Scope Of 3d Printing In Medical And Pharmaceutical Industry: A Review

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Abstract- *Growing demand for customized pharmaceuticals and medical devices makes the impact of additive manufacturing increased rapidly in recent years. The 3D printing technology has caught the attention of medical devices industry and pharmaceutical industry due to its application on various platform in health care industry. This technology allows the fabrication of 3D objects with various geometrics in a layer-by-layer process. In recent years the 3D printing has become one of the most revolutionary and powerful tool serving as a technology of precise manufacturing of individually developed Dosage Forms, Tissue Engineering, and Disease Modelling. This current review focused on different 3D printing technology steps, various techniques with their expectations, applications, limitations and undeniable benefits of 3D printing in pharmaceutical technology.*

Keywords- 3D printing, Dosage Forms

I. INTRODUCTION

The 3 Dimensional (3D) Printing is a procedure that create a 3D model or entity from a computer aided design (CAD) model, usually by properly adding material layer by layer, which is also called as additive manufacturing[1] conventional casting, forging and machining procedures, where material is removed from an inventory item or poured into a mold and formed by means of hammers, presses and dies.[2,3]

1984 – First functioning 3D printer (Charles Hull, inventor of stereolithography,3D System co-founder)

1990s – **Introduction of new printing technologies**, like Fused DepositionModelling and Selective Laser Sintering.

3D Printing covers a various types of processes in which material is linked or coagulate under computer control to carve a 3 Dimensional entity[4] with material being combine together generally layer by layer. In 1990s 3D printing were desirable only for production of structural and aesthetic prototypes, it termed as Rapid prototyping.[5]

The most commonly used 3d printing techniques, materials in 2018 is 46% is fused deposition modelling (FDM), 38% is selective laser sintering (SLS), etc.[6]

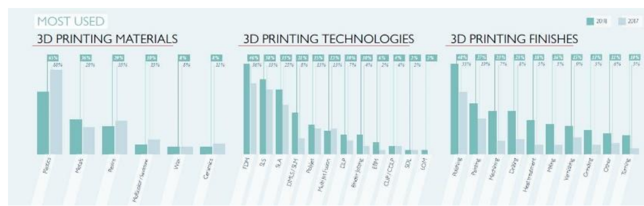


Fig: Statistical Data Of 3d printing technologies and materials

Now a days 3D printing has been used in various fields such as medicine, food industry and recency in pharmaceutical manufacturing.[7] As Pharmaceutical industry switch from batch manufacturing to personalized medicine, 3D printing become the part of production of drugs.[8]

When analysis of the manufacturing procedures of conventional pharmaceutical product, it has lot of advantages like advanced production rates due to its accelerated operating systems, capability to attain high drug loading with desired accuracy and exactitude for potent drugs that are employed in small doses, reduction of material wastage which can relieve in cost of production and flexibility to broad types of pharmaceutical active ingredients.[9]

Various types of drug delivery systems have been developed using 3D printing technology are:-

- Micro pills
- Microchip
- Oral controlled release system
- Drug implants
- Multiphase release dosage forms
- Personalized medicines
- Fast dissolving tablets

- Immediate release tablets[10]

Given personalized dosage forms of drugs are enviable to bypass unessential adverse effects, rectify the dose regimen, and accomplish personalized release profiles, the application of quickly developing 3D Printing technologies also aids the manufacturing of personalized drug delivery systems.[11]

The world's first 3D printing dosage form developed with Aprecia's proprietary 3D printing manufacturing process, ZipDose[R] Technology that helps patients who want medicines that are easily administered. The FDA approved Spritam which contains Levetiracetam, the first 3D printed drug product.[12]

Fig: Spritam

Therefore it is anticipate that 3D printing technology could offers the new approaches in developing novel pharmaceutical dosage forms.

New possibilities in 3D printing may open up a whole new chapter of opportunities for pharmaceutical research. Pharmaceutical drug research and development could be reinforced drastically by 3D printing. There are four ways 3D printing could modify the pharmaceutical world forever like

1. Personalized Drug Dosing
2. Unique Dosage forms
3. Printing Living Tissue
4. More Complex Drug Release Profile
5. Orodispersible High Dose Medication.[13]

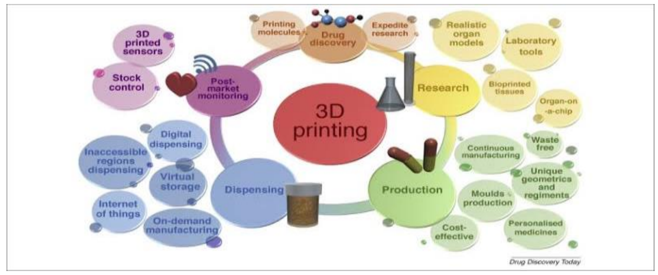


Fig: 3d Printing

Fig: Benefits of 3d Printing

II. 3D PRINTING APPLICATIONS

Customized Drug Delivery Devices and Dosage Forms

3D printing techniques are already being used in pharmaceutical research and development and in fabrication. This technique include accuracy and precise control of droplet size, the quality to produce dosage forms with complex drug release profiles.[77]

