International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 2, pp: 289-297 www.ijprajournal.com ISSN: 2249-7781

3D Printing: a step towards future of printlets.

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Date of Submission: 15-10-2020 Date of Acceptance:02-11-2020

ABSTRACT: The 3D printing industry is an unchartered territory that is yet to be fully discovered. Due to the FDA approval of Levetiracetam(SPRITAM®) in 2015 it has gained a momentum in the pharmaceutical sector. It has specifically gained interest for its precision as the solid dosage form is printed layer by layer so it is beneficial for personalized and multi-layer tablets. The emerging novel approaches for modified release profiles, shapes and sizes have also led to the advancement in the 3DP field. Still much is to be yet discovered and researched in this area of thirst and much it to be also considered.The challenges produced are also critical and blocking point for its further development in large scale production.This review aims to provides the basic information on the different techniques employed in 3DP and the advantages & disadvantages of the same.

Keywords: 3DP, FDM, SLS, Stereolithography, IJP, HME.

I. INTRODUCTION

3D printing also known as Additive Manufacturing (AM) is a process in which with the help of Computer Aided Design (CAD) material is deposited layer by layer onto a substrate. So, this process is also known as Rapid Prototyping (RP), Solid Freeform Technology (SFF).

The WHO describes 3D printing as "fabrication of objects through the deposition of a material using a print head or nozzle or another printer technology".

This technology found its way in pharmaceutical sector when the first drug Levetiracetam (SPRITAM®) by was given approval in 2015. But the earliest technique "stereolithography" was developed by Charles Hull in 1884. After that many techniques like fused deposition modeling (FDM), inkjet printing, zip dose, extrusion 3D printing, Selective Laser Sintering (SLS) were developed.

This technology has made it in the pharmaceutical sector due to its flexibility, time saving and its desirability over conventional dosage form wherein factors like milling, compression, etc. can affect the quality of the drug which is curbed by 3D printing. When compared with the manufacturing process of conventional pharmaceutical product, it has many advantages like high production rates due as it has fast operating systems; ability to achieve high drug-loading with much desired precision and accuracy especially for potent drugs that are applied in small doses; reduction of material wastage which can save in the cost of production and amenability to broad types of pharmaceutical active ingredients including poorly water-soluble, peptides and proteins, as well as drug with narrow therapeutic windows.[1]

It offers numerous advantages, such as increasing the cost efficiency and the manufacturing speed, since a rapid prototyping (RP) can be done in a matter of minutes. However, there is still a significant barrier to ensure that 3D printed medicines have the same efficacy, safety, and stability as the pharmaceuticals conventionally manufactured by the Pharmaceutical Industry.[2]

The major area of interest is being patient specific tailored drug or personalized medicines, the all-fit-one mechanism is not much effective because every patient has a specific need and reactions to certain drugs. Another big use is release-tailored medicines[3], it can also provide medicines of different shapes and compositions and kinetic release profiles.

Advantages of 3D Printing

- The 3D printing industry has yet not gained a momentum in pharmaceutical sector;however, it is better in some areas than conventional dosage form especially for potent drugs which are used in small doses this gives high accuracy and precision, it has high production

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rate as almost everything is done using CAD so has good operating system.

- It includes precise control of droplet size and dose, high reproducibility, and the ability to produce dosage forms with complex drug-release profiles (Lee H & Cho D-W; 2016 b).
- This is also cost effective than conventional as milling, compression, etc. processes are curbed and it also has low waste generation.
- In this the drug is formed layer by layer so it is porous and has rapid disintegration.
- It provides flexibility in dose, dosage forms, shape and sizes and drug release.
- This method is particularly useful for "personalized" medicine which can be specifically tailored according to patient's needs, it helps in patient compliance as patients who have serious illness are administered multiple drugs so in place of it using this a multi-layer drug can be specifically made for the patient.
- It is appropriate for orphan drugs- the medicinal products intended for diagnosis, prevention or treatment of life-threatening or very serious diseases which are rare[4]. Research on these possibilities can then improve the standard of quality life and gain the interest of healthcare industry[5].

