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Review Article

3D PRINTING TECHNOLOGY: A CUSTOMIZED ADVANCED DRUG DELIVERY

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ABSTRACT

Three dimensional (3D) printing has emerged as one of the most promising additive manufacturing technology for producing 3D objects, with applications ranging from engineering prototyping to medications and cell-laden medical models. 3D printing techniques involve the deposition of materials such as thermoplastic polymers or hydrogel in sequential layers one on top of another to produce 3D object, regardless of the type, or underlying theory. The rapid rise in the number of published articles and patents in recent years indicates 3D printing's current momentum in developing various drug delivery systems for pharmaceutical applications. While 3D printing techniques have a promising future, they must overcome a number of challenges before they can be used in commercial-scale production. The current ways of modifying drug delivery while making 3D printed dosage forms with different drug release patterns and properties are discussed in this review. These achievements are related to the delivery and development of patient-specific medicines. Major benefits of each type of 3D printing application, which are discussed; however, a critical review will show the limitations and constraints associated with 3D printing. Future research could focus on developing and adapting the techniques to suit with a wider range of materials. More emphasis on developing cost-effective printing technologies and compatible materials with these printers is needed to broaden the range of applications for 3D printed products.

Keywords: 3D printing, Pharmaceutical application, Fused deposition modeling, SPRITAM, Stereolithography, Pressure-assisted microsyringe.

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INTRODUCTION

Drug delivery is described as an approach through that systems, technologies, and formulation is developed, that helps specific in drug transportation at intervals in to biological fluid and succeeding desired biological effects. With the increased development of science and technologies in pharmaceutical field, there are new ideas in the design of drugs, manufacturing technology, processes, and for better understanding that helps to accomplish high quality of dosage form. In the previous couple of decades, the development of drug product has been under study, and various novel dosage forms and technical method has been developed. Noticeably, in most of the cases, special thought was given for physicochemical and biopharmaceutical characteristics of Active Pharmaceutical ingredients (API) and regulatory requirement throughout every stage of development. Today's diverse ethnic backgrounds, eating habits, circadian cycles, and inter individual differences among patients provide huge hurdles for pharmaceutical scientists seeking to deliver uniformity in medicine. As a result, personalization of medicine has been on the rise in recent years. Over decade, scientists have emphasized the importance of personalizing treatments to the pharmacogenetics of populations and individual pharmacokinetic profiles. Three-dimensional (3D) printing technologies are proving to be the blockbuster in personalized medicine. 3D printing technology was introduced by scientists as a valuable tool for producing innovative formulations and disease modeling. The use of computer-aided drug design and 3D printing technologies speeds up the production of personalized pharmaceutical drug products. Using inkjet printing; in which a semi-liquid binding solution was mixed with powder bed to produces adhesive particles. In recent years, 3D printed pharmaceutical formulations have been effectively developed. Optimization of equipment and processes is required to achieve the desired shape and size of the formulation. SPRITAM was the first 3D printed drug approved by the FDA (in August 2015) (Levetiracetam) [1].

Advantages of 3D printed drug delivery

- High drug loading capability compared to conventional dosage forms.
- Small doses of potent medicaments are produced accurately and precisely for desired activity.
- Comparatively less production cost due to less wastage of materials.
- Suitable for drug delivery of poorly water-soluble and narrow therapeutic windows drugs.
- Drug therapy can be customized to patient of specifically age, gender, genetic variations, ethnic variations, and environment.
- Customized patient treatment for better patient compliance particularly for multidrug therapy with multiple dosing regimens.
- Immediate and sustained release layers can be incorporated to give manufacturing method of dosage form and it helps to provide best therapeutic regimen for an individual.
- Batch-to-batch variations in bulk production of conventional dosage forms can be avoided.
- Small scale batch production is feasible and process can be completed in single run.
- 3D printers require minimal space and economical [2].

Disadvantages

- Problem associated with nozzle are critical challenges as stopping of the print head that can affect the final structure of the product.
- Powder printing blockage is another major issue.
- The ability to change the ultimate structure in response to mechanical stress, storage conditions, and ink formulation effects.
- The effects of printer-related parameters on printing quality and printer costs [2].

Brief outline of recent 3D printing technologies

For the development of solid oral dosage forms (SODFs), a number of 3DP technologies have been investigated. Among them, the most frequent 3DP technologies used in the production of SODFs are as follows:

A. Extrusion-Based 3DP
B. Vat photopolymerization
C. Inkjet 3DP
D. Powder-Based 3DP

Depending on the material used and the type of energy employed, each class of 3DP processes can be subdivided into subcategories. Fig. 1 shows

the 3DP technologies used in the manufacturing of SODFs graphically. The next sections provide an overview of the characteristics, benefits, and limits of each 3DP technology, which are summarized in Table 1.

Extrusion based 3D printing

Extrusion-based 3DP is a most widely used 3DP technology in pharmaceutical sector. In this procedure, the material is extruded using machine driven nozzles [3-5]. Two different extrusion based 3DP technologies can be identified depending on the material used and the need for a melting step to be easily extruded through the nozzle. Fused deposition modeling (FDM) is the extrusion technique that involves material melting; when the melting stage is not required, the pressure-assisted Microsyringe (PAM) is employed (Fig. 2) [6-8].