Fig: 3D printed drug

A. Personalized Drug Dosing

The purpose of personalized drug dosing is to increase quality, safety, efficacy and decrease the risk of adverse effects and reactions.[77,78,79] Oral tablets are common drug dosage form because of easily manufacturing, avoidance of pain, dose is accurate and better patient compliance. This technique has the ability to produce customized and personalized drugs such as pills, or tablets that includes multiple active pharmaceutical ingredients. By providing patients with personalized drug of multiple active ingredient in a single tablet could improve patient compliances.[79]

B. Unique Dosage Forms

These unique dosage forms are produced by using "inkjet powder based and inkjet based 3D printing". In powder based 3D printing drug manufacturing, the inkjet printer sprays the ink on the powder bed. When the ink interacts the powder, it hardens and develops a solid dosage form, layer by layer manner. In inkjet based drug manufacturing, inkjet printers used to spray formulations of active ingredients and binders in small droplets and sizes onto substrate. 3D printed drug included a diversity of active pharmaceutical ingredients like acetaminophen, steroidal anti inflammatory drugs, folic acid, ofloxacin and others.[77]

C. Complex Drug Release Profiles

The innovation of medications with complex drug release profiles is one of the most researched uses in 3 Dimensional printing. Compressed dosage forms are made from a homogeneous mixture of inactive and active ingredients and limited to a simple drug release profiles.[77,80] 3D printers can print binder onto a matrix powder foundation in layers typically 200 micrometers thick creating a barrier between the active pharmaceutical ingredient to facilitate controlled drug release. 3D printed dosage forms can also be manufactured in complex geometries that are porous and loaded with different variety of drugs throughout, encircled by barrier layers that modulate release.[80]

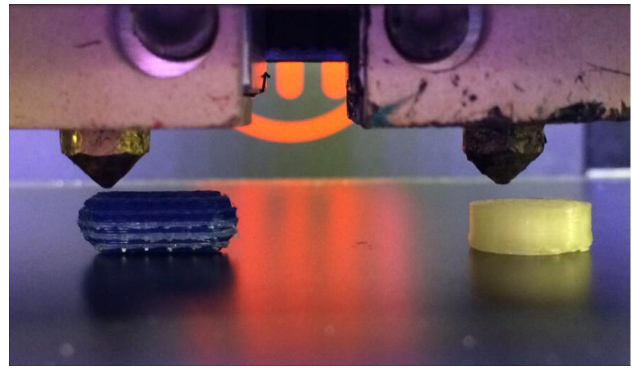


Fig: 3D printed drugs

D. Customized Implants and Prostheses

Prostheses and implants can be made in any imaginable geometry and designs through transformation of X-ray, MRI or CT Scan into digital .stl 3D print files. 3D printing has been used in healthcare sector to make complex customized prosthetic limbs and surgical implants. This approach has been used to manufacture spinal, hip, dental, titanium orthopaedic, maxillofacial implants, hearing aid and orthodontic braces. 3D printing can be used efficiently to make single, customized and complex items.[78,80,81,82,83,84]

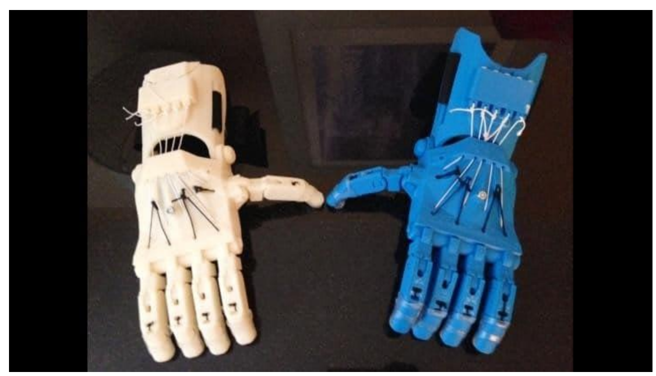


Fig: 3d printed prostheses

Fig: 3D printed prostheses

Fig: 3d printed dental implant

Fig: 3d printed hip implant

E. Bioprinting Tissues and Organs

Organ printing takes the advantage of 3D printing technology for the production of cells, biomaterials or in tandem layer by layer manner directly reinvent 3D tissue like structures. Different materials are available to create the scaffolds, depending desired strength, porosity and type of tissue, with hydrogels suitable for the production of the soft tissues. 3D bioprinting systems can be laser based, extrusion based and inkjet based bioprinting is most common. This technique deposits bioink droplets of living cells onto a substrate to reproduce human tissues and organ.[80,81,83]

