Int. J. Pharm. Investigation, 2020;10(1):8-12 Review Article

# 3D Printing in Pharmaceutical Technology – A Review

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**ABSTRACT**
Three-dimensional printing is a revolutionary technique that uses computer aided design software and programming to create three dimensional objects by placing material on a substrate. 3D printing is an additive layer manufacturing techniques, where consecutive layers of material are deposited or solidified to form a 3D structure. Medicinal substances is configured in three dimensional with computer assisted design module and transformed to a machine legible form which suggests the exterior emerge of the 3D dose form, then it sliced this surface into number of different printable coats and convey these layers to the machine. The different 3D printing techniques has been developing and developed to fabricate novel solid dosage forms, which are among the most well-known and discrete products today. The 3D printing process desires to be espoused by pharmaceutical sector and capable of exploring the marvels fetched by the approach. 3D printing can include a very new possibilities to optimized medicine. The current review is an effort of briefing various methods (Thermal Ink jet printing, Ink jet printing, Fused deposition modeling, Extrusion 3D Printing, Zip dose, Hot melt extrusion, 3D printer, Stereolithography, Selective laser sintering, Laser-Based Writing System, Continuous Layer Interface Production, Powder Based 3D Printing), advantages, limitations, applications of 3D printing in pharmaceutical technology.
**Key words:** Three-dimensional printing, Structure, Print, Laser, Pharmaceuticals, Drugs.

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**DOI:** 10.5530/ijpi.2020.1.2

## INTRODUCTION

Three-dimensional printing is matchless method which uses computer aided drafting technology and programming to make three dimensional objects by layering material onto a substrate.[1] It is a process of making three dimensional solid objects from a digital file.[2] Now a days, 3D printing could be extended throughout the drug development process, ranging from preclinical development and clinical trials to frontline medical care.[3] Different types of drug delivery systems for instance oral controlled release systems, micro pills, microchip, drug implants, fast dissolving tablets and multiphase release dosage forms have been developed using three-dimensional (3D) printing technology.[4] When compared to the manufacturing methods of conventional pharmaceutical product, it has a lot of advantages like high production rates owing to its fast operating systems, capability to achieve high drug loading with much desired precision and accuracy exclusively for potent drugs that are applied in small doses; reduction of material wastage can save the cost of production and pliability to more classes of pharmaceutical active ingredients comprising poorly solubility in aqueous, proteins and narrow therapeutic index drugs.[5]

### History

3D Printing is a platform for personalized medicine from the beginning of 1990. There are major successes in 3D printed medical device, FDA's Center for Device and Radiological Health (CDRH) has revised and cleared 3DP medical devices.[6] The first 3D printing method used in pharmaceutics was attained by inkjet printing, a binder solution onto a powder bed, therefore the particles bind together. The technique was repeated until the final desired structure was obtained. This first happened in the early 90's at the Massachusetts Institute Technology developed and patented by Sachs *et al.*[7] In 1989 Scott Crump filed a patent on another 3D printing technology, fused deposition modeling, to harden the surface where extruded polymer filaments heated into a semi-liquid state and extruded through a heated nozzle and deposited onto a build platform as layer by layer.[8,9] Inkjet printing was the technique used to manufacture Spritam tablets (levetiracetam) for oral use, the first 3D printed drug approved by the Food and Drug Administration (FDA) in 2016 by Aprecia Pharmaceuticals. 3D printing is most advanced technique in the fields such as automobiles, aerospace, biomedical, tissue engineering and now in the pharmaceutical industry (initial phase). FDA motivates the development of advanced manufacturing technologies such as 3D-printing and by means of risk-based approaches.

### Regulatory Expectations

FDA (US) in 2017 issued guidance on Technical Considerations for Additive Manufactured Medical Devices. This guidance outlines the various requirements involving Designs and Manufacturing Process Considerations, Device Testing Considerations and Labeling. It also recommends the validation of the processes involved to provide high degree of assurance according to the conventional procedures. In addition, documentation must confirm to the on-hand guidelines in the Quality System Regulation for device validation. Process validation must be done to ensure and maintain quality. For all devices and its components built in a single build cycle, between build cycles, between machines where the results of a process (i.e., output specifications) cannot be fully verified by subsequent inspection and test. Software also must be validated for its envisioned use according to an acclaimed protocol.[10,11]

### Advantages of 3D Printed Drug Delivery

- ✓ High drug loading capability compared to conventional dosage forms.
- ✓ Accurate and Precise dosing of potent drugs which are administered at small doses for activity.
- ✓ Reduced production cost due to less wastage of materials.

- ✓ Suitable drug delivery for difficult to formulate active ingredients like poor water solubility and narrow therapeutic windows drugs.
- ✓ Medication can be tailored to a patient in particular based on age, gender, genetic variations, ethnic differences and environment.
- ✓ Treatment can be customized to improve patient adherence in case of multi-drug therapy with multiple dosing regimen.
- ✓ As immediate and controlled release layers can be incorporated owed to flexible designs, manufacturing method of dosage form and it helps in pick out the best therapeutic regimen for an individual.
- ✓ Evades batch-to-batch variations met in bulk manufacturing of conventional dosage forms.
- ✓ Manufacture of small batch is feasible and the process can be completed in a single run.[12]
- ✓ 3D printers capture minimal space and are affordable.

### Disadvantages

- ✓ Problems related to nozzle are a major challenge as stopping of the print head which affects the final products structure.
- ✓ Powder printing clogging is another hurdle.
- ✓ Possibility of modifying the final structure on to mechanical stress, storage condition adaptions and ink formulations effects.
- ✓ Printer related parameters and these effects on printing quality and printercost.[13]

## TECHNIQUES IN 3D PRINTING

There are numerous varieties of manufacturing practices intricate in 3D printing, which are grounded on digitally organized depositing of materials (layer-by-layer) to create free form geometries.