Disadvantages of 3D Printing

- This technology is mostly nozzle and computer based. The main con of this is nozzle accuracy if the nozzle does not stop or stops in between process it can alter the product. Problems in CAD can also alter the final product. The large-scale manufacturing by this is till now not feasible than conventional form which is cheaper.
- The other concerns of this technology are printer parameters like cost and printing quality which will affect the overall quality of the product.
- To attain quality of 3D products, some essential parameters necessitate to be optimized like printing rate, printing passes, line velocity of the print head, interval time between two printing layers, distance between the nozzles and the powder layer, etc. [6,7]

II. DIFFERENT 3D PRINTING TECHNIQUES

1. STEREOLITHOGRAPHY

This method was patented by Charles hull co-founder of 3D Systems Inc. in 1986. This method uses stereolithography apparatus (SLA) machine which uses liquid plastic which is then cured or hardened to a solid object. In this a photopolymer layer is exposed to UV laser[8,9,10]which "paints" the pattern on the object. Based on the position it's of two types top-down and bottom-up type.

In the bottom up type the light source is placed under the resin tank and the part is built facing up down whereas in top-down type the light source is above the tank and the part is built facing up and the second layer is formed attached to the first layer.

After this the prepared article is washed with rubbing alcohol to remove excess resin and then cured in UV oven to strengthen the print.[9,11,12]

Advantages

Its biggest advantage against other 3D techniques is that it has good resolution and thermal processes are not involved so thermolabile drugs can be used. In terms of accuracy and resolution, stereolithography is superior to all other solid free-form fabrication (FFF) techniques with accuracy up to 20 μm[13].

Disadvantages

The biggest limitation of this method is the resin/polymer it should be a low molecular weight polymer and approved to be used as excipient in manufacturing.
High cost and cytotoxicity[14].

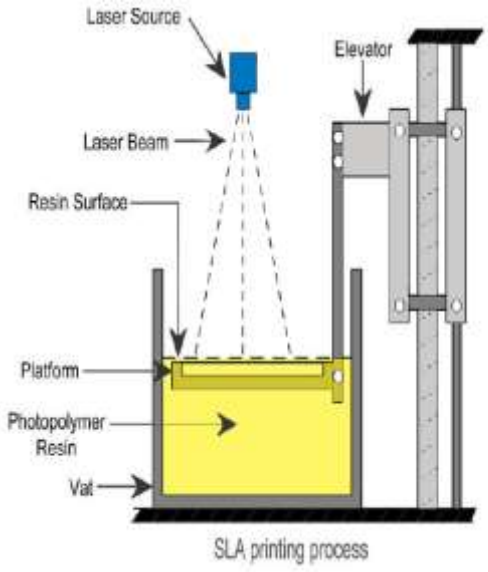

Figure 1- Stereolithography in 3D printing.[15]

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S.no.	Drug name	Formulation	Use	Reference No.
1	Paracetamol	Oral modified release tablet	Anti-pyretic	16
2	Salicylic acid	Anti-acne patch	Psoriasis	17

Table 1- Examples of drugs made using stereolithography

2. SELECTIVE LASER SINTERING (SLS)

SLS process uses a beam of laser to draw the pattern in the powder bed. In this method after the first layer is drawn on the powder bed another powder bed is made on top of it and again the pattern is drawn on it and layer by layer the product pattern is printed and the product is obtained from underneath the bed.

Fine et al used SLS to prepare paracetamol tablet with Kollicoat®IR or Eudragit®L100-55and additionally Candurin®gold sheen was added as it was found to absorb laser light involved in the sintering process[18]The SLS can be a method to obtain porous, rapidly disintegrating and modified dosage form without binding agent.

Advantages

SLS has advantages of high-resolution printing and printing of medicine without the need of the solvent.

