3D PRINTING IN ORAL DOSAGE FORM: A REVIEW

Nachita Desai, Satyajit Sahoo*, Prasanna Pradhan, Rashmi Rajeghorpade
Pioneer Pharmacy College, Vadodara, Gujarat, India – 390019
Corresponding author: Dr. Satyajit Sahoo
Pioneer Pharmacy College, Vadodara, Gujarat, India – 390019
Email: satyajitppdc@gmail.com

ABSTRACT:-
Now-a-days 3D printing is playing a significant role in the pharmaceutical industry. Also, it is predicted that 3D printing will play vital role for the development of Pharmaceutical industry. It will provide promising and effective way in the treatment of patients especially in personalized drug delivery. There has been a growing interest in the application of 3D printing in pharmaceutical science due to the FDA approval of Spritam. 3D printing is a method of manufacturing which involves the layer - by- layer deposition of materials. There are various techniques used to achieve this method of printing including the SLS, SLA, FDM, SSE and PB-inkjet printing. It has been used extensively in tissue and organ engineering, diagnostics, disease modelling, manufacturing of biomedical devices and the design and development of novel dosage forms. It helps the formulation scientists to manufacture solid oral dosage form with desired drug release profile. Moreover, it provides a basic understanding of the various 3D printing manufacturing techniques available to manufacture solid oral dosage forms. The various process parameters and strategies to control the characteristics of printed dosage forms are analyzed and discussed. The review includes the various methods of 3D printing used for manufacturing medicines.

KEYWORDS: 3D printing; Pharmaceutical industry; Drug delivery; Personalized medicines; Biomanufacturing; formulation scientist; oral dosage forms; Patient compliance.

Introduction
According to the International Standard Organization (ISO) defines three-dimensional printing as "the manufacture of objects through the deposition of a substance utilizing a print head, nozzle, or other printer technology." 3D printing was used in bio manufacturing, bone and tissue engineering to create scaffolds. Also, 3D printing was applied in drug development and the fabrication of drug delivery devices. [1,2]. The pharmaceutical industries utilize 3D printing as a process innovation technology to construct digitally- controlled and personalized products by converting a concept into a prototype(additive manufacturing (AM)) using 3D computer-aided design (CAD) or a MagneticResonance Image (MRI) [3,4].

3D printing is also called additive manufacturing. It is one of the most promising future technologies. It is used in the printing of building walls, human implants, medicines and food industry. The research and development department of the various pharmaceutical industry are being funded for the development of new dosage forms using 3D printing. The first FDA (U.S. Food and drug administration) approved tablet, Spritam®, was produced with the help of 3D printing in 2015. The most convenient route of administration is oral route especially for children. It is challenging for the development of personalization of oral dosage forms [5]. The concept of 3D system was developed in 1986 by Charles Hull in California. They developed the first 3D printer "Stereolithography Apparatus" and first commercial printer SLA-250. Thus, 3D printing appears to be the beginning of new technology era [6].

Oral solid dosage forms are the most commonly used forms of medications. They are simple to manufacture and have nearly accurate dosing. It is easy and painless administration that can be achieved without the need for a health care professional [7]. Oral solid dosage forms generate good adherenceand compliance. Thus, it provide good patient outcome. Oral dosage forms prepared by 3D printing has been widely used in pharmaceutical manufacturing [8]. 3D printing is based on the layer-by-layer concept in the fabrication of objects. It is digitally designed. A wide range of materials such as polymers [9], ceramics [10], metals [11-15] , wood [16] and organic tissue can be processed by this technology [17]. The working principle of the most 3D printing technologies are similar. Firstly, the product design, geometry and part sizes are generated using a CAD software. Later on, it is converted into a machine-readableformat and sliced into printable layers. Raw materials are processed into powder, filaments, or binder solutions. These are deposited in a layer-by-layer system to create the physical objects. Finally, certain products may require for postprocessing treatment. Generally, it involves the removal of support or excess materials. 3D printed methods depends upon raw material, equipment and solidification process [18].

3D printing allows the development of SODFs with complex geometries. They are impossible to be manufactured with conventional fabrication methods. Although, multiple active pharmaceutical ingredients (APIs) could be combined into one dosage form. Thus, it may be beneficial for patients who need to daily take many different medicines.
Moreover, patient-specific medicines can be easily manufactured via 3D printing. This can decreases the risk of adverse effects related to SODFs manufactured with the conventional methods. It can follow the "one-size-fits-all" regime and significantly improves patient adherence.[19,20]

Advantages

1. It is easy to fabricate on quality product within a few minutes.
2. It can be useful in situations where time and materials are limited.
3. It is capable to produce delayed release and zero order release formulations.
4. It is used to develop the world's first US Food and Drug Administration (FDA)- approved 3D printed medicine.
5. It is capable to produce immediate and sustained -release formulations.
6. It can improve solubility of poorly soluble drugs.

7. It is capable of forming highly porous dosage forms.
8. It Can be used for Dosage Flexibility.
9. It can be used to improve quality dosage forms such as Design Flexibility, Rapid Prototyping, Customization and personalization with 3D printing, Low - volume production and mass customization, Design freedom and innovation, Reduced material waste and Manufacturing of solid oral dosage forms with multiple APIs.