Fused deposition modeling

Scott Crump invented the FDM technique in 1989. Crump and his wife cofounded Stratasys, which commercialized the first FDM printer a few years later [8-10]. Nowadays, FDM is the most extensively used 3D printing method in the pharmaceutical industry. FDM is based on the layer-by layer deposition of molten thermoplastic filament on the printer building platform, which is controlled by software [8,11]. Hot melt extrusion (HME) is commonly used to make thermoplastic filament. There are three different strategies that can be used. After the extrusion process, the filament can be loaded with the drug by soaking it in the drug solution and allowing passive diffusion of the drug into the filament. In a second approach, the drug can be mixed with a powder mixture of polymer and excipients to produce a drug-loaded filament [8,12]. The manufacturing of an empty shell and the simultaneous or subsequent loading of the shell with a drug in the form of a solid or liquid is a third approach [12]. Because of the larger drug loading the second approach is usually used. The filament is loaded into the printhead by a gear system during FDM printing [4]. To achieve a semi-solid state, the filament is heated above the glass transition temperature inside the printhead [10].The melted filament is then extruded through the printhead nozzle and deposited onto the printer building platform, where it solidifies due to reduction of temperature. After the first layer has solidified, the building platform is lower down to allow the next layer to be placed on top of the previous one. The procedure is repeated till the 3D object is completed [8,13]. The term "dual FDM 3D printing" refers to a type of FDM. Dual FDM 3D printing system features multiple printhead allowing you to print an object with different materials. This technology can be used to produce dosage forms that contain multiple drugs. This is particularly useful for individuals who need to take multiple medications on the same day [8]. FDM systems with multiple printheads may increase mechanical complexity and processing time [14]. Several elements influence the quality of the printed design. These can be divided into two categories, that is, process related factors and feedstock related factors. The temperature of the nozzle, the speed of extrusion, and the density of the infill are among the first [6]. The feedstock's thermal conductivity, density, and glass transition temperature are all elements to consider [15,16]. FDM has a number of advantages in the pharmaceutical industry. First FDM printers are inexpensive, with prices ranging from £500 to £2000. Second, printing parameters like layer thickness and infill % may be easily changed, enabling for the production of dosage forms with differing geometry, complexity, and inner structure [17-19]. The drug release profile can also be modified by accurately setting the printer parameters [15,18]. FDM can even manufacture SODFs that contain multiple APIs [8,19]. Despite the fact that other 3DP technologies require a post processing step, whereas FDM does not. As a result, when the printing process is finished, the object is already solid and ready to use immediately [8,19]. Finally, FDM's final products are characterized by high excellent mechanical resistance [7,15,18]. However, there are some disadvantages of FDM that limited use in pharmaceuticals. Only a few pharmaceutical grade

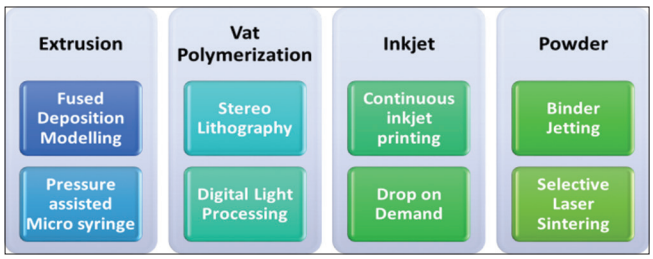

Fig. 1: 3DP technologies used in the manufacturing of SODFs graphically

Table 1: Advantages and limitations of 3DP technologies used for SODFs manufacturing

3DP technology	Advantages	Limitations
FDM	• Inexpensive • Ability to manufacture dosage forms with varying geometries. • Complexity, and inner structure • Ease drug release profile modification • Manufacturing of SODFs with multiple APIs • Post-processing not required	• Limited to low-dosage drugs • Degradation due to heat
PAM	• It is possible to manufacture dosage forms with a high • Drug loading and multiple APIs. • A wide variety of materials • High temperature does not require • A wide variety of material available	• Organic solvents are required • The geometry of the 3DP dosage form may contract or deform • Time-consuming • Low resolution
SLA	• When compared to other photocuring-based 3DP printers, print larger models	• The action of the laser might degrade the API • Printing speed can be quite slow
DLP	• Faster than SLA • High resolution prints • As compared to SLA printers, resin tanks are smaller. • Does not require high temperatures or pressures	• Post processing • The action of the laser might degrade the API
CIJ and DOD	• High accuracy and repeatability • Minimum steps required to develop the final product • Faster printing • Low drug waste	• Not applicable with high drug loading • APIs may be altered due to high shear rates
SLS	• Dosage forms with a variety of shapes and drug release patterns • Accurate control of the dosage form's composition and internal structure • Minimum waste • No need for additional supports • Drying stage not required	• Drug degradation may occur due to high temperatures and high-energy beams.

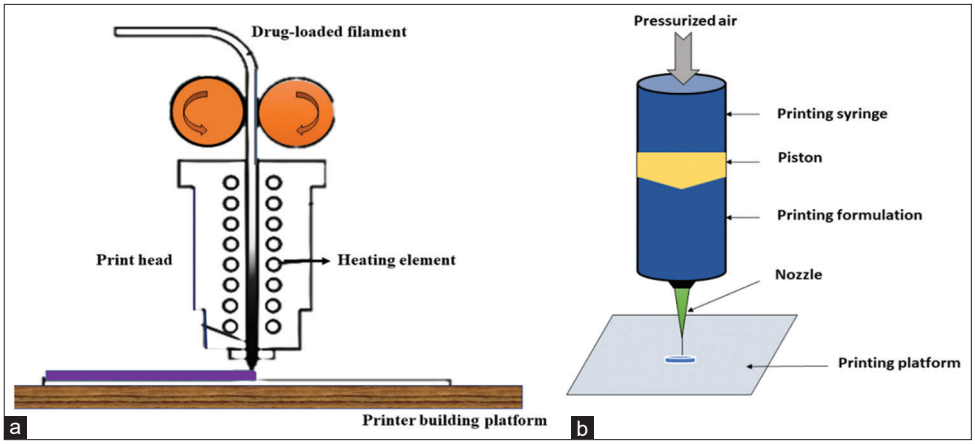

Fig. 2: Schematic representation of FDM (a) and PAM (b)

thermoplastic polymers possess the adequate properties to be used in FDM printing [7,18,20]. Impregnation is used to load the drug onto the filament. As drug loading yields are usually low, FDM may be limited to low dose drugs [21]. Furthermore, the process requires high temperatures, which might cause thermal of thermolabile drugs. These limitations can be addressed by mixing the drug with a polymer with a similar melting temperature [8,18].