Easy removal of powder[14]

Disadvantages

The SLS method was not considered suitable for production of drugs due to high energy lasers which could degrade the drug but now low intensity laser in SLS has solved the drug degradation problem.

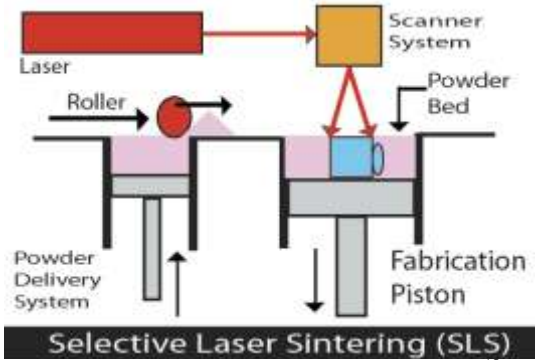

Figure 2- Selective Laser Sintering (SLS).[19]

3. FUSED DEPOSITION MODELLING (FDM)

In FDM, the material is softened or melted through heat extrusion and the melted material is laid on the platform in such a way that it creates the design provided by the software. The melted material is deposited layer by layer which then fuses together.

The melted material is deposited with the help of a nozzle whose tip size ranges from 50-100 µm.In FDM technology, the nozzle moves horizontally, and the build platform moves vertically downwards as the process continues. After each layer, the build platform moves down, and another layer is deposited on top of previous layer (Fig3). The XY resolution of FDM is good but the Z resolution is not very good, and hence, the thickness is not uniform. Extra finishing process therefore may be required if a smooth surface is desired[20].

Genina et al. presented an alternative method of formulating the combination of anti-tuberculosis drugs rifampicin and isoniazid by physically separating the APIs in a unique dual compartment dosage unit designed with CAD and fabricated using 3D printing based on FDM[21].

Advantages

This technique proves to be helpful in manufacturing personalized dose medicine and in delayed release prints without outer enteric coating.

Disadvantages

This technique proves to be difficult due to lack of polymer as they should be thermally stable and non-volatile.

There also seems to be an issue of slow and incomplete drug release as the drug often becomes entrapped in the polymer.

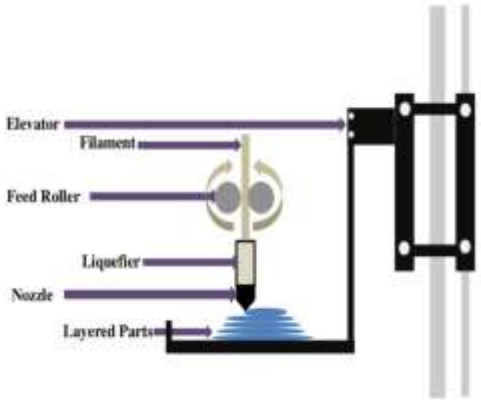

Figure 3- Fused Deposition modeling[22]

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S. no	Drug	Use	Formulation	Reference
1	Ibuprofen	NSAID	Tablet	3
2	Metformin	Anti-diabetic	Tablet	23
3	Prednisolone	Immunosuppressant	Extended release tablets	24
4	Theophylline	Lung disease	Tablet, Capsule	25
5	Nitrofurantoin	Urinary tract infection	Implant	26
6	Hydroxyapatite	Carrier	Implant	26
7	Indomethacin	NSAID	T-shaped (IU, SC rods)	27

Table 2- Examples of Drugs made using FDM

4. INKJET PRINTING (IJP)

In inkjet printing the printing material is extruded by a small nozzle layer by layer the deposited layer is cured and the curing process depends on the material used to print the product. Inkjet printing can be classified as continuous inkjet printing (CIJ) and drop on demand inkjet printing (DoD). Further DoD can be classified as Piezoelectric and Thermal inkjet printing. Based on the print head type it can be classified as drop-on-drop and drop-on-solid.The basic mechanism for all remains the same, in this a powder bed is formed uniformly with the help of a roller, on this powder bed the print head deposits the droplets which then fuse with the powder layer by layer. The mechanism of ejection is what differentiates into piezoelectric, thermal and continuous. After the first layer is formed another layer is laid on the powder bed to form layered product.