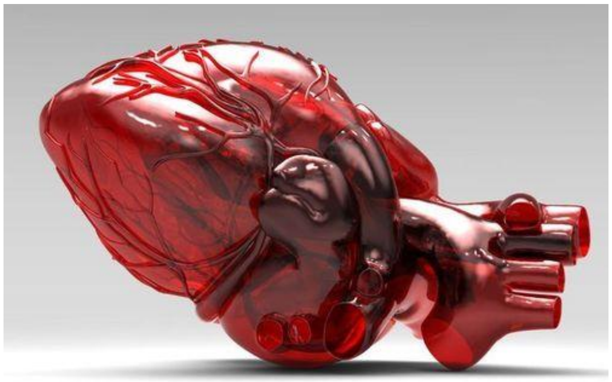


Fig: 3D printed Heart

Fig: 3D printed Tissue

III. 3D PRINTING TECHNOLOGY STEPS

1. Computer Aided Design

The first step in the additive manufacturing process is producing a digital model. For this purpose Computer Aided Design (CAD) modelling is used. There are many CAD programs that use different modelling principles, capableness and pricing policies. For example Autodesk Fusion 360, Solid works, SketchUp could be used. Reverse engineering can also be used to generate a digital entity via 3D scanning.

2. Model in Stereolithography (STL) format

In this step of additive manufacturing (AM) process a CAD entity is converted into a STL (stereolithography) file that is achievable by AM Machines. It is also possible to select a STL model from online depositories like GrabCAD, Pinshape, etc. Some of these depositories offer models for free, some are charged.

3. STL entity analysis and repair

In this step it is required to repair any errors within the Stereolithography file. Veritable errors could be like lacking triangles, non connected edges or anatropous, normals where the “wrong side” of a triangle facet is identified as the interior of the part. There are some softwares for Stereolithography (STL) model manipulations, For example 3DPrintCloud, Meshlab, Netfabb etc. If there are no errors, then some entity corrections like density, geometry changes, sizing could be made. A proper orientation of the 3D entity also could be set up. Once a Stereolithography (STL) file has been generated it is imported into a slicer program which converts it into G-code. G-code is a numerical control (NC) programming language, used in computer-aided manufacturing (CAM) to control automated machine tools like 3D printers.

4. Setting up device

In this device should be prepared for printing. This process demands proper printer setup and control, cleaning from previous build and loading print material. A routine checkup of allcritical build settings and procedure controls is also essential. When hardware is set, build file could be uploaded to the machine.

5. Printing

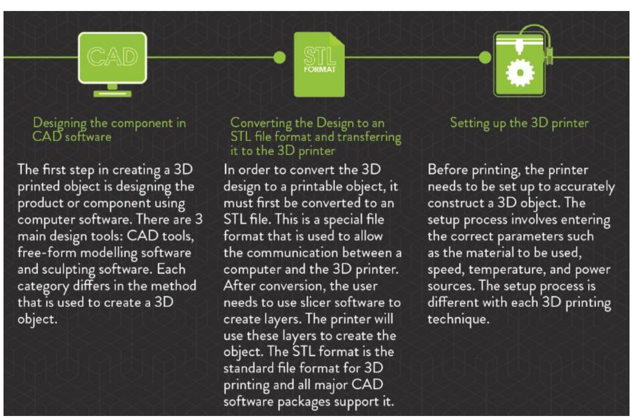
The whole printing procedure is mainly machine driven. Depending on the size of a thing, machine and material is employed, the process might take several hours or even days. There is necessary to check occasionally that there are no errors.

6. Removal of prints

In most cases of non industrial 3D Printing removal of the finished print is a simple task: separating the printed part from the print bed.

7. Post processing

Post processing may vary greatly depending on printing technology and materials used. For example a print made with Stereolithography must be cured under ultraviolet (UV), while print made with fused deposition modelling (FDM) can be handled right away. Post processing of the final product may include high pressure air cleaning, colouring, polishing and other actions to prepare for final use.[14,15,16,17]



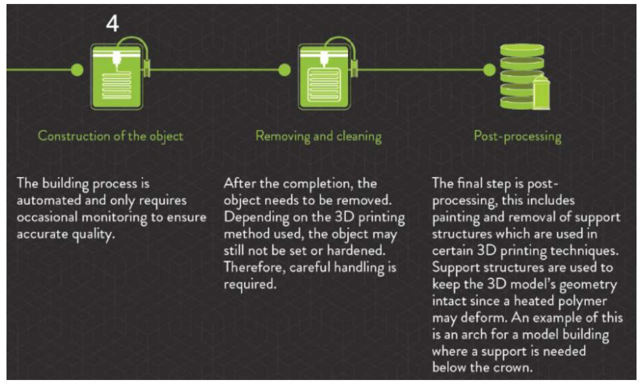


Fig: 3D Printing Technology Steps

MANUFACTURING OF SEVERAL NOVEL DRUG DELIVERY SYSTEMS BY USING 3D PRINTERS

3D printing procedures naturally appeared to be a necessary instrument in research and development area to fit with genuine industrial directions of reducing both time and costs in the first stage of a novel manufacturing thought, reducing the inherent risk of new development to fail at posterior stages. 3D printing in pharmaceutical industry symbolise a well-designed instruments for accurate, designing simple, cheap, functional and custom drug delivery systems.

