doses with dimensions and designs that were difficult to produce by traditional methods. This technology made it possible to produce polypills that contain multiple drugs to treat a certain [1] disease, each drug with a discrete dose and release [6–8]. In addition to the approval of Spritam® by the Food and Drug Administration in 2015, Triastek obtained an FDA clearance for Investigational New Drug Application (IND) for the drug T19 for the treatment of rheumatoid arthritis that has been produced by 3D printing. The complex design and internal geometry of this product allow to control and adjust the onset time, duration, and overall release profile [9]. In 2015, the precision medicine initiative started in the USA supported by Obama, the president at that time to increase the research effort to take into consideration the differences between people in the matter of gene, metabolism, and lifestyle. The current one-size-fits-all concept of drug dispensing is non-compatible with the solutions to implementing precision medicine. With the ability of 3D printing to produce small batches with precise doses and release profiles, it represents a promising solution for implementing precision medicine [10].

Regardless of the steady progress in this technology and the proving of its ability to produce novel pharmaceutical formulations, it is clear that there are still obstacles that delay its application on the ground. When comparing 3D printed dosage forms with the conventional ones, it is noticeable the absence of regulations and safety with questions that have not found complete solutions so far, especially in the matter quality and the available methods to control them.

This review discusses 3D printing and provides an update of its contribution to drug delivery. To begin with, the principles of the different types of 3D printing that have been explored for the production of dosage forms will be defined and explained. This is followed by a detailed discussion of the dosage forms produced by this technique and their superiority over the conventional dosage forms supported by interesting accomplishments of the researchers in the field. In addition, this review discusses the future opportunities of using 3D printing for the production of personalized medicine and the challenges that limit the implementation of this technology.

2. 3D Printing in medicine: technology overview

3D printing techniques is an additive manufacturing technique that involves layer by layer deposition of material on a substrate to build the desired 3D object designed through computer software. All 3D printing techniques involve two basic steps one is the object design via computer software and the other is the object deposition/formation via a 3D printer. The designing of the 3D object can be achieved by using various computer software's like auto CAD (computer-aided design), 3D Slash, SketchUp, Fusion 360, and Solidworks. The next step is slicing the formed design through slicer software like KISSlicer, Slic3r, OctoPrint, Simplify3D, and Cura. This 3D slicer software will convert a 3D design file (STL file) to a 3D printer readable G-code. The slicer software is used to set the printing parameters for the sliced object i.e. no. of layers, infill percentage, initial offset height between the printer head and printer stage/platform, space between each layer, printing speed, and total printing time. Then this formed G-code is uploaded to the 3D printer and with a print command, the printer will run and form an object of the desired size and shape. The object deposition process through a 3D printer varies based on the type of 3D printer used. 3D printers work mainly based on three principles *inkjet-based system, extrusion-based system, and laser-based system.*

2.1. Inkjet-based 3D printing system

The idea of inkjet printing for 3D objects evolved from the traditional desktop inkjet printers which work by depositing ink droplets on a paper substrate. The same principle applies for the printing of 3D objects using various functional materials as inks deposited on edible polymeric substrates [11,12].

Inkjet printing is categorized based on drop generation and deposition into two major types: CIJ and DOD inkjet printing. CIJ involves continuous flow of ink through an orifice and the generation of droplets and deposition onto the substrate will be controlled by piezoelectric transducers at the orifice and the electrostatic field which help the charged droplets to deposit on the substrate [13]. While the DOD inkjet printing, the formation of the droplet is based on the demand by receiving signals and it requires less amount of ink compared to continuous inkjet printing. Two types of print heads are used for drop-on-demand printing i.e. thermal print head [11,14] and piezoelectric print heads [12,15]. Among the two types of printheads, the piezoelectric printheads are more advantageous for drug delivery applications as they can work at room temperature and a wide range of biocompatible less volatile solvents can be used. Whereas the thermal head requires a high temperature and may cause degradation of the active components [16]. The DOD inkjet printing has been further categorized as *drop-on-liquid printing* and *drop-on-solid printing*. The drop-on-liquid printing also called as drop-on-drop deposition technique involves the deposition of liquid droplets on each other under a thermal stream result in the formation of a layer-by-layer structure with the evaporation of the solvent. This technique is employed to develop microstructures with high drug loading capacity and suitable for customized delivery of drugs [17]. The conventional methods of preparing micro structures i.e. spray drying, phase separation and solvent evaporation techniques are associated with problems like low drug loading, the shape of the formed microstructures and wide size distribution. These limitations can be overcome by using the inkjet-based drop-on-drop deposition technique [18].

Drop-on-solid printing also called drop-on-powder deposition involves the deposition of a liquid droplet onto a surface of a powder bed which forms a solid structure through powder fusion [5] as illustrated in Fig. 1.

The liquid droplets act as a binder to the powder particles or may by itself form a solid bed by drying with complete evaporation of residual solvent [19]. The drop-on-solid deposition technique can be employed to develop controlled drug delivery systems for a wide range of pharmaceutical ingredients. The first 3D printed commercial FDA-approved product "Spritam®" has been developed by using the drop-on-solid deposition technique [20]. The API (active pharmaceutical ingredient) can be either incorporated in the powder bed or the binder ink, so high drug loading can be achieved by this technique. Various release rate controlling polymeric material like ethyl cellulose, Eudragit® can be used as binder ink to formulate controlled release and targeted drug delivery systems [21]. color printing of the product can be achieved by formulating inks of different colors which improves patient compliance and help geriatric and pediatric patients. The limitations associated with this technique is that the formed products are friable and brittle due to high porosity, stability problem due to the use of organic solvents, and preparation of ink is a challenging aspect as it may result in nozzle blockage [13,22].

2.2. Extrusion-based 3D printing system

The extrusion-based 3D printing technique is the most explored technique for drug delivery applications. In the past five years, more than 80% of the published scientific data of 3D printing applications for drug delivery utilized the extrusion-based technique [23]. This technique is categorized into PAM-based and FDM-based printing techniques as shown in Fig. 2.

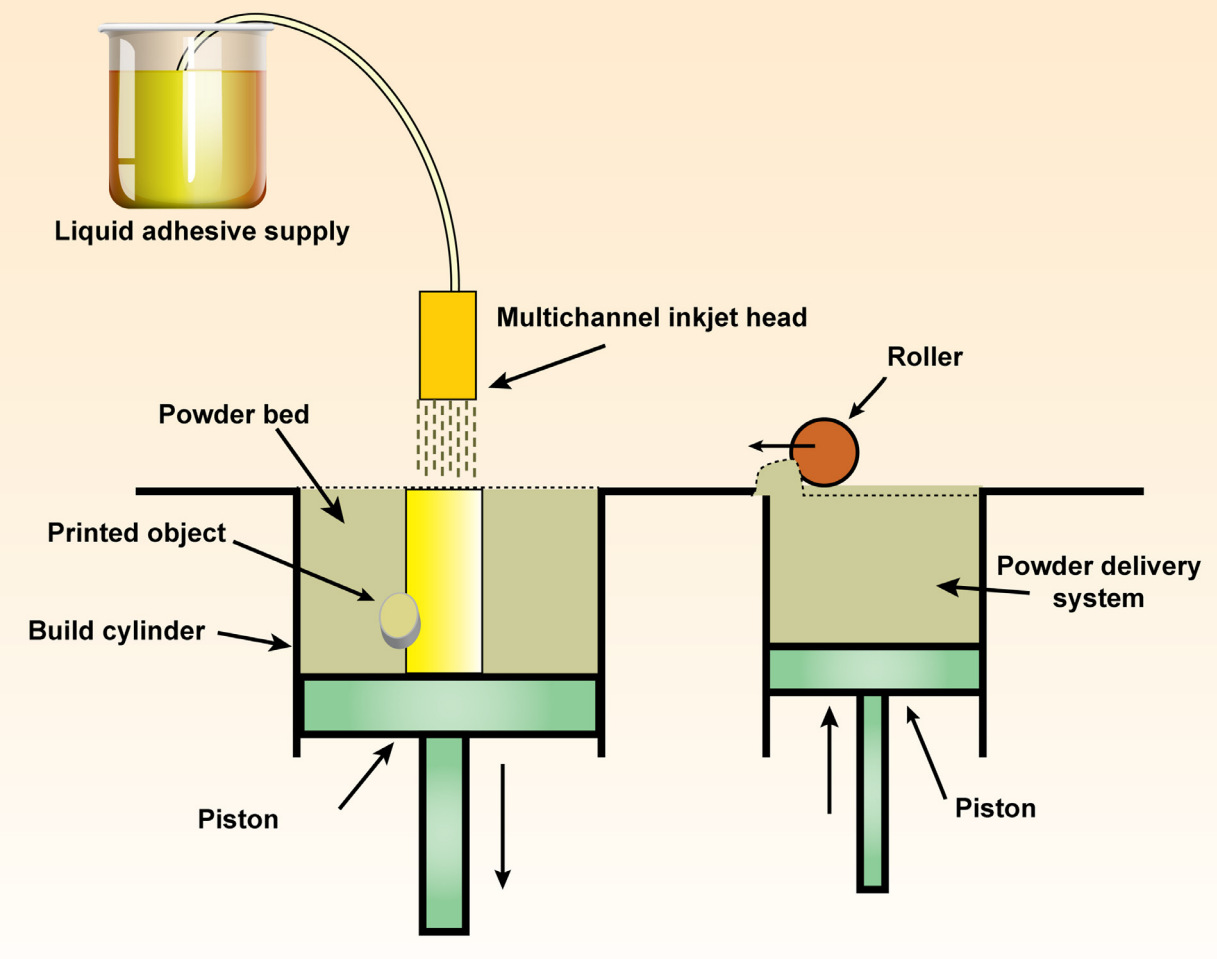

Fig. 1. Illustration of inkjet-based 3D printing technology.