Advantages

It is a tool-less procedure as only the print head nozzle is used and so it is cost effective, minimum maintenance and low waste generation.
The CAD message is given as "direct wire" message. Easily accessible and inexpensive[28].

Disadvantages

The inkjet printers can use comparatively low cell density[29, 30].

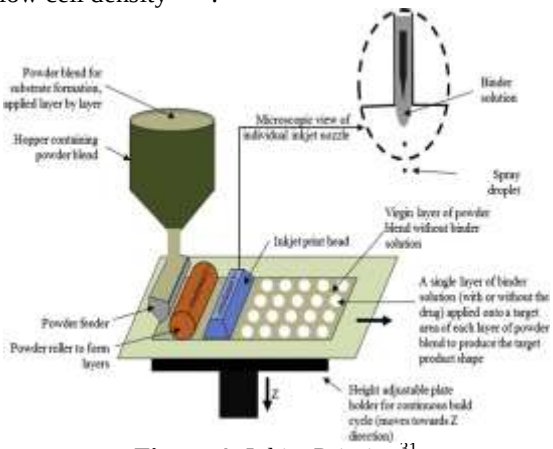

Figure 4- Inkjet Printing[31]

Table 3- Examples of drugs made using inkjet printing:

S. no	Drug	Use	Formulation	Reference
1	Levofloxacin	Antibiotic	Implant	32
2	Piroxicam	NSAID	Capsule	33
3	Rapamycin	Immunosuppressant	Tablet	34
4	Folic acid	Anemia	Nanosuspension	5
5	Rifampicin	Antibiotic	Nanoparticles	35
6	Insulin	Anti-hyperglycemic	Microneedle	36
7	Felodipine	Antihypertensive	Microdots	37

5. HOT MELT EXTRUSION (HME)

It is a continuous process where heat and pressure are employed to melt the materials through an orifice to produce a product of uniform density and shape. The extrusion process can change the physical properties of a substance when it is forced through the orifice or die in hot melt extruder[38].

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Advantages

HME is a solvent free process so it is used over the conventional methods[39].

It has shorter production time, higher process efficiency, and increases drug delivery efficiency in patients[40].

Disadvantages

It requires high energy input required for shear force and elevated temperature, high temperature and shear force can thermal and mechanical degradation to polymers[41].

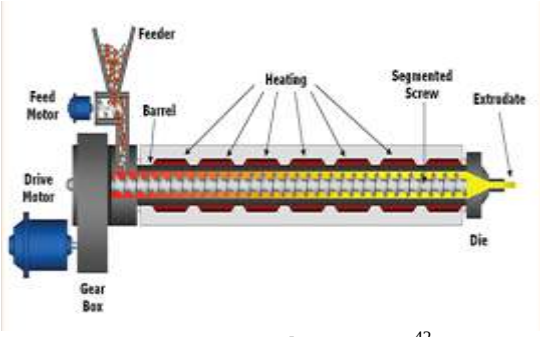

Figure 5- Hot-Melt Extrusion[42].

Table 4- Examples of drugs made using HME.

S. no.	Drug	Formulation	Application	Reference No.
1	Paracetamol	3D printed-cube, pyramid, cylinder, sphere and torus	Analgesic	43
2	Domperidone	Tablet	Parkinson's Disease	44
3	Isoniazid	Compartmentalized shells	Tuberculosis (TB)	27
4	Polymer Polyvinyl Alcohol (PVA), Mannitol and Hydrochlorothiazide (Hctz), Polylactic Acid (PLA)	Three-compartment hollow cylinder	Polymers	45
5	Indomethacin	T-shaped prototypes of intrauterine system (IUS)	NSAID	46

III. MATERIALS USED IN 3D PRINTING[47]

Some of the polymers used in this are

1. Acryl nitrile Butadiene Styrene

It is one of the most widely used 3D printing polymer as it has high temperature withstanding property it is flexible, durable and is easily extruded as it requires less force for extrusion than polylactic acid. Its glass transition temperature is about 105°C and temperature about 210 - 250°C is usually used for printing with acrylonitrile butadiene styrene materials.