Pressure assisted microsyringe

PAM is a 3DP technology that belongs to the extrusion based 3DP class. This involves layer-by-layer extrusion of a semisolid material from a computer controlled microsyringe onto a build plate or a glass slide [13,22,23].The paste must be smooth, homogeneous and must possess adequate rheological properties to be extruded out from the microsyringe and to stop the occlusion of it. The printing is started with the help of syringe once a paste with suitable properties is obtained [19]. The extrusion process is driven by a mechanical, pneumatic or solenoid piston [13]. After the conclusion of the printing, the 3DP dosage form is left for drying to gain enough physical strength. This method does not require high temperatures for drying [22]. This prevents the degradation of thermolabile drugs, which will occur with others 3DP systems [13]. In addition, a variety of materials such as hydrogels, epoxy resins, and even chocolate may be employed [8]. Furthermore, dosage forms with a high drug loading with combination of different drugs are manufactured [19]. The main disadvantage of PAM is that the preparation of slurries usually requires the use of organic solvents that may be harmful to human health [8,15]. Furthermore, 3DP dosage forms may experience shrinkage after drying after printing or [23]. The entire PAM printing process is more time consuming compared to other 3DP technologies [19,24]. Finally, PAM has lower resolution due to different nozzle diameters. Commonly used diameter is (0.4-0.8 mm) [13].

Vat photopolymerization

3D printing from photopolymerization is another popular method of additive manufacturing. The most popular 3D photolithography processes include stereolithography (SLA) and digital light processing printing (DLP) (Fig. 3).

Stereolithography

SLA technology involves a laser beam scanning a resin tank and causing liquid resin to cure onto the build platform [25]. The laser beam is controlled by a set of mirrors called galvanometers that direct the laser beam to a set of coordinates based on CAD to causing a layer of resin onto the build platform [26]. Lift the build plate up for the next layer of cured and repeats the process until a 3D object is formed. Photocurable resin printing usually requires some post processing steps, for example, the printed object is usually washed with isopropyl alcohol to remove excess resin, and then further cured under UV light to strengthen the printed structure [27]. In SLAs, the print resolution is determined by the size of the laser point combined with the increment that the laser beam can move across the resin tank. The main factors that affect the final print quality are the exposure time to the laser beam, the intensity of the laser output, and the scanning speed [28]. SLA printers can print larger models compared to other photocuring based printing technologies. However, the printing speed depends on the movement of the laser beam, so the printing speed can be very slow [29].

Digital light processing

DLP printing uses a digital projection screen controlled by a digital mirror device to project an image of the print layer onto a resin tank and curing the entire layer of the 3D printed design onto the build plate at once. Then the build plate moves up for next layer print to be cured and process is repeated until a complete 3D printed object is formed. In DLP technology, the resolution of the printer's XY axes is determined by the projector pixel size. The DLP process is faster than the SLA process because the projector cures all points on the print layer at the same time. DLP usually also produces high resolution prints in the micron range, but may not be possible with methods such as FDM [22]. DLP printers have a smaller resin tank than SLA printers, making them suitable for small prints that require high resolution. DLP also does not require high temperatures or pressures for printing, which may allow printing of materials that may not be suitable for FDM printing due to thermal sensitivity.

Inkjet printing

Inkjet printing is categorized in two different technologies one is continuous inkjet printing (CIP) and drop on demand printing (DOD) (Fig. 4) [6,7,13]. These 3DP approaches are based on theory of Lord Rayleigh's 1878 of Instability, which describes the separation of a stream of liquid or jet into droplets [15,16,30].

Continuous inkjet printing

In CIP a high pressure pump pushes a continuous stream of ink through a nozzle with a diameter of 50–80 μm. The liquid is driven by a piezoelectric crystal, which allows it to be broken into drops of a specific size and speed at regular intervals. The droplets travel through an electrically charged element after exiting the nozzle to produce the optimum charge. Finally, the charged droplets reach the substrate due to the electrostatic field &producing the 3D product [15,17].

Drop on demand

Droplets having a diameter of 10–50 μm and a volume of 1–70 pL can be produced in DOD. A thermal print head or a piezoelectric print head can control the stream of droplets. Electrical pulses arriving in the resistor and generate heat, which causes small bubbles to form in the ink reservoir when a thermal print head is utilized. The bubbles give the constant pressure to force ink out of the nozzle and

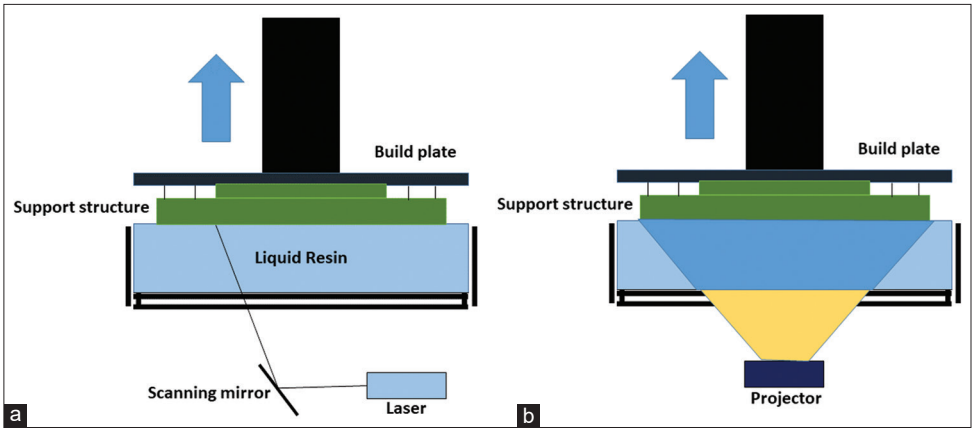

Fig. 3: Schematic representations of SLA (a) and DLP (b)