PAM technique involves the use of semisolid materials or pastes as a printing material which is also called as SSE technique. The PAM-based 3D printer is comprised of a syringe extruder system, a compressor, and a computer with 3D designing and slicing software. The semisolid material or paste is filled in a metal or plastic syringe and mounted in the extruder attached to a pressure-controlled air pump. With the help of the pressure, the material inside the syringe is extruded through small nozzles of different sizes and shapes. The printer head is moving horizontally in different directions to deposit the first layer, then the printer stage moves down to allow a new layer to be created on top of the previous one. This process is repeated to complete the printing of the 3D design.

The computer-aided design (CAD) software and the slicer software (STL file) are used to design and slice the 3D object. Then the G-code is obtained to set the printing parameters. The extruder and the printer stage have the option of an additional heating element to heat or melt the material inside the extruder or to accelerate the evaporation of the solvent from the printed material during the layer formation.

The PAM printing technique requires optimization of several parameters for desirable printing. The consistency of the materials (paste) needs to be optimized for successful extrusion through the nozzle and free from gritty particles to avoid blockage of the nozzle. Both organic and inorganic solvents are employed to prepare the paste. The solvent used should not be highly evaporative as it may result in nozzle blockage due to premature evaporation of the solvent nor it should be slow evaporative as it may delay the drying process of the deposited layers.

The printer parameters such as printing pressure, printing speed, nozzle shape, and nozzle diameter were influenced by material consistency and viscosity. Highly viscous materials may require high pressure and large nozzle size for extrusion whereas low viscous materials may extrude at low pressure and small nozzle size. The material extrusion rate, nozzle size, and applied pressure will control the layer size and thickness. The determination of layer parameters (size and thickness) are the prerequisites for designing 3D object shapes and sizes. Additionally, the viscosity of the printed material also influences the printing speed. The highly viscous material cannot be printed at high speeds as the amount of extruded material will not be sufficient to form the desired layer. Similarly, the low viscous material or rapidly extruding materials cannot be printed at low speeds as it may affect the layer geometry and result in dragging and bloating of the layers [24].

The PAM-based 3D printing technique is suitable for a wide range of pharmaceutical-grade of excipients to prepare the paste and works at room temperature for heat-sensitive materials. High drug loading can also be achieved through the PAM-based 3D technique [8]. The limitations associated with this technique are the use of organic solvents as it may cause stability problems of the API and the drying speed of the printed layers. This technique has less printing resolution compared to the other printing technique which is affected by the nozzle size and the layer formation [25].

FDM is the other type of extrusion-based technique that also has been researched extensively for customized drug delivery purposes. The material is fed to the printer as a filament which is melted and extruded through a heated nozzle. The melted material turns to a

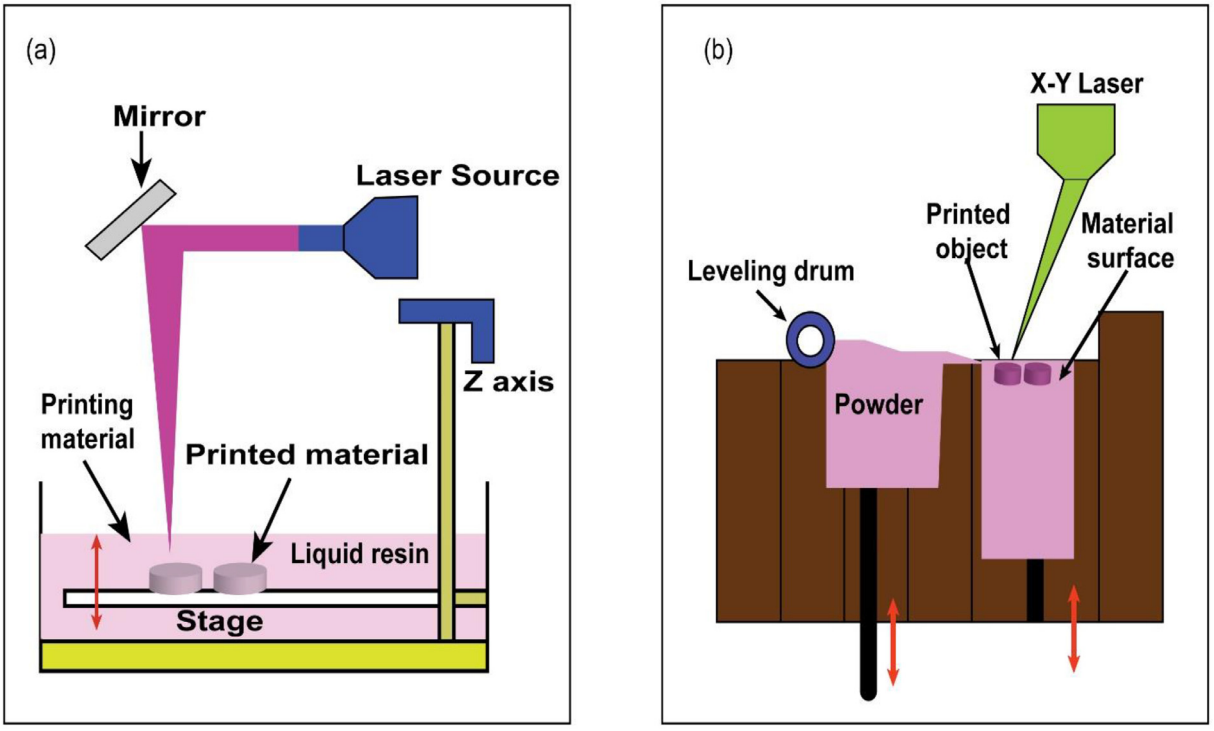

Fig. 3. Illustration showing laser-based 3D printing techniques. **(a)** Stereo lithography (SLA) technique **(b)** Selective laser sintering (SLS) technique.

solid in a short period and forms a layer, and by descending the printer stage, it allows the formation of a new layer, and by repeating the process, the 3D design is formed [26]. The foremost requirement of FDM-based 3D printing is the preparation of filament. Forming pharmaceutical-grade materials into printable filaments is the biggest challenge of applying this technology for the production of pharmaceutical dosage forms. A hot-melt extruder (HME) is used to melt the plastic polymer and extrude it through a hot orifice to form filaments. To print a dosage form using FDM, either the polymeric mixture is made as filament then soaked in a solution that contains the API or the API is mixed with the polymer before the HME step. Then, the filament is mounted on the printing head and extruded through a heated nozzle to form layer upon layer stage to fabricate the 3D shape. The printing temperature is an important parameter that needs to be optimized for an efficient and continuous printing process. The formed filament should have desirable properties to withstand the thermal and mechanical stresses during the printing process to form 3D geometries. The temperature of the nozzle head should be higher than the filament melting temperature for uniform extrudes and no blockage. And the temperature of the printer stage should be less than the filament melting temperature to allow the resolidification of the printed material. The plasticity, rigidity, and brittleness of the filament will have a direct impact on the printing process and the quality of the printed object [27].

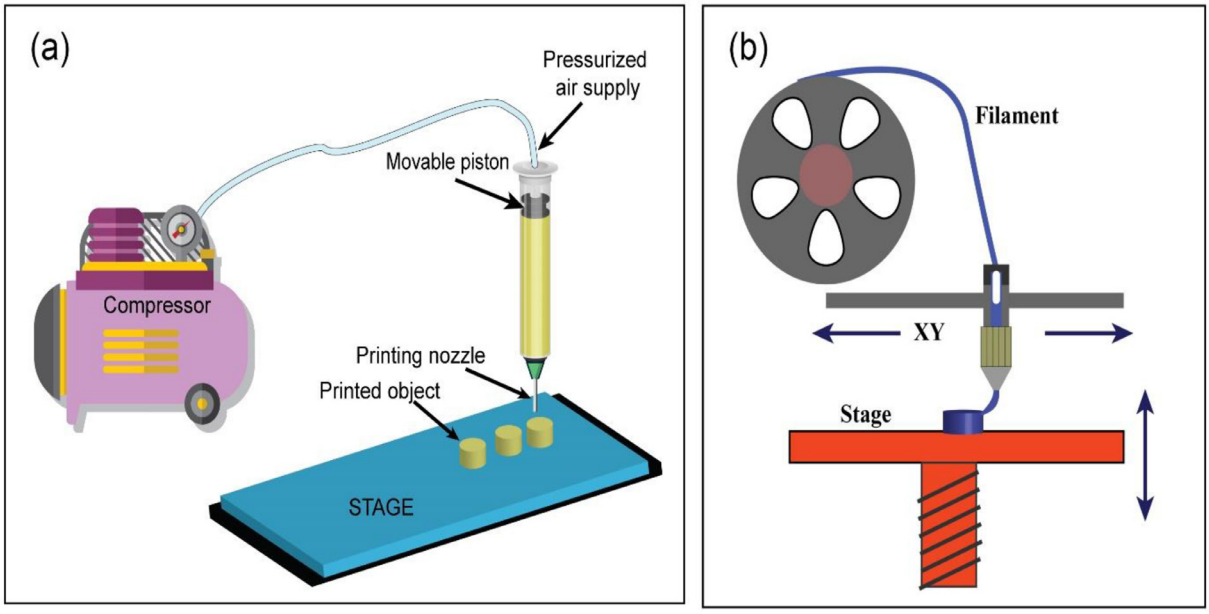

Fig. 2. Illustration of extrusion-based 3D printing technique. **(a)** Pressure-assisted microsyringe (PAM) printing technique **(b)** Fused deposition modeling (FDM) printing technique.