2. Polylactic Acid

It is a biodegradable thermoplastic derived from corn is environment friendly compared to other plastic material, it is also biocompatible with the human body. The structure of Poly lactic acid is harder than the Acrylonitrile Butadiene Styrene material melts at 180-220°C which is lower than Acrylonitrile Butadiene Styrene. Poly lactic acid glass transition temperature is between 60 – 65 ° C, so Poly lactic acid together with Acrylonitrile Butadiene Styrene could be some good options for any of projects.

3.**High Impact Polystyrene**

High Impact Polystyrene filament is made from a High Impact Polystyrene material. This material is well spread in food industry for packaging. It is also used to produce trays in medicine, this filament has bright white colour and it is also biodegradable. High Impact Polystyrene filaments have curling and adhesion problems, which can be reduced by using a heated bed during the printing[48].

IV. APPLICATIONS

It is gaining attention in pharmaceutical industry as it is used in the manufacturing of implants, it also helps in Organ printing to produce cells, biomaterials, and cell-laden materials

individually layer by layer and directly creating 3D tissue like structure[49].Advantages of 3D printing include precise control of droplet size and dose, high reproducibility, and the ability to produce dosage forms with complex drug-release profiles (Lee H & Cho D-W; 2016 b).

As the attention of the sector is moving towards precision and personalized medicine the 3D industry is gaining attention as drugs can be specifically tailored according to the patient's needs. Pharmacists could analyze a patient's pharmacogenetic profile, as well as other characteristics such as age, race, or gender, to determine an optimal medication dose[50] and prepare medication accordingly.

The other area of interest is drugs having complex release profiles as 3D printed drugs are layered the layers can be separated and can give controlled release profile. These are also porous so give high disintegration if desired.

With the help of ZipDose Technology which was used by Aprecia to manufacture SPRITAM® Orodispensable medicines can be made which are porous and rapidly disintegrating and high dose medicines(Dominic Basulto 2015; Robert J. Szczebra 2015; 3D Printing; Aprecia Pharmaceuticals),up to 1000mg can be made without compression.

Implants and prostheses can be made in nearly any imaginable geometry through the translation of X-ray, MRI, or CT scans into digital 3D print files[51,52,53]. This approach has been used to fabricate dental, spinal, and hip implants[53].

V. FUTURE PERSPECTIVES

The advancements in 3DP in pharmaceutical field has opened possibilities of personalized medicines which can be exploited further and we envisage that 3DP we also be needful for solid dosage form due to the challenges of conventional solid dosage forms. It can be predicted in near future the technology will be useful in the development of novel dosage forms and excipients. It will also be helpful for multi-drug preparation to avoid incompatibilities. The activities to develop 3DP from a broader appeal clinically will include:

(i) optimization and improvement of software performance, (ii) development of new excipients or assessment of old excipients for application in 3D formulations; and (iii) development and optimization of manufacturing process for a wide range of drug products, and (iv) clinical studies to assess efficacy, safety and stability of new 3D-based formulations[16].

VI. CONCLUSION

With the advancing technologies the 3DP has also evolved from scaffolds and implants to various dosage form with modified release profiles, shapes and sizes. The area of personalized medicine has also evolved which adheres to patient's specific needs. The technology can also reduce time and cost-effectiveness a printlet can be manufactured within a short period of time. Yet as the technology is still in its developing phase there is a deficiency of safety and regulatory concerns. And there can also be a threat of security as all drugs prepared would be computerized and they can be hacked and stolen.

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