Disadvantages

1. Product may not be aesthetic appeal to patient.
2. It can produce printlets with rough or imperfect surfaces.
3. Products are not aesthetically pleasing to patients, may cause poor patient compliance.
4. The materials used during Stereolithography may cause unknown health risks.
5. Stereolithography and SLS printing may use lasers and high-energy sources may result in degradation of unstable drugs.
6. FDM printing may be restricted to heat sensitive drugs and excipients.
7. The equipment used in stereolithography are expensive.
8. Curing and drying process are required in SLS, SLA and powder bed 3D printing, lengthening the printing duration as apart of post printing process.

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

3DP Technology	**Advantages**	**Disadvantages**
FDM	low-cost feasible to manufacture different dosage forms manufacturing of dosage form containing multiple APIs no post-processing high mechanical resistance of the dosage form	limited to low dosage drugs thermal degradation
PAM	does not require high temperatures specific materials are used manufacturing of dosage form containing high drug loading manufacturing of dosage form containing multiple APIs	requirement of organicsolvents dosage form may show contraction or deformation in their shape time-consuming low resolution
SLA	print larger models compared to other photocuring based 3DP	the action of the laser might degrade the API printing speed can be quiteslow post-processing

DLP	faster than SLA provide high-resolution prints smaller resin tanks compared to SLA printers does not require high temperatures or pressures	chances of drug degradation due to the action of the laser post-processing
CIJ and DoD	high accuracy and reproducibility few steps required to create the final object requires less printing time minimum drug wastage low cost	not applicable with high drug loading chances of alteration in APIs dueto high shear rates
SLS	dosage forms having different shapes and drug release patterns accurate control of the composition and of the internalstructure of the dosage form low wastage no need to add supports no need of drying step low-cost	chances of drug degradation due to high temperatures and high-energybeam

Applications of 3D Printing

Table 2: Applications of 3D Printing

Applications Area	**Dosage Form**	**Method**
ersonalized Drug Dosing	A flexible-dose tablet for immediate and extendedrelease	Fused deposition modelling 3D printing
	Starmix candy like formulationsof indomethacin	Fusion deposition modelling 3D printing
Complex Drug-Release Profiles	Modified-release tablets of 4-aminosalicylic acid and paracetamol	Stereolithographic 3D printing
	Effect of geometry on drugrelease from 3D printed tablets	hot melt extrusion(HME)
	Nitrofurantoin model disk geometries	3D extrusion-based printing
ersonalizedTopical reatmentDevices	Nose-shaped mask, laden with salicylic acid, adapted to the morphology of an individual	Fused deposition modeling as well as stereolithography

Different Steps involved in 3D Printing:

1. Computer Aided Design (CAD) and 3D representation is required
2. 3D model converted into STL file
3. STL file transfer to printing machine
4. Proper machine set-up is required
5. Deposition of Building materials
6. Prepared printlet must be removed from machine
7. Post-processing
8. Application

Table 3: 3D printing techniques used for the fabrication of oral medicine

3D Printing technique	Consolidation source	Material form	Basic consolidation mechanism
Selective Laser Sintering	Laser beam e.g CO_2 Laser	Powders	Powder is deposited in successive layers on a build platform. They are fully or partially melted with the aid of a laser beam.
Stereolithography	UV beam	Resins	Photocurable liquid resins are polymerized by focusing of a UV beam on designated paths to cure the selected resin areas by crosslinking.
Fused Deposition Modelling	Heated nozzle	Filaments	Thermoplastic polymer filaments are passed through a heated nozzle to produce melted polymer matrix. Finally, it is deposited in layers onto a build platform
Powder bed-Inkjet	Binder/thermal energy	Powders	Layers of materials, usually powder are deposited onto a build plate. Later on, consolidated using a binder solution often referred to as ink

1. **Selective Laser Sintering (SLS):**

SLS is a 3D printing technology. It consist of a laser beam which is used to fuse particles of powder layer-by-layer as shown in Fig. 1. The concept of selective laser sintering is based on the spread of layers of powder. It has thickness of 0.05 to 0.3mm followed by the selective laser beam scanning of each layer [21]. The sintered powder creates the part or final structure. The unsintered excess acts as the support structure, which is removed by post-printing processing[22]. SLS is a one-step process. The use of additives to bind the object replaces the use of the laser. It also provides higher resolution due to low wavelength. Thus, it is cost effective, eco-friendly and time efficient. The limitation of SLS is that it creates the high temperature during process. Thus, it may cause the degradation of the active Pharmaceutical ingredient within the powder [23,24.]