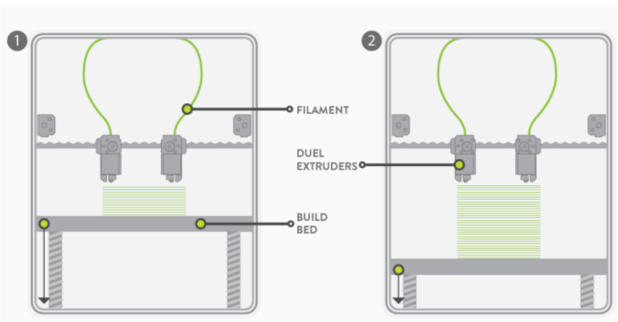
Type of printer and Printer technology	Delivery systems and Dosage forms	API / Drug used	References
Stereolithography 3D printer	Modified-release tablets	4-aminosalicylic acid &Paracetamol	18
3D printer	Multi-layered concentric implant	Rifampicin and Isoniazid	19
Fused-deposition printer	Capsule-shaped tablets	Budesonide	20
Micro-drop Inkjet 3DP	Nano suspension	Folic Acid	21
Multi-nozzle 3D printer	Capsule-shaped solid devices	Acetaminophen & Caffeine	22
Thermal Inkjet printer	Dosing drug Solutions onto oral films	Salbutamol sulphate	23
3D Extrusion printer	Drug encapsulated film of PLGA and PVA	Dexamethasone	24
Fused deposition 3D printer	Immediate release tablets	5-Aminosalicylic acid, Captopril, Theophylline & Prednisolone	25
Fused-deposition printer	T-shaped intrauterine systems and subcutaneous rods	Indomethacin	26
Stereolithography printer	Anti-acne patch	Salicylic acid	27
3D printer	Microfluidic pump	Saline solution	28
Fused deposition printer	Capsules for immediate and modified release	Acetaminophen and Furosemide	29
3D printer	Biofilm disk	Nitrofurantoin	30
Commercial inkjet printer	Nanocomposite structure	Rifampicin and Calcium phosphate	31
3D printer	Biodegradable patch	5-Fluorouracil	32
Electro hydrodynamic atomization technique	Patterned micron scaled structures	Tetracycline hydrochloride	33
Thermal Inkjet printer	Oral solid dosage forms	Prednisolone	34
Ink-jet printer	Solid dispersion	Felodipine	35
Laboratory scale 3-DP™ machine	Capsule with immediate release core and a release rate regulating shell	Pseudoephedrine hydrochloride	36
3D printer	Complex matrix tablet with ethylcellulose gradients	Acetaminophen	37
Inkjet printer	Implant with lactic acid polymer matrix	Levofloxacin	38
Piezoelectric inkjet printer	Microparticles	Paclitaxel	39
Fused deposition 3D printer	Oral pulsatile capsule	Acetaminophen	40
3D printer	Fast-disintegrating drug delivery device	Paracetamol	41
Desktop 3D printer	Bi-layer matrix tablet	Guaifenesin	42
3D printer	Fast disintegrating tablet	Acetaminophen	43
Extrusion-based printer	Multi-active tablets (Polypill)	Captopril, Nifedipine&Glipizide	44
Fused deposition 3D printer	Modified-release drug loaded tablet	5-Aminosalicylic acid & 4-Aminosalicylic acid	45
3D printer	Oral pulsatile tablet	Chlorpheniramine maleate &Diclofenac sodium	46
Fused-filament 3D printing	Tablets	Fluorescein	46
3D printer	Doughnut-shaped multi-layered	Acetaminophen	47

	drug delivery device		
Fused deposition 3D printing	Extended release tablet	Prednisolone	48
3D printer	Tablet implant	Isoniazide	49
3D powder direct printing technology	Microporousbioceramics	Tetracycline, Vancomycin and Ofloxacin	50
3D printer	Tablets	Paracetamol	51
3D extrusion printer	Multi-active solid dosage form (polypill)	Aspirin, Hydrochlorothiazide Pravastatin, Atenolol &Ramipril	52
3D printer	Complex oral dosage forms	Fluorescein	53
Selective laser sintering	Orodispersible tablet	Paracetamol	54
Thermal inkjet printing	Tablet	Prednisolone	56
Thermal inkjet printing	Solid dispersion	Felodipine	70
Inkjet printing	Microparticles	Paclitaxel	71
Inkjet printing	Injection	Nitroglycerine	72
Fused deposition modelling	Intermediate release tablets	Captopril	73
Fused deposition modelling	Catheter, Implant	Nitrofurantoin	74
Hot melt extrusion	Subcutaneous rods	Indomethacin	75
Hot melt extrusion	Compartmentalized shell	isoniazid	75
Stereolithography	Anti acne patch	Salicylic acid	76

IV. 3D PRINTING TECHNIQUES

3D printing includes wide range of manufacturing techniques.