The affordability of FDM printers is the main advantage in all applications. In drug delivery applications, the advantages include, the no use of organic solvents, no further post-processing, good mechanical strength, and better printing resolution, especially when compared to PAM. In general, FDM printing produces slow drug release formulations because of the properties of the printed materials that make it difficult to disintegrate. However, by adjusting the in-fill pattern and in-fill percentage the drug dose and release can be adjusted [28]. The high processing temperature during the filament formation and extrusion is the major limitation of this technique, which makes this technique not suitable for thermos-sensitive API and the low-temperature grade polymers [29].

2.3. Laser-based 3D printing system

Laser-based 3D printing technique involves the use of high energy light i.e. UV laser beam focused on the material surface to form layers that make the 3D shape. Based on liquid and powder solidification there are two types of laser-based 3D printing techniques i.e. stereolithography (SLA) and selective laser sintering (SLS) technique as shown in Fig. 3.

In SLA, the laser is focused on the top layer of photosensitive polymeric liquid resins. This high energy focus solidifies precise area through polymerization of the liquid are to form a solid layer then the reservoir that contains the liquid resin descend to allow the laser to form the subsequent layer another to build a 3D shape [30]. SLA technique could also be employed to fabricate drug-loaded hydrogels and can build microstructures for transdermal drug delivery applications.

The lack of FDA-approved grade of photo polymeric liquid resins is the major drawback that slows down the application of this technique for the preparation of dosage forms. Also, the instability of the printed material due to the use of photosensitive resins and the possible cytotoxicity due to leaching of the entrapped photoinitiator molecules and monomers in the 3D structure [31].

The utmost advantage of the SLA technique is the high resolution of the printed object up to 0.2 μm which is outstanding compared to other techniques where a resolution of 50–200 μm can be achieved. The resolution of the printed object and layer thickness is mainly depending on the intensity and duration of exposure of the laser beam [2].

SLS is a powder solidification technique where a bed of powder material is sintered below the melting temperature of the polymeric material by using a laser beam which causes melting and fusing of the polymeric material and forms a layer. Then the stage is lowered, and a new powder bed is transferred from the feed compartment which subsequently gets exposed to the laser beam and forms layer by layer 3D structure. The layer thickness and resolution of the printed object depend on the laser focus, intensity, speed of laser travel over the stage, and the particle size of the powder mixture [32].

The advantage of SLS is the single-step printing process with high resolution and no use of organic solvents and no need for post-printing drying. This technique has the limitation of API degradation due to the melting process of laser sintering, the limited choice of photosensitive polymers, and the printing of hollow structures is not possible [33].

3. 3D Printing technology in drug delivery

3D printing technology has been explored to design different drug delivery systems by fabricating unique, novel, and specific geometries tuned with tailored drug release characteristics to achieve customized drug delivery profiles. 3D printing technology has been employed as an emerging tool to deliver API in different dosage forms [34] as immediate-release tablets [35], sustained-release tablets [36], modified-release tablets [24], immediate-release films [37], pulsatile release capsular devices [38], controlled-release implants [39] and controlled release transdermal patches [34]. The 3D printing technology approach has been used for the delivery of both hydrophilic and lipophilic drugs. BCS class II and class IV drugs are also fabricated to improve the solubility and bioavailability profiles of these drugs via 3D printing technology [40]. In this section, we will discuss the various drug delivery approaches via 3D printing techniques.

3.1. Oral drug delivery

3D printing technology has proven promising in the development of solid oral dosage forms. This technology allows the production of novel formulations that overcame many limitations associated with conventional drug manufacturing methods. 3D printing has the potential to develop different sizes and complicated shapes with tuned release characteristics to fulfill the demand for personalized medications. Among the 3D printing techniques, extrusion-based are the most utilized techniques in the development of oral dosage forms. The oral drug delivery approaches produced by 3D printing techniques have tuned the drug release characteristics of the API's according to patients need which led to the development of immediate-release systems, delayed-release systems, polypill containing a complete dosage regimen for a diabetic or hypertensive patient in a single pill, gastro-retentive drug delivery system. In this section, some of the recent 3D printing approaches with respect to oral drug delivery have been discussed.

Oral dosage forms are the most convenient route to deliver API and have more patient compliance compared to the other route of administration. Great advances in the conventional manufacturing of oral dosage and a large library of excipients offer a versatile platform for drug delivery. However, the limited geometry and shapes that can be produced by conventional manufacturing have limited the flexibility of this technology. The principle underlying 3D printing, layer by layer formation, allows flexibility to produce geometric dimensions that cannot be produced by conventional methods.

With an approach to compare the conventional manufacturing method with 3D printing technique Fuenmayor et al., developed an oral tablet by three different manufacturing techniques i.e. direct compression (DC), fused deposition modeling (FDM), and injection modeling (IM) [35]. The tablets were prepared with the same composition and are of the same dimensions. The physical and drug release characteristics of the tablets prepared by three different techniques showed a statistical variation. The drug release profile of the tablet prepared by direct compression (DC) method was immediate whereas the tablet prepared by injection modeling (IM) exhibited a sustained release profile for 48 h and similarly the tablet prepared by fused deposition modeling (FDM) exhibited both immediate and sustained release characteristics based on printing parameters. This concept provides evidence that 3D printing techniques have the capability to alter the drug release characteristics [35].

In another approach of delivering two different drugs in a single system to provide a time-delayed drug release profile Matijasic et al., developed a capsular device with two compartments as modular Super-H capsule and can capsule. Dronedarone hydrochloride and ascorbic acid were used as the model drugs and PVA is used to prepare filament by using the FDM method. The capsular device was developed with a difference in layer thickness. The in-vitro studies revealed that the Super-H capsule lag time in an acidic media depends on membrane thickness. The can capsule had shown gastric resistance in acidic media for 2 h and released the drug in alkaline media i.e. in the small intestine. This approach provides an evidence that the 3D printing technique can be utilized to develop personalized drug delivery devices by encapsulating different drugs posing delayed drug release profiles [41].

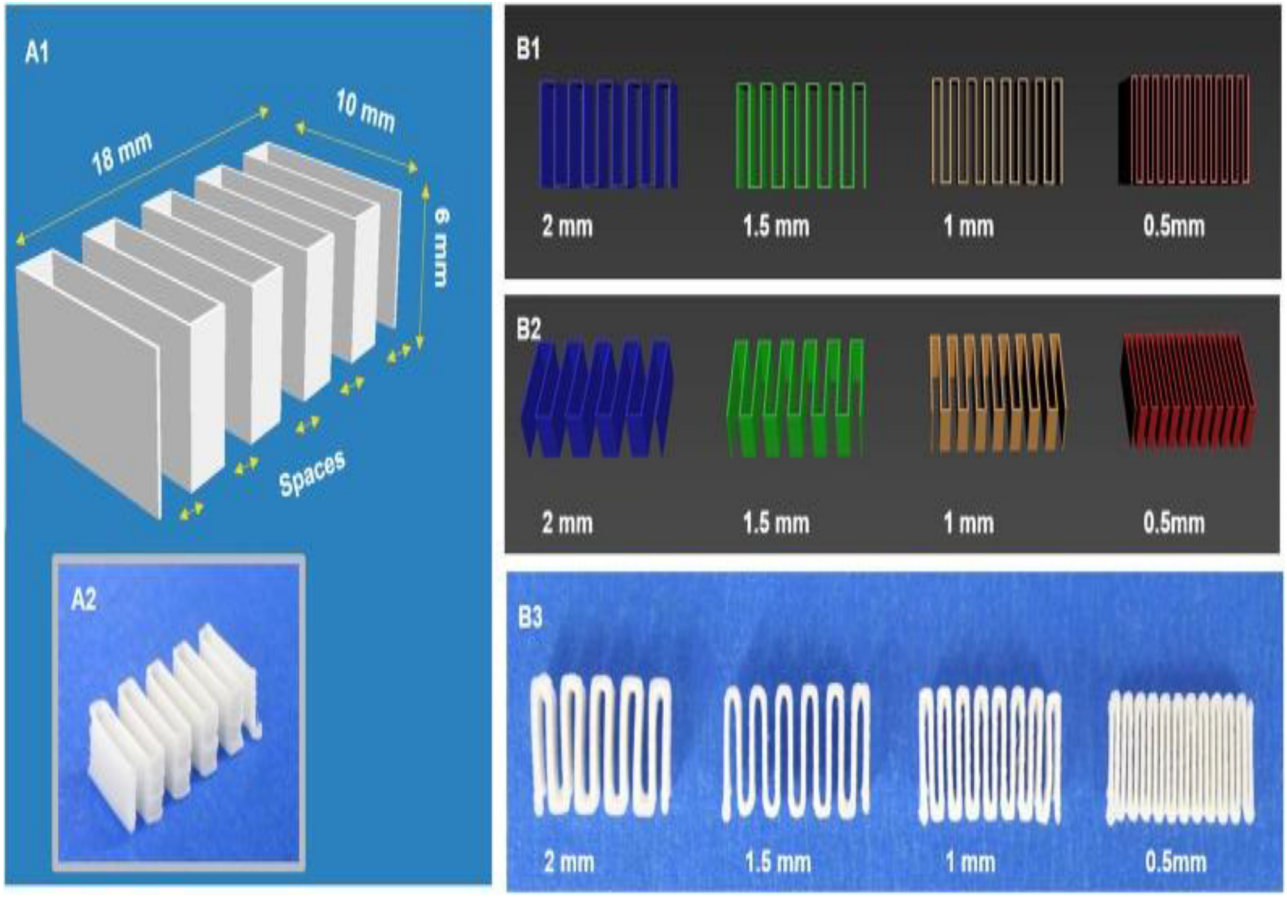

Fig. 4. (A1) Rendered image and (A2) photograph of radiator-like design. (B1) Top view, (B2) side view, and (B3) photograph of radiator-like doses based on theophylline: PEG 6 K: PEO 600 K 30:35:35. (Reprinted from [42]with permission from Elsevier).