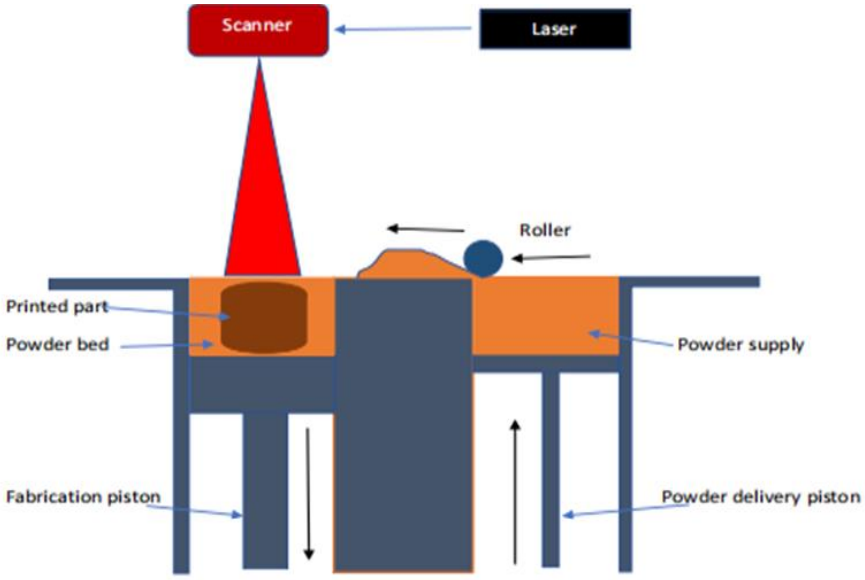


Fig. 1: Schematic diagram of selective laser sintering showing the different parts of SLS

Materials used for Selective Laser Sintering

The starting materials used in SLS must be in form of powder. The flow characteristics of powder allow easy deposition of thin layers. The particle size of powder is generally below 180 µm [25.]

a. SLS processes a wide range of materials including ceramics, polymers, metal, and alloys. The process includes powder mixing with a low melting temperature material. It can serve as a binder. Also, it has the ability to cause sintering without the need of a binder [26.]
b. Selective laser sintering depends on the material used and the desired mechanical properties. The solid state sintering used to process ceramic and metallic powders. The liquid phase sintering used in composite materials [27.] The most widely processed materials in SLS are such as polyamide, polystyrene and polycarbonate are [28,29].
c. The various factors such as bioavailability, biodegradability and biocompatibility of the powder are of great importance in the field of biomedical and pharmaceutical sciences. According to Leong et al [30] PCL and PLLA are the two biodegradable thermoplastic polymers were studied for the fabrication of controlled release tablets.

Table 4: List of different polymers used in manufacturing oral dosage forms using SLS

Polymer	**Active Pharmaceutical Ingredient**	**Material(s) added**	**Printing temperature (^{0}C)**
Kollicoat IR	Paracetamol	Candurin® Gold Sheen	90-110
Eudragit L100-55	Paracetamol	Candurin® Gold Sheen	90-110
Polyethylene Oxide	Paracetamol	Candurin® Gold Sheen	35-50

Ethyl Cellulose	Paracetamol	Candurin® Gold Sheen	110-120
Eudragit RL	Paracetamol	Candurin® Gold Sheen	65-85
HPMC	Paracetamol	Candurin® Gold Sheen	115-135
Kollidon®	Paracetamol	Candurin® Gold Sheen	80-100
Polycaprolactone	Methylene Blue		40
Poly lactic acid	Methylene Blue		60

Characteristics of Sintered Printlets

Firstly, identify the significant parameters to design a SLS printed dosage form. There are various process parameters such as the powder mean diameter, size distribution, density, layer thickness, binder ratio fraction, and the laser scan speed, power, spot size and absorbed energy involved in selective lasersintering [31].

a. During process optimization the identification of significant parameters and the effect of their interaction is necessary. The various printing variables include porosity, yield strength, hardness, surface roughnessand layer thickness affect the properties of sintered parts.
b. According to Leong *et al* [32] the three critical parameters such as laser power,laser scan speed and bed temperature influence the creating dense wall formation and porous infill of biomedical materials. These parameters were used to control the porosity of SLS printed circular discs made for controlled drug delivery by zero order release.
c. According to Leong et al the objective was to create a disc with two concentric circular regions. It has varying porosity, dense outer region for barrier effect and a porous inner region for drug encapsulation. The study include blends of two biodegradable thermoplastic polymers such as PCL and PLLA used powder blends. Methylene Blue (MB) was used as a model drug.

2. Stereolithography:

Stereolithography is a 3D printing method. It involves the layer-by-layers solidification via polymerization of liquid resin by a light beam as shown in Fig.2 Crosslinking occurs when an ultravioletor other light source focused on a tank filled with a photosensitive resin. It forms a polymeric matrix [33]. The platform is lowered after the curing of each layer. A new layer of uncured polymer resin is deposited on the top of the cured layer. Later on, the next curing forms on a bottom-to-top build approach as shown in Fig. 2. An alternative approach involves the curing of resin layer. It is allowed to pass through a transparent plate in the bottom of the resin tray followed by a light source from below. After each layer curing, the platform is raised. The uncured resin is allowed to fill the space between the platform. The plate allowed subsequent layers to be cured in a top- down approach. During crosslinking reaction of resins, the power of the light source, speed of scanning and the quantity of monomer and photo initiator determine the kinetics.

It influence the thickness of cured layer as well as the time of curing [34]. The advantages of this printing method include high resolution, speed of printing [35] and reduced localized heating. Thus, it is suitable for the printing of thermolabile drugs. Also, the high-resolution capabilities of stereolithography enabled the technique to be used in the fabrication of microneedles patches with high quality. It is quite similar to those fabricated microfabrication techniques such as soft lithography [36], though it was originally used to fabricate Nano and Micro patterns for micro electro mechanical systems [37-45.] This method of printing allows the incorporation of miscible materials such as excipients and APIs which may not be polymerisable to be entrapped in the polymeric matrix upon crosslinking [46-47.]