1. Fused Filament Fabrication



Fused Filament Fabrication is the most widely used additive manufacturing technique. It employs a filament (coiled plastic) that is melted through a heated nozzle and the desired part is construct layer by layer. The printer consists of two nozzles able to move along the X and Y axis. It includes a build tray that moves down as each layer is constructed. FFF is mainly used for rapid prototyping. The layer height range is between 0.04-0.4 millimetres. This method is the most accessible since materials are affordable and so are the printers.

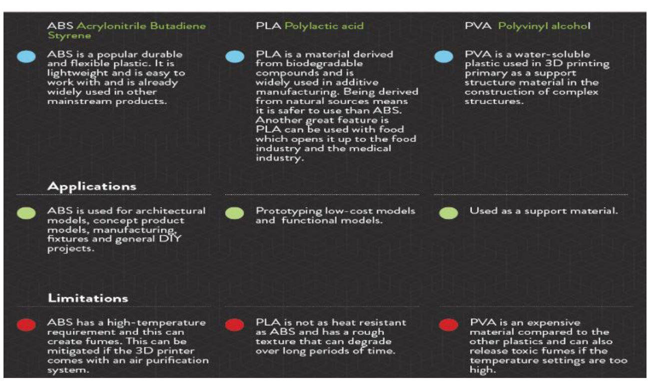
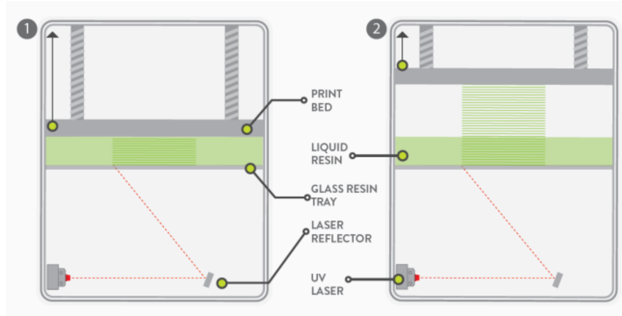


Fig: Fused Filament Fabrication Materials

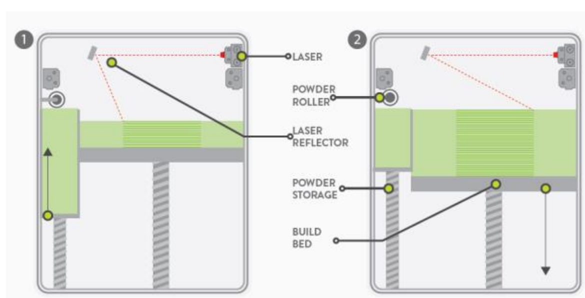
2. Stereolithography And Digital Light Processing



The stereolithography (SLA) technique uses a photosensitive liquid resin that is hardened by using a light source. A focused ultraviolet lasers over the upper side of photopolymerizable liquid in layering manner, SLA utilizes a digital mirror device to originate a chemical reaction in polymer which causes the solidification of the exposed area. In contrast to FFF, an object is created through a developed platform being lowered into the resin and a light source above or underneath hardening the material.

Fig: Stereolithography Material

3. Selective Laser Sintering



Selective Laser Sintering (SLS) is a technique that uses a laser to crystalize a powder material. It works by having a constructed area that is filled with a powder complex and storage compartment. The small amount of powder in the constructed area is heated below its melting point by a laser. As the laser melts the starting layer, the build platform moves down as the powder store area moves up. This method is suitable for structural components and end products. SLS is used with various polymer materials while metallic components are produced using DMLS (Direct metal laser sintering). This procedure is similar but has different power requirements and slightly different processes due to the metal.[55]

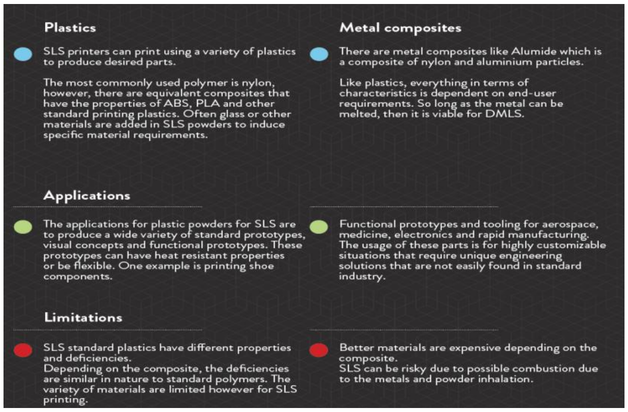


Fig: Selective Laser Sintering Materials

SAFETY COMPARISON TABLE

Hazards	FFF	SLA	SLS
Material Handling	Low: Most filaments come in a solid coil and pose no immediate danger to the user.	Medium: SLA uses liquid resin with many mixtures that can cause irritation to eyes and skin.	High: Powder polymers can easily be inhaled and dropped leading to safety concerns for users.
Flammability	Low: Heated nozzles can reach high temperatures and should not be touched during operation.	Low: Liquid resins are low risk to flammability depending on handling.	High: Metallic powders do have a risk with combustion.
Toxicity	Low: ABS can produce fumes but many printers have air filters.	Medium: Mishandling of liquid resins is a danger and ingestion is hazardous.	Medium: Powder can get into sensitive areas and cause health concerns.
Inhalation	Low: Inhalation main arise from possible material fumes, but printers can be purchased with HEPA air filters.	Low: Resins need to be stored carefully and enclosed.	High: Powders can be inhaled before or after printing.
UV Radiation	None	High: UV radiation is a health risk.	Low: SLS mainly uses lasers to melt powder polymers.
Training requirements	Minimum	Medium	High