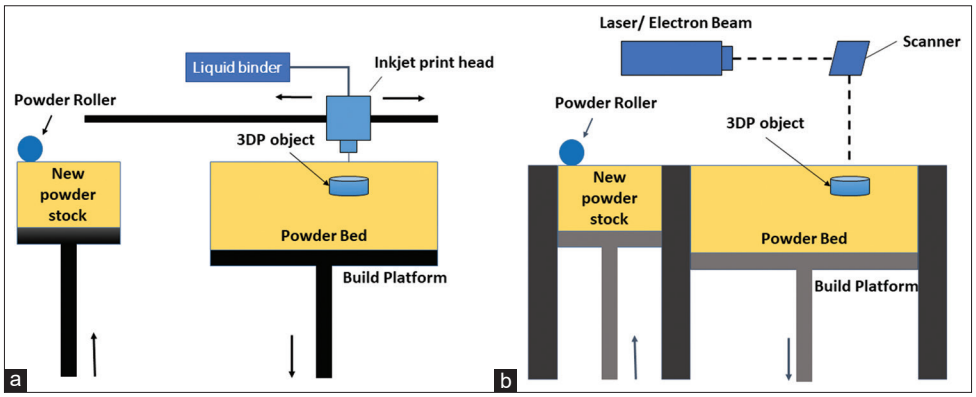

Fig. 4: Schematic representations of binder jetting (a) and SLS (b)

produce drops. The application of voltage induces a fast and reversible deformation of a piezoelectric element, which propagates acoustic waves in the piezoelectric approach. These produce the pressure pulse needed to break the flow of ink through the print head, producing droplets [11,30,31].The piezoelectric DOD method can use a variety of liquids, but the thermal approach is limited to volatile liquids. Furthermore, with the latter method, temperatures of up to 300°C can be attained, potentially affecting API deterioration [7,15]. The main benefits of using inkjet printing in manufacturing of SOD's is it has ability to produce final object higher accuracy and reproducibility [13,17,18]. The number of stages required to make the final product is less than with other available 3DP technologies [18]. As a result, the printing time is reduced [13,15,18]. The release of the drug from the dosage form can be controlled by optimizing factors such as the design's size or surface area, the loading of jetted droplets, and varying the distance between the droplets in the substrate resulting in minimal drug waste [13,22]. Finally, this is a low cost technology [13,18,23].

Powder based 3DP

Binder jetting and selective laser sintering are two types of powder-based 3DP (SLS).

Binder jetting

BJ 3DP is also known as drop on solid (DOS) process in which a binder fluid containing or not containing the API is jetted through the printer nozzle into the powder bed of the printer. As a result, the moistened powder particles contained in the powder bed joined together, allowing the layer to solidify. Solidification of the powder occurs by the formation of binder bridges and the dissolution and recrystallization of particles. Once a layer is completed, the building platform moves downwards, while the powder distribution platform raises a roller is then used to transfer a powder layer from the powder bed to the top of the previously formed layer. The procedure is repeated till the 3DP object is completed. The object is taken from the printer once it has finished printing, and any unsolidified powder is destroyed. SPRITAM, the only 3DP oral solid dosage form now available on the market, was developed using this 3DP technology [13]. BJ 3DP has the benefit of allowing the printing process at room temperature therefore drug deterioration which is a major disadvantage of others 3DP methods, is prevented in this method [8,13]. This 3DP technology can be used to produce low bulk density, highly porous, fast dissolvable tablets with high drug content. Furthermore, depending on the excipients used, the drug in an amorphous state is useful when APIs are poorly soluble. Using the powder bed, highly complicated dose forms can be developed without the need of supports or rafts. The major disadvantage of SODFs produced by BJ 3DP is the high fragility of the dosage forms formed. Another disadvantage is that some binders are suspended or dissolved in organic solvents, which can cause toxicity and that require a long time to be removed from 3DP SODF [13].

Selective laser sintering

Carl Deckard and Joseph Beaman first introduced SLS, also known as powder bed fusion, in 1989 [22,23]. This process involves layer by layer sintering or fusion of powdered material particles in a spreading platform, assisted by the action of a high energy laser beam. A SLS printer is made up of three basic components: a spreading platform, a powder bed and a laser system [13]. The powder is dispersed in the powder bed by a powder dispenser, and the surface is leveled by a rollerblade. The laser beam then selectively scans the powder layer on specific areas, melting and curing it according to predefined CAD models. The powder bed is then shifted downwards, and the next layer is deposited and fused [13,19]. The procedure is repeated till the 3DP object is finished. Once the object has cooled, it is manually or with the aid of a sieve removed from the printer [13]. The powder used in SLS

should have appropriate flow characteristics, particle size uniformity, and spherical shape. Kollidon VA 64, Eudragit L100-55, Eudragit RL, and Kollicoat IR are the most commonly used SLS powders in 3DP of SODFs. SLS can be used to produce a variety of dosage forms with varying shapes and drug release patterns. Furthermore, it allows for accurate control of the composition and internal structure of the developed dosage form [18,19]. Furthermore, the powder material that remains after the printing process can be taken from the printer and reused, resulting in minimal waste [18]. Unlike other 3DP technologies, SLS usually does not require the addition of supports to the object, thus the operator does not have to deal with the difficulties of removing it [20]. Furthermore, after the printing process is finished, the object can be used immediately without it to be dried [18]. Finally, this is a low-cost technology [11,18]. The main disadvantage of this 3DP technology is the risk of drug deterioration as a result of the high temperatures and high-energy beam [11,18,19].