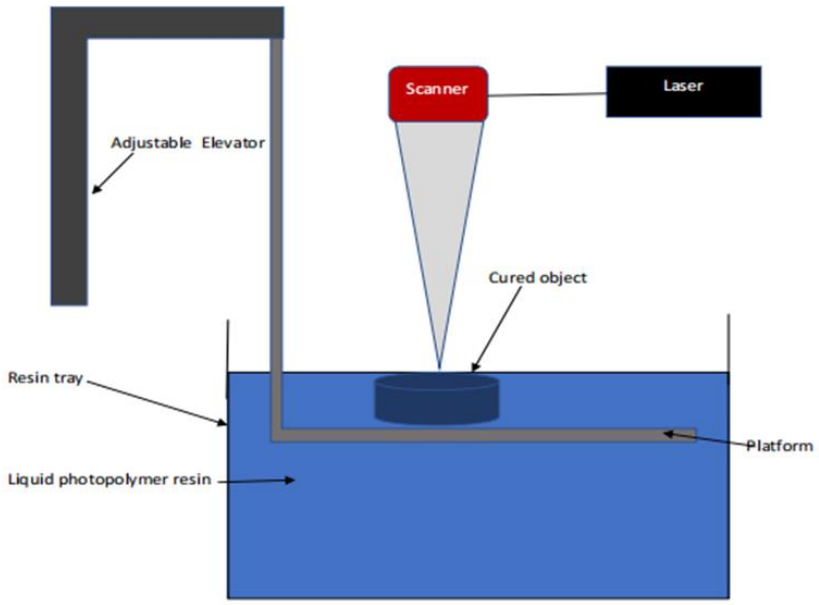


Fig. 2: Schematic representation of stereolithography showing different parts of 3D printer

Materials used for Stereolithography

Stereolithography requires the use of photo polymerizable materials. A number of photo polymerizable materials have been developed such as PEGDA, PHEMA, PEGDMA and PPF/DEF [48.] Hydrogels are 3D polymer networks. It has been applied in tissue regeneration and engineering due to their high water content. They have diffusive and mechanical characteristics that are adjustable. It is influenced by the extent of crosslinking. Thus, it may be ideal in drug delivery applications [49.] Photo polymerization of hydrogels has been explored extensively in terms of

materials and methods. This has led to the synthesis of several biocompatible hydrogels of various characteristics like PEGDA. Alternative bases of these hydrogels may include 2-(diisopropylamino)ethyl methacrylate, chitosan derivatives or gelatin chondroitin sulphate and hyaluronic acid [50]. As a result, stereolithographic 3D printing was used in tissue engineering and scaffolding. Recently, it has been used to produce microparticles. A few studies were done on the use of stereolithography in drug delivery. PEGDA as the polymer of choice for printing was mostly employed. Although hydrogels have proven to be very applicable in the design of drug delivery systems with controlled release.

Characteristics and Drug Release Properties of SLA Printlets

Vehse et al fabricated a drug loaded PEGDA scaffolds using diode laser curing in 2014. According to their study, the photo polymerization initiator DPPO was used to aid the process. The various the parameters such as laser power, scan speed and hatch distance were optimized prior to printing. The UV-resistant antiplatelet drug, acetylsalicylic acid was mixed with the resin. The strength and drug delivery characteristics of the scaffold were analysed. Different concentrations of the drug were prepared and successfully incorporated into the scaffold. It was able to release 95% of the drug within 3 hours. It was observed that the compressive strength of the scaffold reduced with increased drug concentration showing that the drug interfered with curing. According to Martinez *et al*. Ibuprofen loaded hydrogels based on PEGDA were fabricated. They found that it is feasible to produce pre-wetted hydrogels with the same SLA printing technology. It has the ability to crosslink for entrapping the non- photo polymerizable water component within the matrix. Thus, allowing for the production of moist drug loaded hydrogels. The formulations contained DPPO as the photo initiator, produced printlets with irregular shape. DPPO polymer is toxic. Riboflavin triethanolamine combination is safer than DPPO polymer. Hydrogels containing PEGDA causes brittleness. PEG 300 was added to the formulation. Thus, it create a plasticizing effect and reduce brittleness. Drug release was dependent on water content. If there is higher water content then it produced faster drug release. It was concluded that SLA 3DP method can be used to prepare drug loaded hydrogels. [51.]