Similarly, an FDM based 3D printing technique has been employed to develop a bilayer tablet Containing two anti-diabetic drugs i.e. metformin and glimepiride. The objective of this study was to develop a single pill with a specific dosage regimen for personalized drug delivery. Eudragit® RL and polyvinyl alcohol (PVA) were used as the polymer matrix filament for the formulation of bilayer tablets. The results of the Microfocus computed tomography (μCT) imaging revealed that the printing accuracy was in the range of -100, +200 μm and the drug was in amorphous form in the polymer matrix evidenced by X-ray diffraction (XRD) studies. The drug release studies revealed an immediate drug release profile of glimepiride (75 min) and a sustained drug release profile (480 min) for metformin. Thus 3D printing approach can develop patient-specific drug delivery systems with different release characteristics [36].

Similarly, an oral dosage form with an innovative design was fabricated by Isreb et al., using FDM based 3D printing technique [42]. In this approach, the author developed a unique and novel geometry for the oral dosage form in the shape of a radiator (illustrated in Fig. 4).

This innovative design has boosted the drug release profile. Polyethylene oxides (PEOs) and polyethylene glycol (PEG) of different grades were used to develop the filament and theophylline were used as the model drug. The filament was prepared by the hot-melt extrusion method by using a blend of polymers. The drug-loaded filament was used to fabricate a radiator-like design with parallel plates with a varied interplate spacing of 0.5, 1,1.5, and 2 mm. The characterization of drug-loaded filament showed sufficient mechanical strength. The molecular grade of the PEOs influenced the flow behavior during the printing process. A higher molecular grade PEOs showed increased shear viscosity and hindered the flow and printing process. The results of this investigation revealed that the innovative geometry of the fabricated structure boosted the drug release. The novel radiator-like design with an interplate spacing of 1 mm showed the fastest release profile. This approach provides a proof of concept that the 3D printing technique can be exploited to tune the geometries of the drug delivery systems [42].

Oral delivery via the development of fast dissolving films offers a rapid drug delivery by providing fast drug dissolution and absorption profile. With this intention, Ehtezazi et al. fabricated fast dissolving oral films with single and multiple layers using the FDM printing technique coupled with hot-melt extrusion (HME) to fabricate the films and filament [37]. PVA and PEO were used as filament-polymer and paracetamol and ibuprofen were used respectively to develop the drug-loaded filament. The thickness of the single-layer and multiple-layer films were 197$\pm$21 μm and 298 $\pm$ 15 μm respectively. The disintegration time exhibited by single layer and multiple layer films were 42 s and 48 s respectively. With this approach, rapid disintegrating films were developed without using a disintegrant [37].

3D printing technology has overcome the drawbacks associated with the conventional method of manufacturing a pill containing multiple drugs. 3D printing has led to the development of a polypill containing multiple drugs with a customized dose and drug delivery profile. Considering this fact, Khaled et al. developed a polypill containing five drugs fabricated as an immediate release compartment containing two drugs aspirin and hydrochlorothiazide, and a sustained release compartment containing three drugs i.e. pravastatin, atenolol, and Ramipril [7]. The fabrication of polypill was done by

using a semisolid extrusion-based PAM 3D printing technique. This approach has shown promising drug release characteristics as per the fabricated system design. An immediate drug release of aspirin and hydrochlorothiazide followed by sustained release of pravastatin, atenolol, and Ramipril was achieved [7].

In another instance, from the same research group, a pill containing multiple drugs has been designed by using a semisolid extrusion-based 3D printing technique. The pill contains an osmotic pump compartment with captopril and a sustained release compartment with nifedipine and glipizide intended for the treatment of hypertensive and diabetic patients. The drug release profiles showed zero-order release kinetics from the captopril compartment and first-order release kinetics or Korsmeyer-Peppas release kinetics from the nifedipine and glipizide compartment based on the drug-polymer ratios [43].

With the same mindset, a polypill was fabricated by using FDM based 3D printing technique. PVA filament containing four drugs i.e. Lisinopril dihydrate, indapamide, rosuvastatin calcium, and amlodipine besylate was extruded through the printer to form a multilayer matrix design. The release of these drugs depends on the position of the drug in the multilayer matrix. The filament extrusion process and 3D printing process were carried out by using water as a co-plasticizer which in turn decreased the processing temperatures. The processing temperatures were reduced from 170 °C to 90 °C and 210 °C to 150 °C for extrusion and 3D printing processes respectively due to a reduction in the thermal stress of the materials. X-ray powder diffraction (XRPD) studies showed indapamide and rosuvastatin calcium was in amorphous form and Lisinopril dihydrate and amlodipine besylate were in the crystalline state in the 3D pill [44].

3D printing technique has been employed to develop a gastro-retentive drug delivery system that retains the drug in the stomach for a prolonged period. An improved gastric retention time will enhance the drug absorption profile for drugs that shows stomach absorption and the drugs which exhibit a better solubility/dissolution profile in acidic pH. With this perspective, Kimura et al. developed a 3D printed floating tablet of Itraconazole by using HPC and PVP polymer. The FDM-based 3D printing technique was used to develop a hallow structure enwrapped shell with varied thicknesses. PVP is used to enhance the solubility of the drug whereas HPC polymeric matrix is employed for design development and to improve tablet floating time. The results of this investigation revealed that the gastric floating time was enhanced and sustained release of the drug was achieved based on the thickness of the shell. Thermal analysis showed no degradation of the polymer and drug during the printing process [45].

Recently, a gastro retentive tablet shell was developed by Dumpa et al. using FDM-based 3D printing. In this approach first, an immediate release compressed tablet of theophylline was prepared by direct compression method and then it is placed inside the 3D printed HPC and ethyl cellulose-based floating shell of varying thickness. The results showed an outstanding floating behavior of the tablets and a pulsatile drug release was achieved based on infill percentage and shell wall thickness [38].

Similarly, by using semisolid extrusion-based 3D printing Qijun Li et al. developed a floating tablet of dipyridamole using HPMC and MCC as the polymer to form a fine lattice structure of the tablet. The fabricated 3D printed tablet showed a floating time of more than 12 h due to air entrapment in a lattice structure and the drug release was dependent upon infill percentage [46]. Moreover, a 3D printed floating tablet of domperidone was designed by Chai X et al. using HPC as the polymer by FDM technique. The floating tablet was designed as a hollow structure. A sustained drug release profile was exhibited by the 3D printed tablets. The radiographic images of the tablet showed a floating time of more than 8 h in the rabbit stomach. This provides a proof of concept for the successful development of a gastro-floating tablet [47]. In another approach, Fu et al. developed a floating tablet of riboflavin by using FDM based 3D printing technique. PLA filament is used to design the capsular device with two compartments. One compartment was filled with air and the other eccentric net compartment is used to place the compressed tablet. The results of this investigation revealed an enhanced floating time of up to 72 h. The drug release achieved was 62% at 72 h. The shell acts as a barrier for the achieved drug release profile [48].

In a novel approach, Algahtani et al. developed a 3D printed controlled release shell to encapsulate an immediate release commercially available marketed product by using PAM-based 3D printing technique (illustrated in Fig. 5) [24].

Propranolol HCl marketed tablet was encapsulated in an empty shell developed by using cellulose acetate, PEG 6000, and D' mannitol as the polymer mixture. The commercial tablet exhibited more than 95% of drug release within 20 mins whereas the same tablet enclosed inside the shell exhibited around 85% of drug release in 12 h. A sustained drug release profile was achieved for the commercial tablet enclosed inside the shell. This investigation aims to provide a proof of concept that 3D printed can be employed to modify the release of already available commercial products at the point of care [24].

In another instance, the same research group has led to the development of an oral 3D printed tablet for a lipid-based self-nanoemulsifying drug delivery system (SNEDDS) without using an adsorbent [49]. A self-nanoemulsifying 3D printed tablet of dapagliflozin propanediol monohydrate, a poorly water-soluble drug was designed by using extrusion-based PAM (pressure-assisted microsyringes) 3D printing technique to achieve an immediate drug release profile. This 3D printed antidiabetic drug containing self-nanoemulsifying tablet upon self-nanoemulsification in gastrointestinal fluid generate drug enclosed nanoemulsion system for faster drug absorption (illustrated in Fig. 6).