PRACTICAL CONSIDERATIONS WHILE FORMULATING TABLETS USING 3D PRINTING TECHNOLOGY

In contrast to traditional tablet manufacturing technology, which involves a number of unit operations such as granulation, drying, milling, compression, and coating, each of which has a number of critical processing parameters such as granulation time, drying time, mill speed, compression force etc. Tablet manufacturing using 3D printing involves fewer unit operations and, as a result, fewer critical processing parameters. This helps the formulator only to alter the formulation variables without considering the process related factor. Since the formulation includes a drug, a polymer, and a plasticizer (with or without a plasticizer), the formulation variables are minimal. The printing speed, percent infill, nozzle temperature, bed temperature, and printing pattern are the most important process parameters. The drug release can be easily modified by altering the shape of the dosage form. The geometrical shape of the dosage form has an effect on drug release, according to Goyanes *et al*. [6,32]. The release rate for the cube, pyramid, cylinder, sphere, and torus shapes was investigated. The results reveal that erosion-mediated release is dependent on the ratio of surface area to volume rather than just surface area, with the pyramid shape showing the fastest release and the sphere and cylinder showing the slowest. The drug was found to be molecularly dispersed, with a loading of approximately 4% w/w. As a result, using 3D printing, this strategy of changing the geometry design can be used to customize drug release [33]. The shape of the dose form is also affected by machine-related variables such as nozzle size. In comparison to traditional manufacturing methods, 3D printing technology can be quickly adapted to meet the needs of the pharmaceutical sector.

3D PRINTING OVER CONVENTIONAL MANUFACTURING

Individualized treatment and precise control of drug release are two advantages of 3D printing technology for oral solid dosage forms. The lack of quality control procedures for the dosage forms printed at hospitals or pharmacies, which can influence the products' *in vivo* performance, is main drawbacks of this technique that has drawn a lot of attention. Another concern is the potential for a cyber-attack on the computer used for 3D printing, which might put the recipe in jeopardy. Furthermore, if the technology is licensed to a hospital or pharmacy, any side effects resulting from the printed product become the licensing firm's partial liability. The risk can far outweigh the benefit of licensing the recipe to the small pharmacies or hospitals. Although the current regulatory framework cannot oversee the operations in every pharmacy or hospital that manufactures products using 3D technology, its use in pharmaceutical companies holds promise. Because of the accuracy with which drug release is controlled, 3D printing can reduce the cost of producing complex products by reducing human intervention and the number of unit procedures. It is safer from a safety standpoint because it does not use any organic solvents. Furthermore, it is considerably easier to contain dust generation throughout the blending and extrusion operations, resulting in the elimination of any health and safety risks. It would save money on expensive gowning and dust control requirements. To make 3D printing a feasible option for manufacturing oral solid drug products commercially, a company must weigh the benefits of the technology against the opportunity cost of slow production and initial development costs. SPIRITAM® is a good example of this technology's viability, as the porous structure formed by 3D printing allows for quick oral dispersion that would be difficult to control and manufacture using traditional manufacturing techniques [6,14].

APPLICATION OF 3D PRINTING IN PHARMACEUTICALS

Pharmaceutical applications of inkjet printing

The production of oral disintegrating film formulations is one of the most common uses of inkjet printing in pharmaceuticals. They are single or multilayered sheets made of appropriate materials with drugs loaded on them that quickly liberate the drug in the mouth to produce a solution or suspension in the saliva without chewing or drinking water [34]. Thabet *et al*. printed Enalapril maleate onto hydroxy propyl cellulose (HPC) based ODFs that were either drug free or contained HTCZ using PIJ printing. Inks based on water or methanol were utilized for this. Enalapril and hydrochlorothiazide doses on hydrochlorothiazide films could be modified to obtain various fixed dose combinations [35]. On three distinct edible substrates, such as rice paper, coated rice paper, and icing sheet, TIJ was used to develop ODFs of propranolol hydrochloride in a mixture of water and glycerol. To improve palatability, saccharin was utilized as a sweetener, which was added with a casting knife [36]. By modifying a commercial TIJ printer, a novel strategy of dosing two drugs simultaneously and independently on ODFs was discussed. T3 (liothyronine sodium) and T4 (levothyroxine sodium) were printed on HPMC substrates, with ink solutions made from ethanol, DMSO, and PGmixes [37]. TIJ was also utilized in combination with fused deposition modeling to produce mucoadhesive buccal films (FDM). Ibuprofen ink was coated on HPMC films manufactured using FDM technique in this study [38]. PIJ was used to develop another oromucosal dosage form, in which lidocaine hydrochloride was printed on electrospun gelatin substrates with or without piroxicam [39]. As a result, the effectiveness of combining two technologies to manufacture pharmaceuticals has been established. The majority of these films used for oral delivery have a limited amount of ink, and drug loading efficiency. To address this, edible solid foams that have been porous and suitable for inkjet printing of larger volumes of ink were developed [40]. Apart from small molecule deposition, there has been study on printing biologics on a suitable substrate with an inkjet printer for buccal delivery [41,42]. Transdermal delivery has also benefited from inkjet technology. PIJ technology was utilized to manufacture transdermal delivery films, which were used to load indomethacin in ethanol ink formulations on polythene films [42]. Inkjet printing has also been used to coat microneedles for transdermal delivery [44,45]. Dropwise additive manufacturing of pharmaceutical products (DAMPP) has been developed to manufacture a variety of dosage forms using DODtechnology [46]. Self-emulsifying drug delivery systems (SEDDS) have been developed using this technology to improve drug solubility. Icten *et al*. developed a DAMPP-based formulation by coating a tablet with a self-emulsifying mixture and polymer-based films [47]. Apart from these formulations, carvedilol and ropinirole tablets have been prepared with inkjet and photoinitiation [29,48]. In addition, solvent inkjet printing was employed to produce thiamine hydrochloride tablets [49]. Aerogel microspheres for pulmonary delivery as well as drug loaded mesoporous silica nanoparticles, were two other formulations developed employing inkjet technology [50,51].

Pharmaceutical applications of binder jet printing

There has been a lot of research on the use of BJ for tablet manufacturing. The type and concentration of excipients employed in the binder jetting tablet manufacturing process have a significant impact on tablet properties. Filling agents with high water solubility, moistening agents with high water content and binders with a high viscosity in solution have been shown to improve the hardness and binding strength of

tablets while also extending their disintegration time [52]. Another study that found at HPC as a potential binder found that the tablet friability was highly dependent on the binder particle size [53].

The usage of linear and 4 arm star polyvinyl pyrrolidone as a binder was studied in another study. They came to the conclusion that the compressive strength of a tablet was determined by the amount of polymer in the binder.