Incorporating APIs into Polymer Filaments for 3D Printing

a. S**olvent immersion :**

a. Filaments from pharmaceutical grade polymers incorporated with active pharmaceutical ingredients (API) are not commercially available[52.] The various commercially available filaments such as PLA, PVA and PCL are suitable mechanical properties for printing. Presently, it is a challenging to load these filaments with APIs.
b. The first filaments used for FDM printing of oral dosage forms were loaded with APIs. It was done by soaking commercial filaments in volatile solvent solutions [53]. According to Goyanes et al [54] production of amino salicylic acid loaded with PVA filament in drug-saturated ethanol. This allowed the drug to passively diffuse into the filament and stay trapped on drying.
c. The advantage of this method that it was cheap, simple and required no heating. The percentage drug content reported for this method was rather low recording 0.004% for 4-ASA and 0.001% for the less soluble 5-ASA.

b. Hot Melt Extrusion (HME):

Hot Melt Extrusion (HME) is the latest method of producing API loaded filaments. It involves pelletizing and grinding of commercially available filaments mixed with active ingredient prior to a hot melt extrusion. Grinding is done to ensures uniform particle size of the API (powder) and polymer. Mixing pellets with drug powder would lead to poor encapsulation. As a result, poor drug loading [55.] PVA filaments were cut into small cylindrical pellets that were roughly 2mm in length. Later on, it is ground to fine powder and

was passed through a sieve of mesh size 1000µm. Budesonide was mixed with the powdered polymer. Then, the mixture was extruded with the help of a single screw extruder [56.] The advantages of this method produced filaments with higher percentage of drug content and good mechanical strength. Thus, this method is used to improve the bioavailability of poorly soluble drugs.

Fused Deposition Modelling (FDM):

FDM involves the layer-by-layer deposition of a molten polymer onto a platform to create a 3D object. The deposition of building material is done by the feeding of a polymer filament into the heated printer-head. The melted semi-solid form extruded onto the printer platform. The nozzle extrudes the polymer along x and y-axis to form a layer. Later on, the stage lowered to accommodate the next layer. Thus, the material build up along z-axis as shown in Fig. 3. The geometry and size of the printed material is designed with the aid of CAD software. Excess residual solvent was observed in inkjet printing. This method is simple, cheap and easy accessible [57]. The limitation of this method is thermal degradation of ingredients, slow drug dissolution speed and poor drug loading [58-59.]

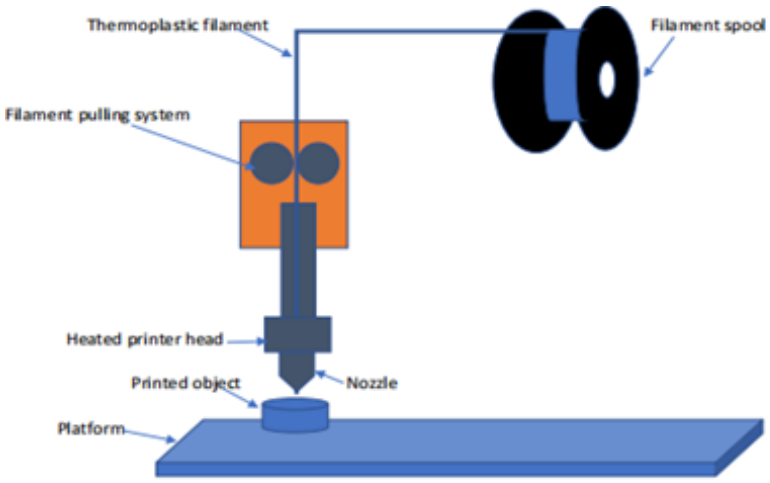


Fig. 3: Schematic diagram of fused deposition modelling and its different parts

Polymer Filaments for Fused Deposition Modelling

FDM printing are made up of thermoplastic materials. Filaments are produced mainly by hot melt extrusion of polymers. The first commercially available filaments produced for FDM printers were plastics. They are such as PLA, ABS, high impact polystyrene (HIPS) and polyethylene terephthalate glycol-modified (PET-G) [59] These plastics produced in the dimension range of 1.75mm and 2.85-3mm. Generally, it provides high melting temperatures and good mechanical properties. It can be fed easily into the printer heads and withstand the heat and forces exerted by the extruder/printer gears. There are many commercially available high quality filaments suitable for FDM printing. Filaments are made from polymers which are not suitable for pharmaceutical applications due to its poor thermal and mechanical properties [60.] Now-a-days, there is a growing interest and search for ways to improve the properties of available polymers and filaments to make them more printable or

pharmaceutically suitable. Some materials such as PLA, PVA and PCL were used to print oral dosage forms by FDM. [61-64.] PLA is a biodegradable polymer of great interest due to its advantages. PLA is a naturally occurring organic polymer produced from a non-toxic renewable source. According to FDA, PLA is safe (GRAS) [65]. It is also eco-friendly, biodegradable, recyclable and compostable. Although it is widely applied in the field of biomedical science [65.]

Characteristics of FDM printlets

Swelling and disintegration accompanies drug dissolution in conventional compressed tablets. The FDM printed tablets shows very low dissolution speed compared to compression-based tablets. This is due to the nature of polymers used and also depends on compactness of the melted filaments. FDM has been broadly applied in many studies to produce modified (extended and sustained) release dosage forms [66]

Though FDM printing has been focusing on extended-release tablets until recently, almost 70% of immediate release form are orally administered [67.] Adaptation of FDM printing has great importance to drug products and pharmaceutical materials that are intended to release active ingredients immediately. One of the earliest attempts was presented in a study by Pietrzak et al [68] which explored the use of HME 3D printing methods and FDM for controlling the release of theophylline from a range of polymers including HPC SSL and Eudragit Ewhich are commonly used polymers for immediate drug release. The result shows that unprinted polymer filaments were able to release majority of drugs within 25 minutes the printed form release over a longer period.