The design of solid-based 3D printed SNEDDS was based on the incorporation of PEG 6000 which acts as a solid matrix and poloxamer 188 which acts as an emulsifying and solidifying agent for the incorporated oil/ liquid phase (capryol 90, octanoic acid, and PEG 400). The 3D printed tablet of these SNEDDS revealed >75.0% of drug release within 20 min [49].

While focusing on inkjet printing, orodispersible films of enalapril maleate were fabricated by using a continuous inkjet printing technique. In this approach, drug-free and hydrochlorothiazide containing macrogol-based orodispersible films were imprinted with enalapril maleate. The printed orodispersible films exhibited therapeutically relevant fixed-dose combinations [50].

3.2. Transdermal drug delivery

3D printing technique has been focused as a potential approach for transdermal drug delivery through fabricating complex and customized geometries for pharmaceutical drug products and medical devices. 3D printing technique has been successfully demonstrated in various transdermal formulation approaches like implants, microneedles, masks, and patches for local and systemic delivery of API according to the patient's need.

An approach by kempin et al. developed an implant that can be administered to a specific application site and the geometry of administered implant was tuned according to the application site by using a 3D printing technique. This work demonstrated the formulation of an implant by using fluorescent dye quinine as a model drug. The method used to fabricate this implant was the extrusion-based FDM technique coupled with hot-melt extrusion of different polymers to form a drug-loaded filament. The polymers used in this method are polycaprolactone (PCL), Eudragit®RS, and ethyl cellulose (EC). The printed implant model was a hollow cylinder. The fluorescent dye quinine distribution was able to be visualized in the filament and implants. The results of this study showed the fastest drug release of 76% within 51 days from PCL implants, whereas only 5%

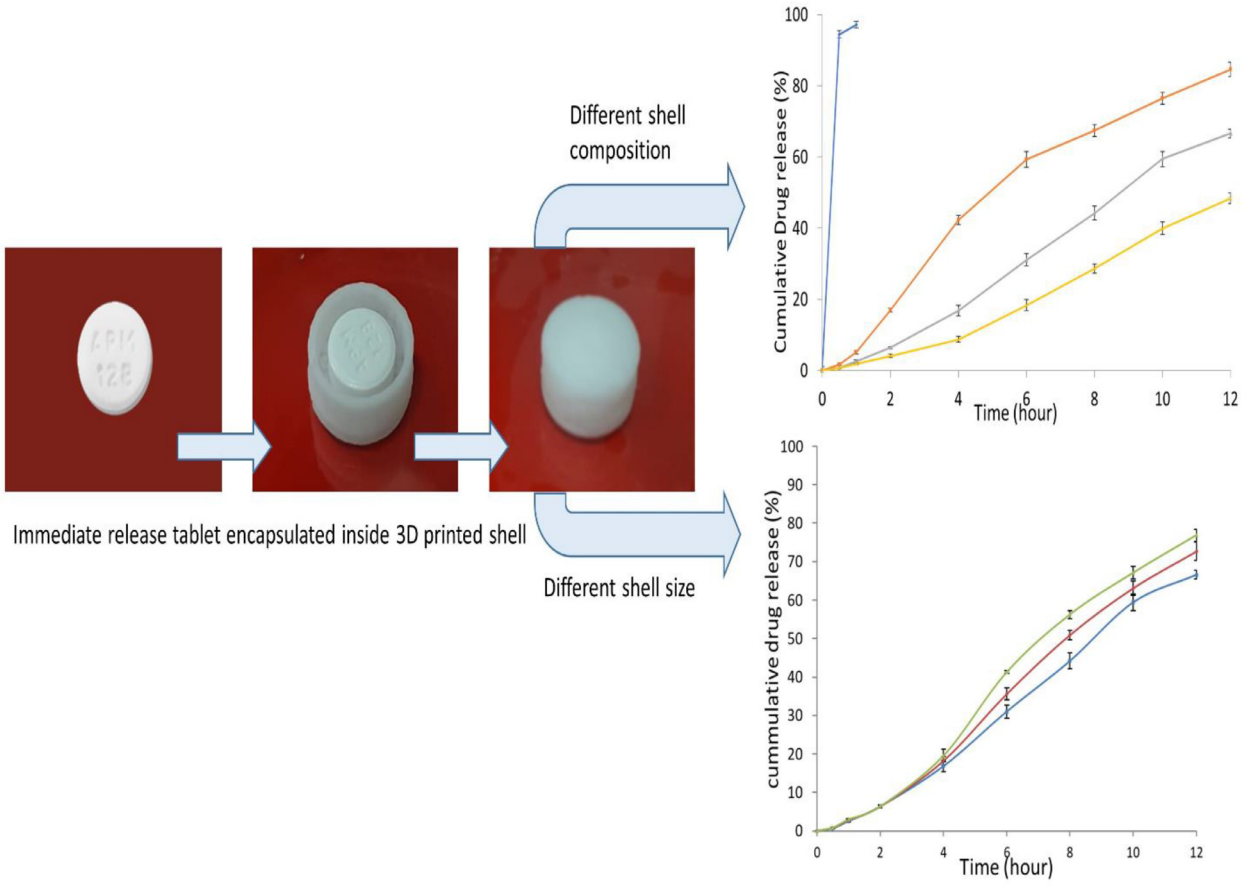

Fig. 5. 3D printed coating shell to control the drug release of encapsulated immediate-release tablets. (Reproduced from reference [24], copyright open access by Creative Commons Attribution License).

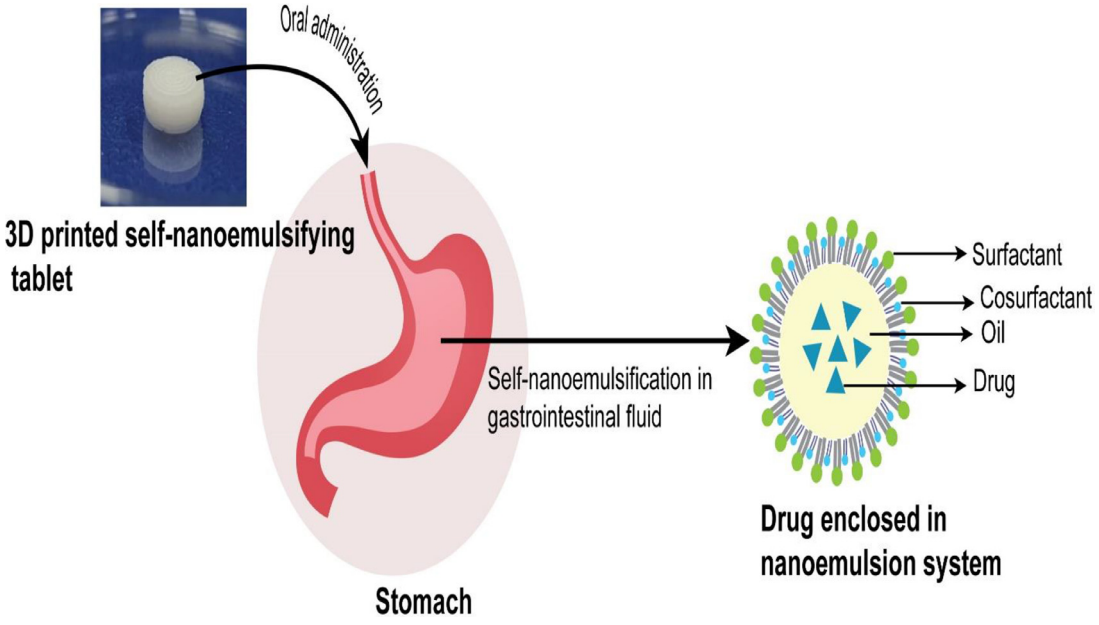

Fig. 6. Schematic illustration presenting a generation of drug enclosed nanoemulsion system upon self-nanoemulsification of 3D printed self-nanoemulsifying tablet in gastrointestinal fluid. (Reproduced from reference [49] copyright open access by Creative Commons Attribution License).

drug release was achieved through Eudragit® RS and ethyl cellulose (EC) in 78 and 100 days respectively [39].

In an approach, Allen et al. developed dissolvable micro-needles employing the piezoelectric inkjet printing technique. The developed dissolvable micro-needles were fabricated by drop-on-drop deposition technique resulted in controlled droplet formulation of encapsulated seasonal influenza vaccine. The product disclosed stabilization of the vaccine for percutaneous administration [51].

In another approach, Goyanes et al. fabricated a nose mask for the specific treatment of acne using topical delivery. In this approach, the patient's nose scan was taken to fabricate a customized size mask by using FDM based 3D printing technique. Flex EcoPLA™ (FPLA) and Polycaprolactone were used as a polymer to fabricate the mask of the patient's nose size. The 3D printed anti-acne mask showed <187 μg/cm2 of drug release within 3 h. [52].

In a similar approach, Muwaffak et al. developed a patient-tailored wound dressing nose and ear-shaped masks by employing FDM based 3D printing technique. In this approach zinc, silver, and copper metals were used as an anti-microbial agent. The Advantage of this approach was fixed adherence to custom-made wound dressings at the site of the application when compared with normal flat dressings. The PCL fabricated masks with silver and copper showed enhanced anti-microbial treatment [53].