Fig: Safety Comparisions of FFF, SLA, SLS.[55]

4. Thermal Inkjet Printing

Thermal inkjet printing comes under the category of inkjet printing, in this technique the aqueous ink is converted into vapour form by the application of heat and push the ink drop out from the nozzle.[56] Thermal inkjet printing is used in the preparations of the drug containing liposomes and microspheres, this method is efficient in producing or developing films of biologics without conciliatory the activity of the protiens.[57,58]

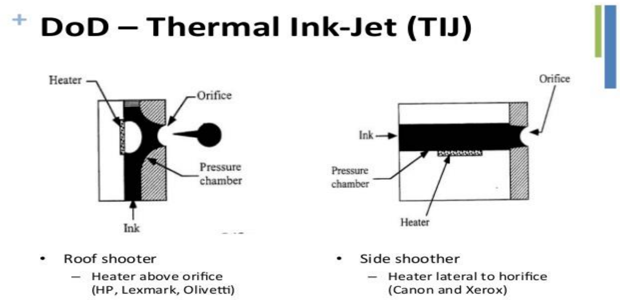


Fig: Thermal Inkjet Printing

Thermal inkjet printers are a low-cost option for printing and print at a fast speed with a high quality finish. They can print on a wide variety of surfaces, including regular and specialty papers, plastics, metals and cartons. Most of these printers are simple to use and require no training or practice. They do not have a warmup or cool down cycle, so they're always ready for you to use.

Fig: Advantages Of Thermal Inkjet Printing

5. Fused Deposition Modelling (FDM)

Fused deposition modelling widely used technique in 3D Printing, in this method the materials are melted and soften by the application of heat to create an entity during printing[59] , this technique of 3D printing aids in manufacturing of delayed release prints and also provides customised dose medicines.[60] This technique predicts the several limitations of system like lack of desirable polymers,[61] gradual and often fractional drug release because the drug remain entrapped within polymers.[62,63]

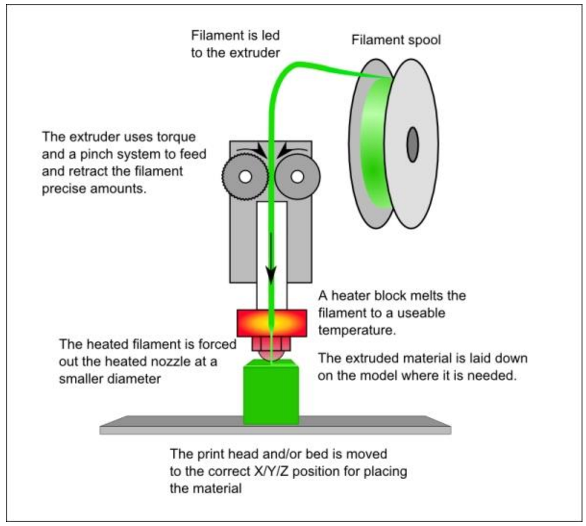


Fig: Fused Deposition Modelling

1. Speed

Parts produced with FDM can be ready in a few minutes or couple of hours, making it one of the fastest choices in 3D printing. For example, CAD drawings can be transformed into finished products in only one step.

2. Accuracy

FDM printers use a thermoplastic filament that is heated to a melting point and then extracted in layers to create a three-dimensional object. The process is accurate to within .005 inches, according to the School of Computer Science at Carnegie Mellon University.

3. Affordability

The FDM process uses thermoplastic and ceramic filament that is affordable compared to the alternatives. The modest size of the printers also means parts don't have to be manufactured in a large facility, helping to lower the expense of producing small components.

4. Ease of Use

FDM printers can create any item designed in a CAD program. Production is set up on a computer in an easy-to-use application and is entirely controlled by the machine.

Fig: Advantages of Fused Deposition Modelling

6. Powder Based 3D Printing

Powder based 3D printing uses powder bed to distribute the thin layers of powder and employ liquid binder drops with the aid of inkjet.The ink contains active pharmaceutical ingredients and binders is dispersed over a powder bed in 2D manner to create the final product.[64]