Powder-Bed Injkjet Printing

Inkjet printing commonly denotes deposition of materials dispersed in a solvent by ejecting them onto a substrate through a nozzle [69.] Out of the three mechanisms which are commercially used in droplet generation [70], the DoD has been frequently published work. Whereas EIJ printing been becoming more commercially available DoD is more precise and less wasteful. This is mainly due to the size of the droplets in the range of 1pl to 1nl range as the droplets are mechanically placed in predetermined positions rather than in steering while in motion. Two commonly used systems of droplet formation in DoD printing; the piezoelectric and thermal printing methods. In case of Piezoelectric, the applied voltage to piezoelectric material resulting in deformation and hence an ejection of liquid droplet through the nozzle.The advantage of piezoelectric method is it offers more control about droplet formation. Hence, it is more appropriate for pharmaceutical claims. In case of thermal inkjet system droplets, Ejection normally occurs when localized heating of liquid causes bubbles to form and expand [71.] But this has additional risk of heat generation and heat degradation also restriction in solvent and meager mechanical strength. Due to the high level of automation, precision and reproducibility of the technology, Inkjet printing has been applied in various genomics, drug delivery, materialscreening, biomaterials and life sciences [72-75.]

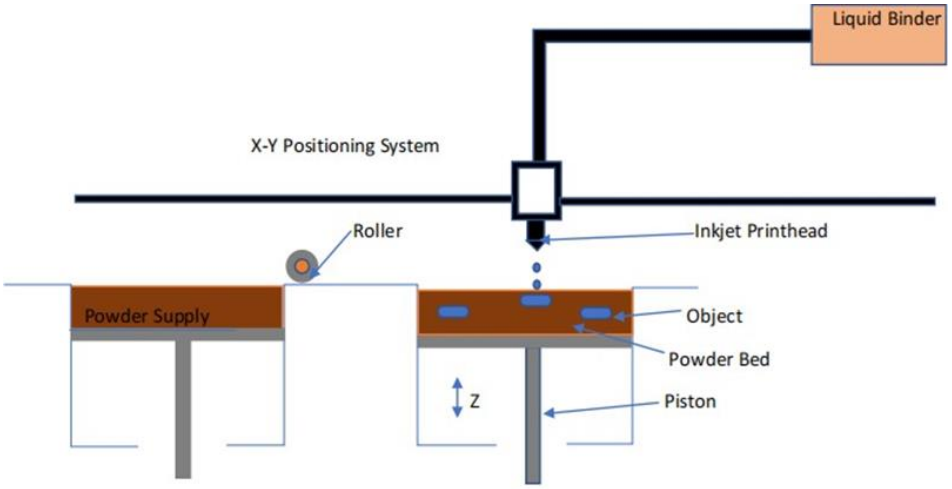
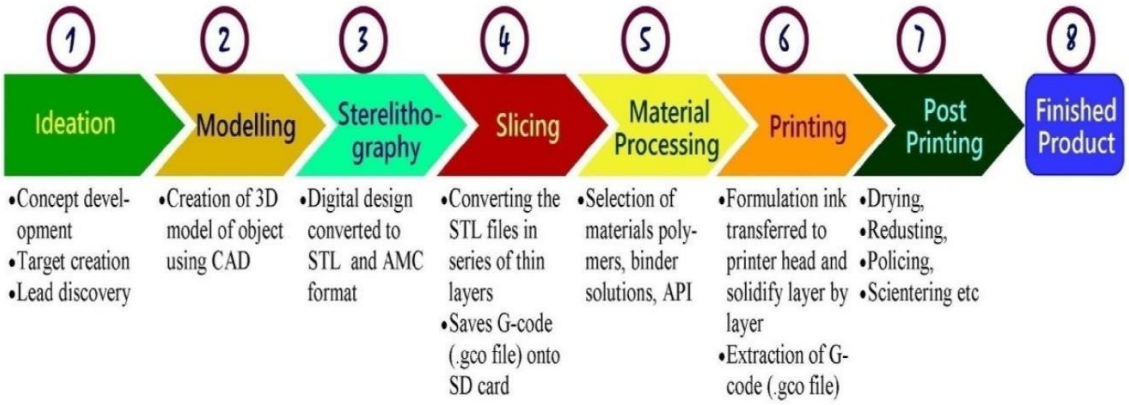
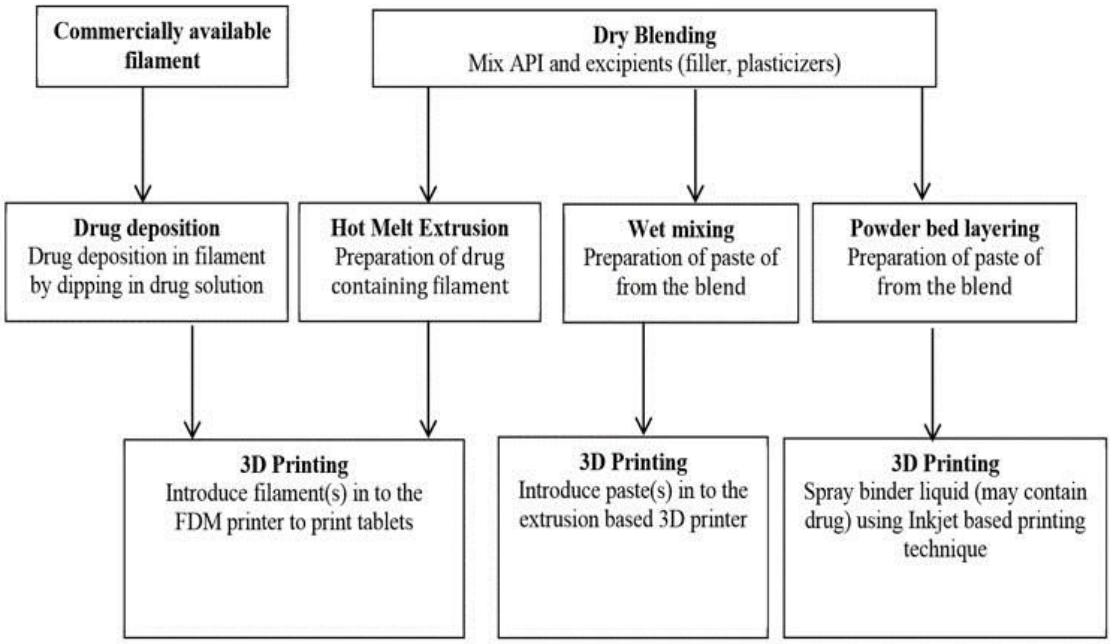