Because 4 arm star polymers have lower viscosities than their linear counterparts, they could be jetted at higher concentrations, resulting in stronger tablets. Furthermore, acetaminophen showed sufficient physical properties at a concentration of 5–50% in each tablet [54]. BJ was used to manufacture tablets of several APIs in various shapes and release profiles. CPM tablets were produced with Eudragit E-100 and Eudragit RLPO binder solutions and ethanol and acetone as solvents, respectively. The tablets have six layers of placebo on the bottom, eight layers of active component in the middle, and six more placebo layers on top [55]. Another study developed dosage forms of captopril using their form process, using mannitol as the bulk excipient along with Maltitol, Maltodextrin or Polyvinylpyrrolidone as powder additives [56]. Apart from that, tablets of pseudoephedrine, acetaminophen, 5-fluorouracil, and amitriptyline hydrochloride were developed using BJ [17,57-59].

Pharmaceutical applications of fused deposition modeling (FDM)

A number of researches have been done on FDM's ability to develop different pharmaceutical products. The pharmaceutical applications are summarized in Table 2.

Pharmaceutical applications of selective laser sintering

Due to the high energy laser, which may degrade the drugs, SLS is not commonly utilized in the manufacturing of drug-loaded formulations [76]. Various drug loading devices employing SLS have been investigated [77,78]. SLS has recently been investigated in the production of oral drug-loaded formulations. Two polymers, Kollicoat and Eudragit, were used to produce 3D printed paracetamol tablets (printlets), which showed no signs of drug degradation [76]. Orally disintegrating printlets of paracetamol were produced utilizing the polymers HPMC and kollidon [77]. After inclusion into cyclodextrin with mannitol and kollidon, printlets of ondansetron were employed for complexation [79]. Several mini-printlets containing paracetamol and ibuprofen with customizable drug release patterns were also evaluated. The polymers polyethylene oxide, Eudragit, and ethyl cellulose were also used to produce paracetamol-loaded gyroid structures [79].

Pharmaceutical applications of stereolithography

Despite its benefits, this printing method is only used in the pharmaceutical industry to a limited extent. One factor is the lack of suitable polymers for pharmaceutical applications, none of which have been classified as generally recognized as safe (GRAS). As a result, they are not suited for human use and due to their photosensitivity they have stability concerns. Another issue is that photoinitiator fragments may become trapped in photo-polymerized structures, and when they are released, they can be cytotoxic [80]. In addition, one of the researchers discovered an unanticipated chemical interaction between the photopolymer and the drug, namely, a Michael addition reaction [81]. Using polyethylene glycol di-acrylate as the monomer and diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide as the photo-initiator, Wang *et al*. successfully printed paracetamol tablets with changed release profiles [82]. It was also employed to develop various-shaped paracetamol tablets with distinct release characteristics [83]. This technology has also been used to produce hydrogels. Martinez and his colleagues developed ibuprofen loaded hydrogels composed of cross-linked polyethylene glycol diacrylate. As water may be trapped in the matrices, it was demonstrated that hydrogels that contained and retained water could be printed by adding water to the resin composition [44]. The polymer poly (ethylene glycol) di-methacrylate and riboflavin as the photo-initiating ingredient were also used to make ascorbic acid loaded solid hydrogel. Various transdermal microneedles were also developed, which were subsequently coated with the drug utilizing inkjet printing [44,84]. For drug delivery systems containing drug depots, an unique hybrid manufacturing technique was developed, in which the DDS matrix was formed using SLA and the drug depots were loaded using inkjet printing [85]. Microreservoirs for transdermal and implanted delivery have been developed [86]. Using FDM and SLA, Goyanes *et al*. developed salicylic acid-based anti-acne masks. Mixtures of PEGDA and PEG were used to make the SLA masks. Because of its higher resolution, larger drug loading, and lack of drug degradation, SLA was found to be the best approach [87].

Pharmaceutical applications of pressure assisted microsyringe

Aita *et al*. developed levetiracetam immediate release tablets that were free of organic solvents using a pressure-assisted microsyringe (PAM). The matrix was polyvinyl alcohol-polyethylene glycol graft co-polymer, and the effect of a different polymer, Polyvinylpyrrolidone-vinyl acetate copolymer, on the tablets was investigated. The tablets containing more PVP-PVAc had a faster dissolution and disintegration time [88]. The same group then produced tablets with a polyvinyl acetate/polyvinyl pyrrolidone co-polymer, HPMC, and highly dispersed silicon dioxide, with different dissolution profiles depending on how much HPMC was used [89]. PAM was used to make HPMC based gastro-retentive ginkgolide tablets. To increase the formability, lactose and microcrystalline cellulose were employed to make a homogeneous paste [90]. Using hydrogel based printer inks; mucoadhesive oral films of HPMC loaded with catechin were developed [91].

Table 2: Pharmaceutical applications of FDM

Dosage form	API	Excipients	Salient features	Reference
Tablets	Tramadol	HPC, PEO	Modified release, abuse deterrent	[60]
	Bicalutamide	Kollicoat IR	Modified release	[61]
	Dronedarone HCl	PEG, PVA	-	[62]
	Metformin HCl	PVA	Egg- shaped tablet— Egglet, abuse deterrent	[63]
	Isoniazid	HPC, HPMC, PEO, Eudragit, Kolliphor	Modified release	[64]
	Rebamipide	Hypermellose phthalate	Controlled drug release	[65]
	Metformin HCl	PVA	Ethanol-water (9:1) increased drug loading	[66]
	Carvedilol, haloperidol	PVA	Rapid drug release	[67]
Osmotic tablets	Diltiazem	Core—PVA Shell—cellulose acetate	Shape of CA varied which modified release	[68]
Bilayer tablets	Metformin , Glimepiride	Eudragit PVA	Combination of two release profiles	[69]
Gastro-retentive Tablets	Theophylline	HPC	Controlled release	[70]
Gastro-retentive floating devices	Acyclovir	PLA	Tablet in device, controlled release	[71]
	Theophylline	HPC, ethyl cellulose	Tablet in device, pulsatile drug release	[72]
	Baclofen	PLA	Tablet in device, sustained release	[73]
	Amoxicillin	PVA	Capsule in device, prolonged drug release	[74]
Caplets	Theophylline	HPC, Eudragit, PEG	Sustained release	[75]

CHALLENGES OF 3 D PRINTING IN PHARMACEUTICALS

Despite the benefits of 3D printing technology, several technological challenges and constraints must be overcome promptly to expand the use of DDSs. The current limitations in the research of excipients, the development of printing software and tools, the optimization of the preparation's mechanical properties, and the current regulatory landscape are described in these sections [92].