PAM-based extrusion technique has been demonstrated by Hee-Gyeong Yi et al. developed an anti-cancer patch with a local drug delivery approach (illustrated in Fig. 7) [54]. The patch is fabricated by using polycaprolactone and poly (lactic-co-glycolic acid) as the polymeric material and 5-fluorouracil was used as an anti-cancer drug for pancreatic cancer growth suppression. The developed patch exhibited prolonged drug release up to 4 weeks and showed a correlation between the drug release profile and geometry of the patch. Thus, the 3D printing technique act as a promising approach for local drug delivery [54].

On the other hand, the inkjet printing technique has also found its application in transdermal drug delivery. In an approach piezoelectric inkjet printing technique has been employed to develop transdermal films containing indomethacin for customized drug delivery. The developed films exhibited efficient drug permeation and improved anti-inflammatory activity with respect to a higher printing density of 600 dots per inch (DPIs) [55].

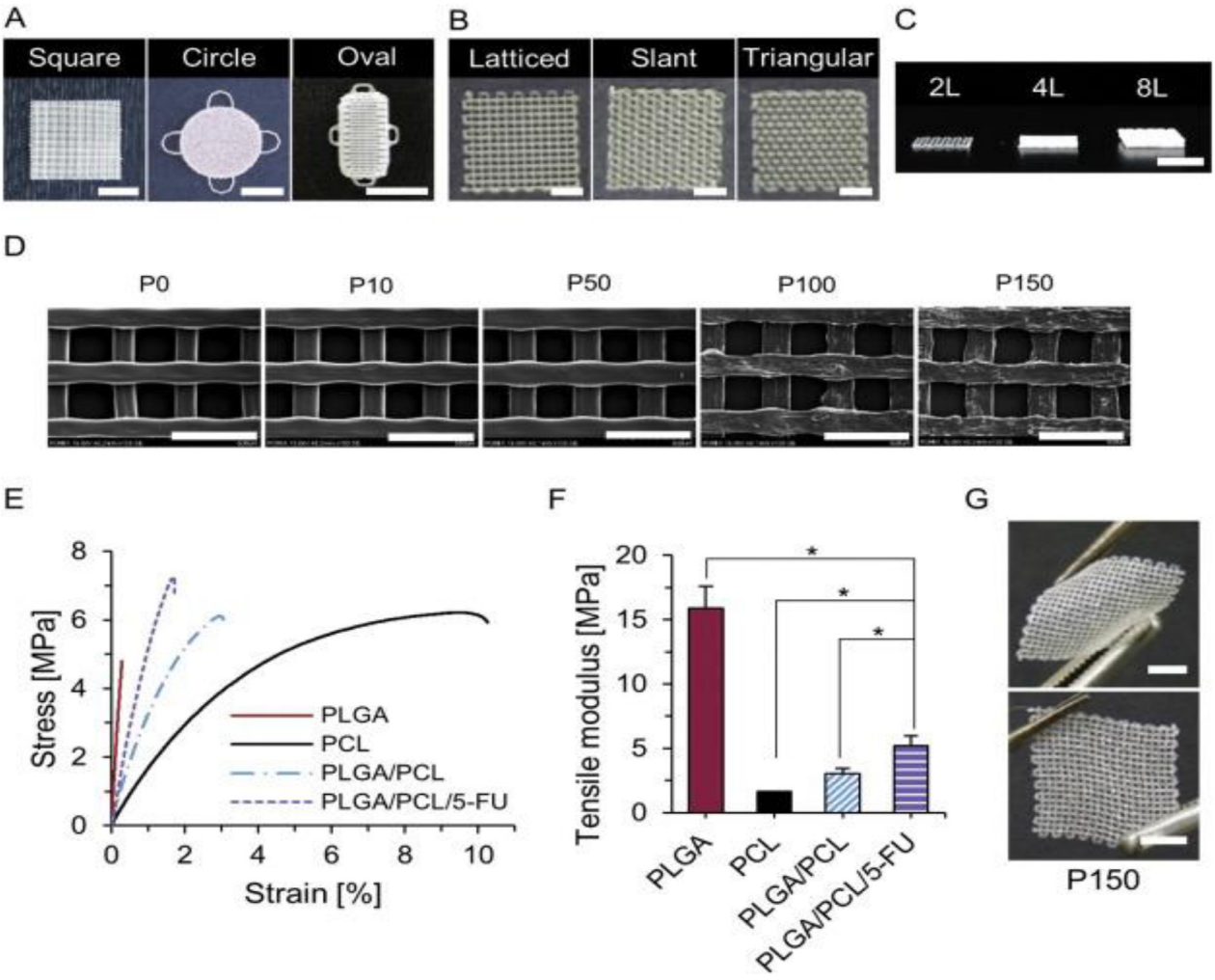

Fig. 7. 3D-printed P150 patches with various structures. (A) Three shapes of the patches: square without loops; circle and oval shapes with loops on each side for suturing. Scale bar: 5 mm. (B) Three types of pores: latticed, slanted, and triangular. (C) Lattice patches layered 2, 4, and 8 times (denoted as 2, 4, and 8 L, respectively) Scale bar: 2 mm. (D) SEM images of the surface of P0, P10, P50, P100, and P150 patches. Scale bar: 500 μm. (E) Stress-strain curves and (F) Tensile moduli of PLGA, PCL, PCL/PLGA with or without 5-FU. *: $P<0.05$ difference versus PLGA/PCL/5-FU (G) Photographs presenting the flexible and stretchable properties of the P150 lattice patch. *Scale bar: 2 mm.* (Reprinted from[55] with permission from Elsevier).

3.3. Pulmonary drug delivery

3D printing as an emerging technology is used to treat respiratory diseases by fabricating 3D printed medical devices and models.3D printed prototypes of lungs support the medical specialist to better understand the diseased condition and potentially provide a means to diagnose and treat respiratory organ diseases. These approaches will further aid to develop personalized inhaled medicines by using 3D printing techniques.

The use of 3D printing in pulmonary treatment is demonstrated by Morrison et al., who fabricated 3D printed bioresorbable airway splints for the treatment of tracheobronchomalacia in pediatric patients. The 3D printed airway splints were found to be an effective alternative to reduce airway collapse in patients and provide a root map by fabricating customized devices for the treatment of life-threatening diseases [56].

Before this, Zopf et al. fabricated a novel 3D printed, Tracheobronchial bioresorbable airway splint which improves the survival efficiency in a porcine animal model by reducing the airway collapse in severe conditions of tracheobronchomalacia [57].

3D printing technique also provides an advancement in the development of medical devices for the treatment of asthma and breathing problems. A "sneezometer" was fabricated by using 3D printing technology by a group of researchers which measures the airflow and sneeze speed [58]. This device is more precise and faster than a conventional spirometer. This device determines the airflow rate in patients suffering from asthma and other breathing problems and provides a means for better treatment by fabricating advanced design inhalers by using 3D printing technology. A 3D printed ergonomic and friendly asthma inhaler was designed which is an effective assistive solution to improve the usage of the inhaler devices by people suffering from asthma [59]. This 3D printed object is an assistive technology designed to make asthma treatment more effective, convenient, and friendly by improving the ergonomy of any standard asthma inhaler available on the market.

Moreover, in the treatment of lung cancer also 3D printing technology has been employed by developing a prototype of lung tumor movement simulator by Quinone's et al. This device helped to find out the movement of the tumor during respiration and provides a means for radiotherapy treatment in lung cancer [60].

3.4. Intrauterine drug delivery

3D printing methods have been employed to fabricate drug delivery devices and implants for Intrauterine drug delivery. The 3D printing technology provides a reliable solution for fabricating personalized size and shape devices for local and systemic delivery of API through the intrauterine route. These devices will deliver a precise dose of the API with tuned release characteristics.

In an approach, Hollander et al. developed a T-shaped prototype intrauterine device by using FDM based 3D printing technique. The drug release profile of the model drug indomethacin from the 3D printed devices fabricated by using poly-caprolactone was found to be faster compared to extruded filament itself. The drug release was through polymer diffusion and the efficient drug release profile was achieved through the 3D printed devices because the drug was found to be in an amorphous state in the devices compare to the crystalline existence of the drug in the filament [61].

In another approach, the same group of researchers demonstrated the effect of ethylene vinyl acetate (EVA) as a polymer to fabricate intrauterine systems (IUS) and subcutaneous rods (SR) by using FDM based 3D printing technique. The custom-made T- shaped 3D printed prototype devices exhibited a faster drug release profile for 30 days. This concept provides a testbed to develop drug-loaded implantable devices by using ethylene vinyl acetate (EVA) as a polymer suitable for 3D extrudable printing [62].

Similarly, Fu et al. developed customized shaped vaginal rings of progesterone by using FDM based 3D printing technique [63]. In this approach, PLA and polycaprolactone were used as a polymer to form filament by using the HME method. The drug-loaded filament is fabricated into vaginal rings of different shapes designed as O, Y, and M shape (Illustrated in Fig. 8).

Among the three geometries shape, O exhibited higher drug release characteristics compare to Y and M due to higher surface area and geometrical characteristics. This approach provides a means to develop customized shape and size contraceptive devices by using the 3D printing technique [63].