Fig. 4: A Schematic diagram of Powder bed-inkjet printing and their parts

Inkjet printing was used to load micro-needles [76]. It improves dissolution properties of poorly soluble drugs and control release of dosage forms by ensuring content uniformity [77]. The fabrication of 3D printed objects with high resolution can be achieved with the help of Inkjet printing technology. It was observed that multiple and successive deposition of jetted layers of materials onto a flat platform. It was reported that there is involvement of layer by layer inkjet deposition of curable resins and thermoplastics [78]. Thus, there are limited pharmaceutically approved materials that can be used for these processes. Usually, for the printing of pharmaceutical dosage forms, the powder bed method of 3D printing is employed, as most approved polymers are in form of powder materials.





Flowchart of 3D printing using various Techniques

Different Formulation of 3D Printing:

The various types of dosage forms such as immediate release tablets, osmotic drug delivery Systems can be produced by 3D printing techniques. List of various Dosage forms prepared by 3D Printing Technique are shown in Table 5.

Table 5: List of various Dosage forms prepared by 3D Printing Technique

Dosage form	**3D printing technique**
Immediate release tablet	FDM
Orodispersible films	FDM
Floating drug delivery system	FDM
onolithic Sustained releasetablets	FDM
Pulsatile drug release tablets	FDM
Biphasic release tablets	Extrusion based 3D printer
Multi-active solid dosage forms	Extrusion based 3D printer
Fast disintegrating tablet	Powder-based 3D printing
Zero order release tablets	TheriForm™(Inkjet based 3D printingtechnique)
Enteric release tablets	FDM
blets with polymericnanocapsules	FDM

A. Immediate release tablets

An immediate release tablet can be prepared by a filament of drug and a hydrophilic polymer with or without plasticizers. Hydrophilic polymers like povidone, hydroxy propyl methyl cellulose, hydroxy propyl cellulose or recent graft polymers like Soluplus®. Such filaments are fed in a FDM based 3D printer to produce an immediate release tablet. According to Okwuosa et al., an immediate release tablets of theophylline and dypridamole using PVP as polymer, tri ethyl citrate (TEC) as plasticizer and talc as filler at ratio of 10, 50, 12.5, and 27.5 % wt. More than 90% of the drug was observed to dissolve in 30 min for both the drugs with 10% loading, demonstrating the utility of 3D printing in formulating an immediate release tablet [79.]

B. Orodispersible films

According to Jamróz et al., orodispersible films of aripiprazole using polyvinyl alcohol as polymer was prepared, using FDM based 3D printing technique. The disintegration time was found to be 43.00 ± 1.00 s compared to 27.50 ± 4.23 s for placebo tablets. When compared to casted films 3D printed films showed improved dissolution. The conversion of aripiprazole to amorphous form showed high surface area of the printed films. Although, mechanical properties of the casted films were slightly better due to their continuous structure [80.]

C. Floating drug delivery system (FDDS)

The shells and infill are the key parameters in FDM 3D printing. It may define the outline shape and inner support structure of an object. At least one shell is neededto print an object and additional shells will add body's strength and weight. The disadvantage of FDDS is that it consumes more printing time and materials. Moreover, infill percentage is another parameter. It could be adjusted from 0% to 100%, generating the object fromcompletely hollow structure to fully solid filled structure. The overall density can be decreased by keeping the structure hollow that impartsbuoyancy. It was reported that the optimized tablet design with density of 0.77 g/cm3. Also it had 2 shells and 0% infill, had the capability floated for more than 10 h in dissolution batch. Also, tablets prepared with shells more than 3 or infillpercentage more than 20% had densities above 0.9 g/cm3 which caused them to sink in less than 1 h. The release rate was sustained for 12 h which was not significantly affected by the number of shells or the infill percentage [81.]