Active pharmaceutical ingredients

The overall quality of product depends on the quality of raw materials and finished products. Particle size and its distribution can be one of the critical parameters, since this property affects layer thickness and the risk of segregation. It can impact the risk of clogging for jetted suspensions. Water content may also be critical factor, especially when the RMs are cohesive. After layering, the QTPP is achieved by binder deposition in jetting of small binder droplets which ultimately depends on the surface tension and viscoelastic properties of the binder solutions. Process development for a particular printing method may focus on controlling mass and energy transfer, which is thought to affect CQA such as appearance, identity, content uniformity, assay, drug release, impurity level, hardness, friability, crystallinity, and API polymorphic form. In some cases, thermal and electrical properties including electrical conductivity, capacitance, heat capacity, and thermal conductivity may be critical. But these properties generally covary with concentration for a given binder solvent system. Binder infiltration into the powder bed is another significant RM characteristic that is affected by powder density and surface energetics. Physical properties of RMs, such as particle size distribution variability, may also play an important role. Traditional quality assessment techniques proposed by the FDA and pharmacopoeias may require to be revised specific to 3D- printed formulations. For example, the widely accepted criteria of tablets are to demonstrate <1% weight loss in friability tests is supposed to be too stringent for binder jet printing, which commonly demonstrates poor mechanical strength. Techniques like FDM and SLS use heat and laser, respectively, posing the risk of degradation of API(s). Furthermore, The HME and FDM processes have shown to alter the physical conditions of drugs molecules (e.g., amorphous/crystalline states), thus influencing their solubility, dissolution rates and stability. The technique urges real time analytical assessment to assess the product.

Excipients

Due to their distinct printing principles, all types of 3D printing technologies have specific requirements on the qualities of excipients throughout the preparation process. Because the printing process in FDM technology includes heating and melting processes, it's critical to choose the right drug carrier. PVA is the most commonly reported carrier excipient, although it's melting temperature is relatively high, making it unsuitable for thermally unstable medicines such as 4-ASA or Levetiracetam. In recent years, a growing number of researchers have attempted to combine HME technology with 3D printing technology or low-temperature 3D printing technology using excipients such as PVP, HPMC, Kollidon, talc, and triethyl citrate to prepare low-temperature printed filaments to solve the problem of drug degradation and improve drug loading. The excipients for SLA and SLS technologies are limited to photopolymers and laser sinterable materials, which are not on the FDA's GRASlist. Only a few excipients have been used for printing thus far, and the most of them are expensive, poisonous, and stinky, as well as requiring light protection to avoid premature polymerization. In addition, drug manufacturing will require safety manufacturing. One of the major benefits of DOP and SSE is the ability to use these technologies to a wide range of active pharmaceuticals and excipients, including epoxy resins, cheese, hydrogels, and chocolate. Even so, organic solvents would be linked in both methods. Organic solvents are used as printing inks in DOP technology. The use of organic solvents is primarily utilized in SSE technology to make a soft paste. As a result, the presence of residual solvents in some of the final 3D printed tablets is a significant constraint. There are particular acceptance limits for the solvents, according to ICH recommendations Q3C (R5), thus the choice of solvents is limited, and each solvent has a minimum tolerated residual level. To overcome this constraint, multidisciplinary research must be strengthened, such as through the development of new types of 3D printers. In comparison to traditional pharmaceutical methods, the excipients available for 3D printing technology are relatively limited. Selecting the correct excipients may be necessary, especially for specific dosage forms of individual administration. Furthermore, many of the materials used in the printing process are nonpharmaceutical grade, which makes their use in pharmaceutical formulations difficult due to compatibility issues and hazardous side effects. Moreover, SLA is known to induce toxicity due to the usage of non pharmacopoeial grade excipients. As a result, to expand the use of printing techniques in the pharmaceutical industry, research into nontoxic, biodegradable, biocompatible, and physicochemically stable excipients must be accelerated [92].

Printing software and instrument

Modeling, slicing, printing, and post processing are the four basic processes in the 3D printing process. The computer is used to create a printing model and slice it to specify the printing path of each layer in the printing process, and then the formulation with a complex structure is fabricated using the prefabricated model. As the complexity of the required structure increases, modeling and slicing software must be updated regularly to fulfill higher printing standards. However, few software programs and models are known to be specialized to 3D printing technology. The print head must be stopped and restarted several times for DOP technology, which place a greater demand on the print head's stability. Furthermore, the clogging of 3D printing nozzles, the migration and leakage of binders, and the difference in powder feed have all affected the printing completion rate and the performance of printing formulations. However, to achieve diverse formulas, the location of the two nozzles may be inaccurate, which has a significant impact on product attributes such as content uniformity, hardness, and friability. As a result, 3D printers' mechanical equipment, operating processes, driving control system, and critical components must be urgently improved and upgraded. In addition, in the printing process of SLS, SLA, and DOP, the recovery and disposal of excess powders must be considered in production, as well as potential occupational health hazards. In general, the technological challenges of using 3D printers to prepare pharmaceutical formulations continue to restrict the development of the technology; furthermore, health-care 3D printers do not follows the good manufacturing practice (GMP) standard, requiring validation of the process and products to ensure that they are safe for human health. Nonetheless, 3D printer development and use are expected to continue [92].