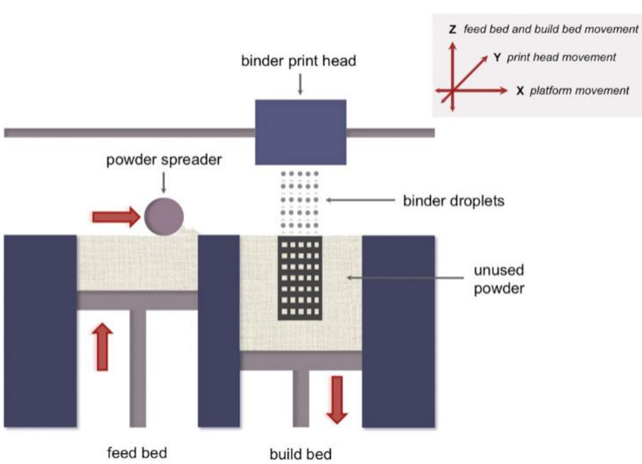


Fig: Powder based 3D printing

- **Low cost** – Comparatively low cost. Manufacturing cost has come down in the recent past due to the price drop in powder bed fusion machines cost.
- **No or minimum support** – Mostly these do not need the use of support structures as the powder acts as an integrated support structure. But to get more accuracy sometimes the bottom build plate is used as the support.
- **Wide material choice** – A large range of materials including ceramics, glass, plastics, metals and alloys can be used to make 3D objects
- **Powder recycling** – Powder could be recycled in some cases although to getter better parts some time there is a need to preheat the powder which might make the powder stick together

Fig: Advantages of Powder based 3D printing

7. Hot Melt Extrusion

Hot Melt Extrusion (HME) has been used in a wide spread way in enhancement of solubility applications for polymer based amorphous solid dispersion (provided the drug substances is thermally stable). Powders of drug with polymer are fed into heating processing zones within extruder. Modular twin screws imparts a high degree of shear stress and mixing or converted into the molten mixture and create a homogeneous mass, the molten extrudate is rapidly cooled and crystalized. HME has the capability to improved the solubility and the bioavailability of unsatisfactory soluble drugs. The applications of HME is solid dispersion, controlled release and microencapsulated particles.[65]

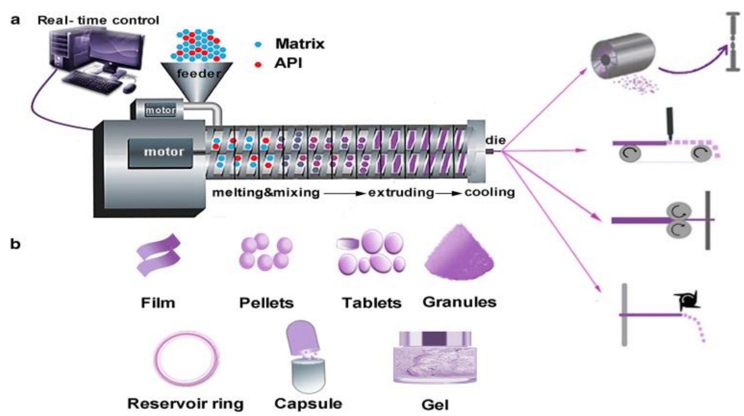


Fig: Hot Melt Extrusion

- Enhanced bioavailability of poorly soluble compounds
- Economical process with reduced production time, fewer processing steps, and a continuous operation
- Clinically advantaged dosage forms, such as drug abuse and dose dumping deterrent technology
- Sustained, modified and targeted release capabilities
- Life cycle management / Intellectual property positioning

Fig: Advantages of Hot Melt Extrusion

8. Zip Dose

The world's first 3D printing dosage form developed with Aprecia's proprietary 3D printing manufacturing process, ZipDose^{R} Technology that helps patients who want medicines that are easily administered. The FDA approved Spritam which contains Levetiracetam, the first 3D printed drug product. Zipdose has unique feature of digitally coded layering and zero compression procedure, it is used for formulating a high dose tablet with rapid disintegration.[66]

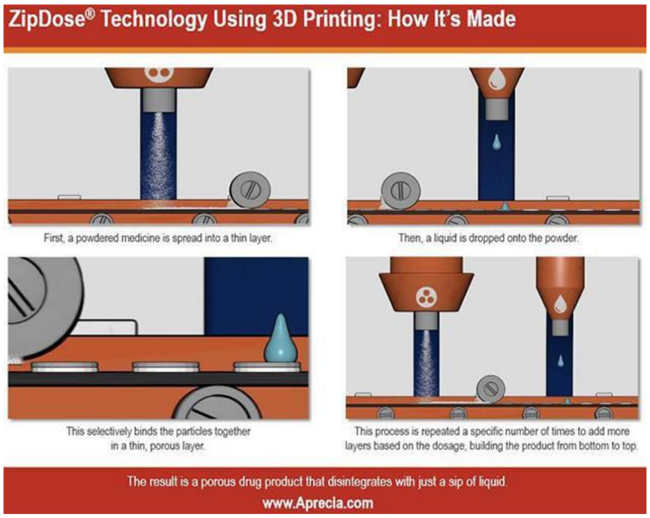


Fig: ZipDose 3D printing

9. Binder Jetting

Binder Jetting is a 3D printing process that uses two types of materials to create the objects: a powder-based material (gypsum) and a bonding agent. The "bonding" agent acts as a strong adhesive to create the bond between the powder layers together. The printer nozzles extrude the binder in liquid form. In case of other powder bed systems, once a layer is completed the powder bed drops and roller or blade smoothen the powder over the surface of the bed.[67]