D. Monolithic sustained release tablets

5-aminosalicylic acid of sustained release tablets were prepared by using drug loaded polyvinyl alcohol (PVA) filaments. The filaments were prepared by loading drug from its ethanolic solution on polyvinyl alcohol (PVA) filaments. The drug loading of the filament was found to be 0.06%w/w and 0.25% w/w for 5-ASA and 4-ASA respectively. Dissolution test of sustained release tablets containing 5-ASA was performed in modified bicarbonate buffer (pH 6.8). It was found that tablets with 90% infill showed 100% release over 4 h time period. Also, it was observed that 50% of 4-ASA degraded during preparation of tablet. It may be due to high extrusion temperature (210 °C) for PVA filament. So, thermolabile drugs cannot be applied by this technique.

E. Multi-active solid dosage forms

According to Shaban et al., they prepared a tablet containing nifedipine, captopril and glipizide using extrusion-based 3D printing at room temperature. Also, they have prepared polypill containing 5 drugs in a single tablet. Aspirin and hydrochlorothiazide drug were immediately released whereas atenolol, pravastatin, ramipril drugs were sustained release.

F. Fast-disintegrating tablets

According to Yu et al., prepared a fast-disintegrating tablet. They incorporated loose powder in the core region surrounded by printed binder region. The loose powder was deposited in Hollow core region. It was created by printing binder solutions in three phases printing. Firstly, solid circular region to form a base. Secondly, several layers of rings to form a cavity. Lastly, solid circular region to cover. The hardness, friability and disintegration time was found to be 54.5 N/cm2, 0.92% and 21.8 s.

G. Enteric release tablets

According to Goyanes et al., they formulated enteric coated tablets of paracetamol using HPMCAS (Hydroxy Propyl Methyl Cellulose Acetate Succinate). Hot melt extrusion method was applied to prepare Filaments of drug using enteric coated polymer. These filaments were used to manufacture tablets using single filament fused deposition modeling (FDM) based 3D printing. About 50% drug loading was achieved [82]. Alternative approach to prepare enteric coated tablets than a conventional enteric coating process. Thus, it is safe compared to conventional coating process involving organic solvent.

H. Zero order release tablets

Zero order-release tablets was prepared and it regulates shell around an immediate release core. The release rate regulating shell can be composed of water soluble and insoluble polymers. Generally, these can be used for sustained release membrane coating of tablets or pellets. The release rate is controlled by the hydrophilic fraction of the shell. It regulates the diffusional pathway for the drug. According to Wang et al., they prepared a near zero-order controlled-release pseudoephedrine hydrochloride (PEH) formulations using 3- Dimensional Printing (3-DP™) technology. The dosage form had a cubic design with multi-chambered cubic core containing drug. The substrate was a mixture of Kollidon SR and HPMC. a level A IVIVC correlation was possible with the formulations prepared by different Kollidon SR-HPMC ratio [83.]

Regulatory Challenges and Quality Control

3D Printing provide a promising improvement in the field of pharmaceutical sector. There are many challenges while using this technique. These include thestandardization of printers, the poor availability of biocompatible materials, development of analytical methods for the quality control of the final products and regulatory aspects.During manufacturing of Personalized medicines, it was observed that a lot more similarities with compounded medicines than manufactured dosage forms especially in terms of level of possible risks. Although risks associated with customized medicines made for individual patients may not be as hazardous as compared to traditional medicines.

Care should be taken to ensure that safety of use of medicines. Regulation to be framed to prepare 3D print medicines for the safety of patient. Also evaluation parameters to be framed for 3D Printed medicines.3D printed personalized medicines are produced in small quantity. So, some non-destructive tests could be carried out. It has been reported that some non-destructive analytical techniques may be useful for personalized medic

According to Trenfield et al., they evaluated the use of process analytical technology (PAT) on paracetamol loaded 3D printed tablets. Near infrared spectroscopy was used to develop a calibration model. It could predict drug concentration with impressive linearity and accuracy. Raman confocal microscopy is another method to demonstrate distribution of the drug within the tablet. According to Vakili et al, similar non-destructive quality control was tested on inkjet-printed theophylline formulation using hyper spectral imaging technique[84].

If non-destructive techniques of testing are not available or applicable, then the destructive quality control tests can be performed. Moreover, regulatory measures need to place more emphasis on other quality assurance and management steps. Thus, it can lead up to product formation by devising approaches to ensure quality throughout the production process.

Conclusion

Personalized medicine is gaining interest among the patient. The need for a personalized dosage forms came into existence with the technological advancement in additive manufacturing technology. 3D printing is one of the latest technology in manufacturing of dosage forms. 3D printing technology require improvement for the manufacturing of different dosage form. The various methods of 3D printing technologies are fused deposition modelling, semi- solid extrusion, selective laser sintering, inkjet printing and stereo lithography have been used in printing oral solid dosage forms. There are various pros and cons of 3D printing. FDM was an easy and cheap option for printing oral solid formulations. Although, it affects the stability of thermos-labile drugs. Thus, only limited polymers are available for filament manufacturing. It has been reported that the desired drug characteristics to suitable type of 3D printing or devising ways around known limitations. Regulatory changes will be observed due to the advancement of 3D printing. It is evident that with all the new and potential developments in medications 3D printing will come several regulatory adjustments to accommodate these changes.

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