Mechanical properties

To ensure that the manufactured tablets are reproducible and acceptable for post processing, the mechanical properties of the dosage forms are used as a quality control parameter. Because of the unique printing principle used in 3D printing, different polymers or powders are stacked on top of each other, resulting in a rough surface and objects with low mechanical strength. The performance of the products is influenced by factors such as adhesive viscosity, surface tension, and nozzle fineness. Furthermore, post-printing operations like as drying methods, drying time, and drying temperature may have an impact on the products' appearance and quality. These are critical for DOP, FDM, and SSE-based 3D printing methods. In terms of DOP, despite the fact that SPRITAM® made with this technology has a high porosity that offers it a competitive advantage over other fast-disintegrating tablets, its poor mechanical resistance (40N) remains a disadvantage. As a result, it's critical to improve product mechanical characteristics by modifying printing equipment such computer control programs, fine-tuning adhesive nozzles, and fine-tuning printing process parameters [92].

REGULATORY ASPECT OF 3D PRINTING IN PHARMACEUTICALS

Although specific considerations must be given to the control techniques for process parameters, RMS, and manufacturing defects,

3DP is distinct from other pharmaceutical processes, providing with its own uniqueness. In comparison to medical devices, surgery, education, and training tools, the regulatory requirements for drug products are more stringent. The main benefit in terms of product development is that it allows for faster trials for studies such as excipient compatibility and drug release. However, when compared to established dosage forms and manufacturing processes/tools, the lack of clinical history and post marketing data poses several challenges in terms of regulation and safety. Local pharmacies and hospital pharmacies may see their roles completely altered in the future, and their inventory methods may be radically changed. They may not need to stock a wide range of products (both branded and generic), and the distinction between compounded and manufactured medicine is a key issue in the regulation of 3D-printed medicines. This question has much consequence for the regulatory framework regulating 3D-printed products. In 2017, the USFDA issued a guidance titled "Technical Considerations for Additive Manufactured Devices" to provide the FDA's initial thoughts on technical considerations associated with additive manufacturing, as well as recommendations for testing and device characterization. However, there are currently no clear criteria for 3D-printed drug products. Several questions must be answered, such as which regulatory pathway would innovators follow to approach such non-traditional products? Will the "pharmaceutical ink," 3D printer, and finished product be included in the regulatory process? Through its own research, the FDA is attempting to gain a better understanding of 3DP. The Laboratory for Solid Mechanics and the FDA's Functional Performance and Device Use Laboratory, both part of the FDA's Office of Science and Engineering Laboratories (OSEL), are working in the same direction. More lessons regarding approval of 3D fabricated products can be learnt from medical devices, approximately 85 3D-printed therapeutic appliance and implantable have gained FDA clearance. Several pathways exist to obtain FDA approval, amongst which are the 510 [k], PMA, *de novo*, HDE, etc., are frequently used. To date, all approved medical devices and implants generated using this technology were granted clearance through the Premarket Notification – also called PMN pathway by proving that "3D- printed product is considerably commensurate to a legitimately marketed device" What should be the important process parameters of a 3D-printed product, and what are the critical factors affecting the printability of different types of materials? These are the major questions that regulators must address. Furthermore, current commercial 3D printers were not designed with good manufacturing practice (GMP). Theoretically, tablets fabricated through 3D printer contain a "personalized dose of the drug;" but it is the legal authority of the regulatory agencies which ensures that an accurate amount of drug is being given to a patient, so there should be some mechanism of validation [93].

CONCLUSION AND FUTURE PERSPECTIVES

3D printing may evolve as a transformational technology that can revolutionize the healthcare and other sectors. It will become a central aspect of industries, production, and everyday life. Most healthcare institutions and product manufacturers are expected to invest in a 3D printing to create personalized products such as dosage forms, medical devices, and prosthetics on request. The incorporation of numerous drugs into a single dosage form will ensure that the complete prescription treatment is administered on time, with the highest level of safety and minimal toxicity. This will ensure that patients have access to health care that are efficient, affordable, and timely. Manufacturing on demand is anticipated to minimize institutions' overall investment in healthcare products. New and better approaches for personalizing medication (pharmacogenomics) are predicted to emerge, allowing complete dosage form properties, including release profile, to be customized to an individual's needs. With the expanding importance of pharmacogenomics, personalized nutraceutical products can be developed to meet the nutritional needs of individuals who take supplements to improve their health. In cosmeceuticals, customized products with necessary ingredients in required quantities can be 3D printed at the outlets to address the specific skin issues based on professional recommendation for the individuals. Because some people are allergic to one or more of the ingredients commonly found in cosmeceuticals, 3D printing can help to eliminate the usage of such allergens in personalized products. Efficient reactions were incorporated into 3D printers to produce various chemical products using precursors as input will be developed in near future. This ensures that pharmaceutical products are available whenever and wherever they are needed. Biofabrication of artificial tissues and organs, such as an artificial kidney, heart, blood arteries, artificial bones, skin grafts, and so on, has been the subject of extensive research appears to be promising in the treatment of organ failure related illnesses. Biofabrication has the potential to produce biosensors with great spatial sensitivity for application in high-precision detectors and diagnostic instruments. Furthermore, this has the potential to change the drug development process by accelerating the process and allowing for more efficient evaluation of the safety and effectiveness of NCEs. To aid the drug development process, 3D printing of biological models will be used as models for preclinical drug testing, physiological, and toxicological investigations. To fulfill the patient's therapeutic needs, novel carriers and drug delivery systems based on various polymers for specific drug targeting might be 3D printed. 3D printing can help in the production of customized tablet coatings, in which multiple polymers of varying concentrations are utilized to produce desired dosage form properties such as stimulus triggered release, changed release pattern, and duration according on the therapeutic needs of a patient. The use of 3D printed models and demonstrations will improve teaching and learning easier and more effective. It will also make practicing surgery and rehearsing procedures easier, allowing for more effective development of associated medical skills. Overall, this technology will advance to the point where it will become an integral part of daily life, bringing convenience, and comfort.

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CONFLICT OF INTEREST

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