In a similar outlook, an intrauterine device was fabricated by using a selective laser sintering technique containing two different drugs progesterone and 5-fluorouracil exhibiting synergistic effects in the treatment of endometrial and ovarian cancers. The 3D printed device was fabricated at two different laser powers i.e. 3 W and 5 W. The device fabricated with 3 W laser power exhibited a higher drug release profile due to higher porosity and rapid diffusion. Progesterone showed zero-order release kinetics throughout the dissolution profile and 5-fluorouracil exhibited initial burst release followed by a sustained release for >35 days [64].

Overall contemporary research carried out in the field of 3D printing of medicine for drug delivery applications and their significant outcomes are summarized in Table 1.

4. Opportunities and challenges for implementing 3D printing in medicine

The pharmaceutical industry and its method of mass production could not meet the calls to switch to personalized medicine and did not keep pace with the steady progress in this field. The development in 3D printing of various types and the proof of its ability to produce drugs in small batches and customized doses and release profile made this technology a future solution to fill the gap for personalized medicine. There is a noticeable acceleration to implement this technology for drug dispensing, which began in 2015 with the approval of the 3D-printed Spritam® by Aprecia. Recently Triastek company obtained an FDA clearance for the 3D printed dosage form containing T19 drug for the treatment of rheumatoid arthritis. The product is designed to have multiple infills that result in different doses and release profiles for personalized medicine.

3D printing has a potential application in the early development stage of the drug industry because of its flexibility and adaptability to produce the drug to suit that stage. In the early stage of drug development, there is a need to produce the drug in small quantities, doses, and different additives to adjust the appropriate dosage of the drug [65]. Several experiments have tested this technique for the drug development at the preclinical stage, for example, giving rats warfarin sodium, produced with FDM technology, to evaluate different doses of this drug as an anticoagulant and the extent to which it could be an alternative to a splitting marketed tablet [66]. FabRx has successfully conducted the first clinical study to evaluate the 3D-printed drug Isoleucine for the treatment of a rare metabolism disorder called maple syrup urine disease (MSUD). The dose given for this medicine must be accurate based on age, weight, and blood profile. The study showed similarities in Isoleucine blood levels with the preparations formulated in the hospital with means closer to the targeted dose and with less variability [67].

Orphan drugs do not represent an attraction to the pharmaceutical industries due to the relatively small quantities required and the difficulty to dedicate production lines without financial feasibility. Production in small batches, which is the feature of 3D printing compared to the conventional industrial methods, makes it a promising solution for providing orphan drugs with no shortage. Aprecia, the company that produces Spritam has announced the collaboration with Cycle team company specialized in orphan drugs based in

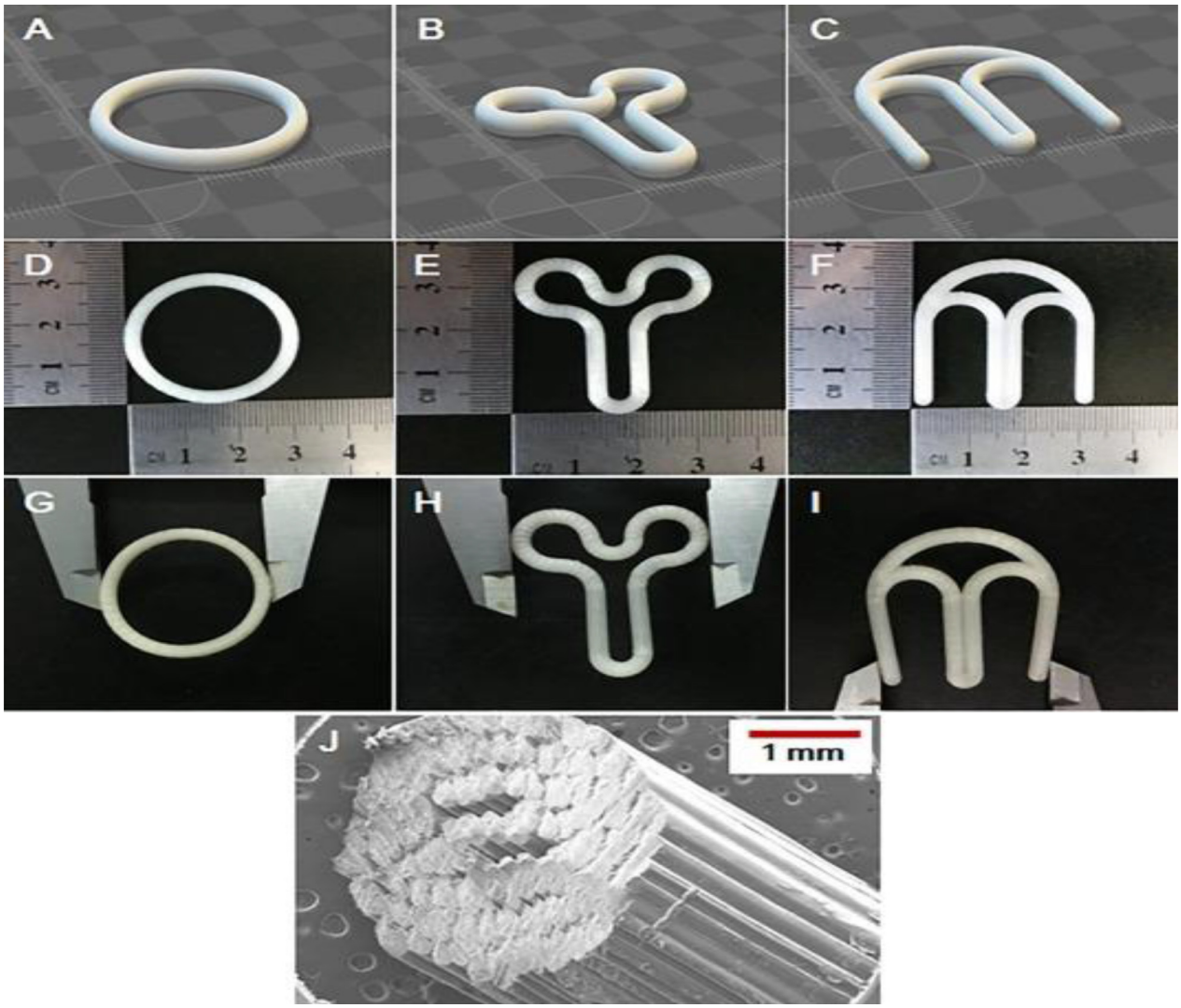

Fig. 8. Images (A-C) of the vaginal rings designed by CAD (computer-aided design) and pictures of 3D printed vaginal rings (D-F) with the shapes of "O", "Y", and "M", respectively. Graphs G, H, and I show the rings compressed with a caliper. Graph J is the SEM image of a cross-section of rings. Reprinted from [63] with permission from Elsevier.

Cambridge. The collaboration aims to produce orphan drugs using Zipdose™ technology owned by Aprecia [68]

High interest noticed from the practicing pharmacists to implement this technology as a method of drug dispensing as the belief in the importance of personalized medicines for more effective and safe treatment, despite their expectation that this method may cause a change in the traditional workstream in the clinical practice [69].

Despite this support and promising theoretical prospects for this technology, the road is still long and the technical and regulatory challenges have not been overcome to see the real implementation of this technology in the healthcare system. The lack of regulatory guidance for the production of medicine using 3D printing technology is the biggest obstacle that slows down the move forward to implement this technology. The regulation issued by the FDA that regulates the use of 3D printing in the medical field focus on the use of this technology for medical devices and prosthetics and does not include drug production [70]. If the drug production using 3D printing is considered a manufacturing process, the standard regulations that are applied to the conventional pharmaceutical products cannot be applied to on-demand produced personalized medicine. The emerging Technology Team (EET) within FDA already started working on this behalf. The main aim of EET is to inspire technological innovation in production and design like 3D printing in pharmaceutical research [71]. The Center for Drug Evaluation and Research (CDER) also started similar programs related to manufacturing science for investigating the usage of innovative technologies like 3D printing [72]. In 2018 Health Canada also published guidance for the 3D printing of medical devices for ensuring quality in personalized drug therapy as well as treatment solutions for patients, immediately after FDA guidelines. The guidance describes an outline of the 3D printing process, important device design considerations, design parameters needed for meeting customization as well as and also a description of the key features of manufacturing operations. In 2019 some regulatory agencies like Health Canada, Therapeutic Goods Administration (TGA, Australia), The European Medicines Agency (EMA), Agencia Nacional de Vigilancia Sanitaria (ANVISA, Brazil), Health Sciences Authority (HAS, Singapore), and Pharmaceuticals and Medical Devices Agency (PMDA, Japan) discussed the possible opportunities of the emerging 3D printing technology under the International Coalition of Medicines Regulatory Authorities (ICMRA). Three out of the six agencies started developing new regulatory frameworks (HSA and ANVISA) or implementing new legislation (Health Canada) for facilitating innovative product development. Under this new framework and legislation, 3D bio-printed products will be addressed. [73,74]. All these agencies urged the requirement of clear-cut regulatory aspects on 3D printing with regards to the design of the printer, its components,

Table 1
Summary of contemporary research carried out in the field of 3D printing of medicine for drug delivery applications.