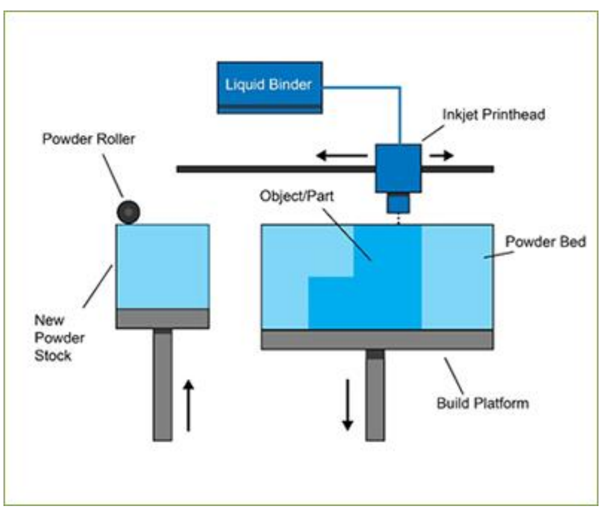


Fig: Binder Jetting 3D Printing

- **Doesn't require supports**: means less post-processing time and less materials are used up compared to technologies such as fused deposition modeling and stereolithography.
- **More economic**: 100% of unused powder can be reused in future prints. In SLS 3D printers only approximately 50% is reusable.
- **No warping or shrinking:** doesn't use heat so there is no warping due to differential cooling, as with FDM 3D printers. Note however that some shrinking can occur with sintering after printing. The lack of warping means that Binder Jetting 3D printers are great options for scalable part production.
- **Full color options**: very few technologies have this option commonly available, just Multi Jet Fusion and Material Jetting.

Fig: Advantages Of Binder Jetting

10. Inkjet Printing

In inkjet printing the ink is deposited on the substrate in the form of Drop on Demand (DoD) or Continuous Inkjet Printing (CIJ) printing. The ink is oriented through an orifice of 50-80 micrometre in diameter creating a continuous flow of the ink. The fluid is flow and break down into drops at a specified speed and size at regular interval or quantity by using a piezoelectric crystal. Inkjet printing is suitable for drugs with low therapeutic doses.[68,69]

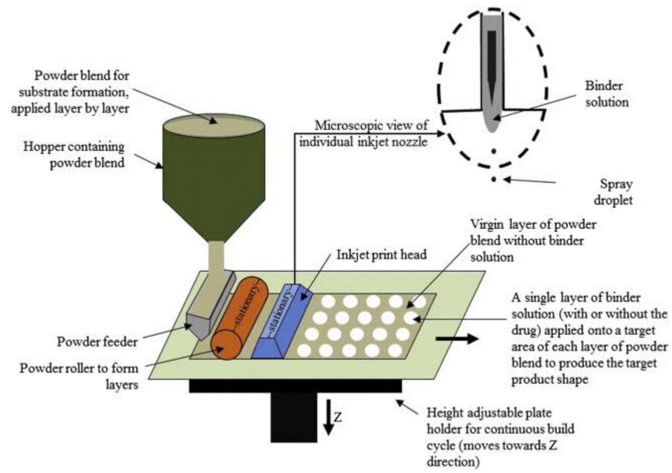


Fig: Inkjet Printing

1. They are quieter in operation than impact dot matrix or daisywheel printers.
2. They can print finer, smoother details through higher resolution.
3. In combinations to technologies like thermal wax, dye sublimation and laser printing, inkjets have the advantages of practically no warm up time and often lower cost.
4. Some types of industrial inkjet printers are now capable of printing at very high speeds, in wide formats or for a variety of industrial applications ranging from signage, textiles, ceramics and 3D printing into biomedical applications.

Fig: Advantages of Inkjet Printing

V. CONCLUSION

3D printing has become a useful and potential tool for the pharmaceutical sector, leading to personalized medicine focused on the patients needs. 3D printing technology is emerging as a new horizon for advanced drug delivery with built-in-flexibility that is well suited for customized medication. 3D printing technology will revolutionize the pharmaceutical manufacturing style and formulation techniques. Various 3D printing techniques have been developed and categorized into subgroups, by its working principles. This technology makes it possible to fabricate highly sophisticated and complex dosage forms of drugs and has enhanced the freedom to control the shape and microstructures of dosage forms. Furthermore, 3D printing technology is an innovative and highly promising way for on demand manufacturing and dosage form personalization, which may improve patient compliance and drug effectiveness, reduce the side effects, resolve the stability issues of drugs with limited shelf-life and eventually lead to the patient - specific health care with on - demand tailored medications. A continuous innovation and refinement in 3DP methods overcome many technical and regulatory challenges, rapidly evolving 3DP technology will be more widely applicable to various drug delivery systems and accelerate the clinical practice of more patient - friendly personalized dosage forms in the future.

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