S. No.	3D printing technique	Drugs/therapeutics	Dosage forms	Route	Outcomes	Ref.
1.	FDM and injection modeling (IM) technique	Caffeine	Tablet	Oral	The drug release profile of the tablet prepared by direct compression (DC) method was immediate whereas the tablet prepared by IM exhibited a sustained release profile for 48 h and similarly the tablet prepared by FDM exhibited both immediate and sustained release characteristics based on printing parameters.	[35]
2.	FDM	Dronedarone and ascorbic acid	Super-H and Can-capsule	Oral	The *in vitro* studies revealed that the *Super-H capsule* lag time in acidic media depends on membrane thickness. The *Can-capsule* had shown gastric resistance in acidic media for 2 h and released the drug in alkaline media i.e. in the small intestine.	[36]
3.	FDM	Theophylline	Dosage form with innovative radiator-like design	Oral	The novel radiator-like design with an inter-plate spacing of 1 mm showed the fastest drug release profile and validate the proof-of-concept that the 3D printing technique can be exploited to tune the geometries of the drug delivery systems.	[38]
4.	PAM	Propranolol HCl	Coating shell to encapsulate tablet	Oral	3D printed coating shell to control the drug release of encapsulated immediate-release tablets.	[23]
5.	PAM	Dapagliflozin propanediol monohydrate	Self-nanoemulsifying tablet	Oral	This 3D printed antidiabetic drug containing self-nanoemulsifying tablet upon self-nanoemulsification in gastrointestinal fluid generate drug enclosed nanoemulsion system for faster drug absorption. The 3D printed tablet of these SNEDDS revealed >75.0% of drug release within 20 min.	[47]
6.	Piezoelectric inkjet printing	Hydrochlorothiazide, and enalapril maleate	Orodispersible films	Oral	It is feasible to develop therapeutically relevant fixed-dose combinations utilizing 3D printing technology. The enalapril maleate doses were successfully printed onto drug-free and hydrochlorothiazide orodispersible films during an in-line continuous manufacturing process	[48]
7.	FDM coupled with hot-melt extrusion	Quinine	Implants	Transdermal/ subdermal	The drug release of these 3D printed implants in phosphate-buffered saline solution pH 7.4 was highly dependent on the used polymer. The desired drug release profile might be controlled by the choice of the polymer and the drug load.	[49]
8.	Piezoelectric inkjet printing technique	Seasonal influenza vaccine	Microneedle patch	Percutaneous	The 3D printing technique was utilized to precisely fabricate bilayer dissolvable microneedle patches as novel dosage forms for the percutaneous delivery of vaccines.	[50]
9.	PAM	5-fluorouracil	Patch	Transmembrane local delivery at the tumor site	The anticancer drug containing flexible patches released the drug over four weeks, and thereby suppressed the growth of the subcutaneous pancreatic cancer xenografts in mice.	[53]
10.	FDM	Indomethacin	T-shaped intrauterine systems	Intrauterine	The efficient drug release profile was achieved through this 3D printed intrauterine system composed of poly (ε-caprolactone). This technique is successfully exploited to fabricate the controlled release implantable devices.	[58]
11.	FDM	Indomethacin	T-shaped intrauterine systems and subcutaneous rods	Intrauterine	The efficient drug release profile was achieved through this 3D printed intrauterine system composed of ethylene vinyl acetate. This technique was successfully exploited to fabricate the drug-loaded implantable prototypes.	[59]
12.	FDM	Progesterone	Vaginal rings	Vaginal	The vaginal rings showed the long-term sustained release of progesterone for more than 7 days and O-shaped rings exhibited higher drug release characteristics compare to Y-shaped and M-shaped rings. It is due to the higher surface area and geometrical characteristics.	[60]
13.	SLS	Progesterone and 5-fluorouracil	intrauterine device (IUD)	Intrauterine	The 3D printed IUD exhibited zero-order release kinetics throughout the dissolution profile for progesterone while 5-fluorouracil exhibited initial burst release followed by a sustained release for >35 days. The developed IUD in the present investigation has great potential for future applications in cancer treatment, particularly for endometrial and ovarian cancers.	[61]

printing materials, software as well as the production process. EMA and The Medicines and Healthcare Products Regulatory Agency (MHRA) planning to develop a manufacturing master file to provide accurate regulatory surveillance to the point-of-care production. As per this concept, one licensed master site will oversee assuring its satellite sites are qualified for and comply with the expected regulatory requirements. According to Health Canada, printed products are complex products and require evaluation through the Advanced Therapeutic Products Pathway, in which integration of biologics and medical device components and production method, is used to produce personalized therapeutic strategies [73,74].

Technologies used in 3D printing utilize factors such as heat, solvents, and light to stack layers to produce the 3D shape. These factors may affect the stability and quality of the printed drug. Therefore, quality must be ensured and solutions should be found to evaluate the post-printing product, especially if it is produced in clinics and pharmacies away from the industrial sets. The quality control of traditional pharmaceutical products that are commonly conducted inside the pharmaceutical industry and production lines have a destructive manner, laborious and expensive and it is not compatible with the concept of on-demand production of personalized medicine. Several approaches have been proposed to quantify the drug content in the printed dosage forms using NIR and Raman spectroscopy which are non-destructive and reliable and could provide a real-time evaluation of drug product quality at the site of production such as clinics and hospital pharmacies [75,76].

Several types of 3D printers have been explored for their ability to produce pharmaceutical dosage forms, and some of them have a preference for implementation over others such as PAM and FDM due to their flexibility, ease of use, and the possibility of using safe materials that fall under GRAS (generally recognized as safe) excipients, while other types such as VAT polymerization have the problem of using non-GRAS materials. But in general, all of the printer types available in the market are specifically designed for drug production and not compliant with the GMP standards. Since this technology is expected to serve for the drug dispensing in the health system instead of factories, there is a need to manufacture compact printers that are easy to use and produce medicine in a safe and high-quality manner. Several companies took the initiative and exploited this shortage and developed 3D printers specialized in producing medicine and meeting the requirements of GMP and quality control. For example, FabRx [77], which developed the printer M3DIMaker™ intended for use in clinics and hospital pharmacies, in addition to other companies such as Vitae [78] and Triastek. The Recent collaboration of Merck [79] with AMCM (additive manufacturing customized machines) targets GMP conforms industrial application of 3D printers to make drug development more faster and flexible [77,78].

Despite the significant progress in proving the effectiveness of 3D printing in the production of personalized medicine in research, there is still hesitation in its implementation in reality and the lack of sufficient confidence from regulators and stakeholders. Therefore, the cooperation and participation of regulators and health practitioners are needed with the developers of this revolutionary technology to accelerate its implementation and transfer from mere theorizing and applied research to reality.

5. Conclusion and future directions

3D printing in drug formulation is becoming a novel approach for many patients since it brings the manufacturing close to them and offers individualization of therapy. Current advances in technology and increased research in this field can assure more safe and effective treatment. Even Though this technology is still in its infancy, it seems to be a revolutionary tool that offers more flexibility in drug manufacturing and is expected to transform drug delivery systems to a different level, in near future. The unlimited potential, as well as applications of 3D printing technology for the development of various drug delivery systems, are briefed. 3D printing has proven its ability to develop advanced drug delivery systems in which multiple drugs are delivered at different release rates. The most common techniques in drug manufacturing include stereolithography, nozzle-based deposition, inkjet printing, and laser-based systems.

Since conventional pharmaceutical manufacturing is a large batch process and generally does not support personalized therapy the idea of tailored medication for therapy has achieved wide attention these days. Many formulations printed out of this technology have indicated that their distinctive structure and shape cannot be achieved by the traditional method of manufacturing. To facilitate the manufacturing of novel and distinct dosage forms, massive researches have been carried out by scientists in the past decade on a variety of 3D printing methods to optimize the printers, in order to pave the way for customized therapy. Multiple drugs can be conveniently administered by this outstanding technology. Therefore formulations with many drugs and varying release patterns can be easily achieved. Indeed, the 3Dimentional technology commenced in getting more attention from pharmaceutical industries and is in the process of developing unique formulations to offer customized medicines by controlling the release rate of the drugs.

Substantial and exciting innovations in technology can lead to the designing of a single printing device competent enough to produce multiple release formulations. Some studies have already proven the immediate as well as the sustained release of different drugs from distinct partitions from polypills.

3D printing technology has tremendous application in novel drug delivery systems too. Which includes hyaluronan-based synthetic extracellular matrix microcapsules, antibiotic printed micropatterns, mesoporous bioactive glass scaffolds, nanosuspension, and multi-layered drug delivery devices. This technology looks to be a hopeful methodology for developing mucoadhesive films and similar layered structures, which was advocated by some research.

Hence, this rapid prototyping tool is proposing the potential for creating limitless dosage forms which sequentially will take the manufacture of therapeutic delivery systems to a brand-new stage, even though they have one or other limitations. Nevertheless, one can expect this 3D printing as a routine production method once the technology is properly established along with easily available resources. The positive prospect of 3D technology is expected to depend on its ability to offer 3D printing procedures which can manufacture on-demand personalized doses in real-time in decentralized locations. It is expected that the makeover of conventional pharmaceutical production to more flexible 3D printed products will be very soon with much more formulations in the market. Finally, the commercial achievement of 3D printing technology will be dependent on the proficiency of translation of unique dosage geometries as per patient requirements while considering the cost.

Declaration of Competing Interest

The authors declare no conflict of interest.

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