### Thermal Ink-Jet Printing (Figure 1)

In thermal inkjet printing, the aqueous ink fluid is transformed to vapours state through heat, expands to push the ink drop out of a nozzle.[14] It is used in the preparation of drug-loaded biodegradable microspheres, drug-loaded liposomes, patterning microelectrode arrays coating, loading drug eluting stents.[15,16] It is also an effectual and applied method of generating films of biologics without negotiating protein activity.[17]

### Inkjet Printing

Inkjet printing known as 'mask-less' or 'tool-less' approach for its desired structure formation mainly depends upon the inkjet nozzle movement or substrate movement for an accurate and reproducible formation. In this methodology, the Ink is deposited onto a substrate either in the form of Continuous Inkjet printing / Drop on demand printing. Hence it provides a capability of high-resolution printing. It has a low cost, rate of processing in printing and generation of low level of wastes. It gives CAD information in a 'direct write' manner and process material over large areas with minimal contamination.[18,19]

### Fused deposition modeling (FDM) (Figure 2)

Fused deposition modelling (FDM) is commonly used method in 3D printing, the materials are softer or melt by heat to create objects during printing.[20] Fused deposition modeling 3D printing helps in manufacturing delayed release print lets without an outer enteric coating and also provides personalized medicines doses. This 3D Printing indicates some limitations for system like lack of suitable polymers,[21] slow and often incomplete drug release, because of the drug remain trapped in the polymers, miscibility of drug and additives with the polymers used was not valued.[22]

### Extrusion 3D Printing

In this method the material is extruded from the automated nozzle onto the substrate without any higher support material. It is only utilized to fabricate tablet containing Guaifenesin act as expectorating. The components that can be extruded are molten polymers, suspensions, semisolids, pastes.[23,24]

### Zip dose

Zip dose is the world's initial and only FDA-approved, commercial-scale 3DP in current therapeutic areas for pharmaceutical manufacturing areas. It has a distinctive digitally coded layering and zero compression practices, used for tablet formulation with large dosage and prompt disintegration. Hence, it helps in overwhelming a difficulty in swallowing.[25] Spritam-R (Anti-epilepsy drug) is an oral dispersible tablet, marketed by Aprecia Pharmaceuticals based on powder bed fusion by layer-by-layer production system. In which it consists of the active ingredient, excipients and a binder liquid to produce a matrix tablet.[26]

### Hot melt extrusion (HME)

Hot melt extrusion (HME) is the method of melting polymer and drug at elevated temperature and the pressure is employed in the instrument sequentially for blending.[27] It is a continuous manufacturing technique that involves feeding, heating, mixing and shaping.[28] In recent years, it has proved that Hot melt extrusion capable to optimize the solubility and bioavailability of moderately soluble drugs.[29]

### 3D Printer

The 3D printer was an exclusive tool is used to create optimized medications with tailored release profiles and for patients' comfort.

### Stereolithography (Figure 3)

Stereolithography is the method of computer regulated laser beam is used to make liquid polymer/resin as solid, by this means creating a 3D structure.[30] Stereolithography has several advantages over former types of other 3DP, predominantly it's astonishing resolution and dodging of thermal practices can be harmful for specific drug molecules.[31]

### Selective laser sintering (Figure 4)

Selective laser sintering (SLS) act as a way in the powder bed to bind. The laser is designed to draw a specific pattern on the surface of the powdered bed during the printing process, thus creating a 3D structure. For example, Paracetamol is an Orodispersible tablet prepared by this manner. It is currently used for industrial manufacturing of plastic, metallic and ceramic objects.[32]

### Laser-Based Writing System

On grounded to the photo polymerization principle, the free radicals which can contribute to the numerous diseases are released then to the interactions in among the photo originator and Ultra Violet light.

### Continuous Layer Interface Production

It is an advancement in the technology in relation of speed of printing. But the method negotiates in the 3D structure manufacture through non-layer fashion. The speed is amplified by the oxygen enclosing zone which assists and promises photo-polymerization. Inkjets print free form structures that get hard drop-by-drop. Usually jetted materials are molten polymers, waxes, UV curable resins and compound several component fluids. The intact formulation desires to be formulated for jetting and rapid solidification.[33]

### Powder Based 3D Printing

This method customs powder jetting/powder bed to feast thin layers of powder and instantaneously applying liquid binder drops with ink-jet printers. The ink (binders and APIs or binder solutions) is sprinkled over a powder bed in two-dimensional (2D) approach to make the decisive product in a layer by layer fashion. The adaption of this approach into pharmaceutical manufacturing is at ease than other approaches as powder and binder solutions are broadly used in the pharmaceutical industry. The own disadvantages of this approach are; to remove solvent residues additional drying is required, during printing excess powder accumulates and contributes to wastage and due to the permeable design of the powder the drug delivery system's mechanical strength may poor.[34]

## CHALLENGES IN 3D PRINTING TECHNOLOGY

- Although proved promising results are there in drug delivery, still under the developing stage.
- Several challenges such as versatile use, appropriate excipient selections, post treatment method to advance the enhancement of 3D printed products and to magnify the application scope in novel drug delivery systems.
- The built-in flexibility might be a most important resource of liability from safety point of view for re-designing through 3 Dimensional printing.
- The primary parameters are to be modified to improve quality of 3DP such as printing rate, passes, print heads line velocity, printing layers interval time, nozzles and powder layer distance etc.

## APPLICATIONS OF 3D PRINTING

- Potential use in improving process, modifying performance for industrial design, aerospace, medical engineering, tissue engineering, architecture, pharmaceuticals.
- It mostly targets on the two potential sites to rise pharmaceutical product development to unexplored areas, manufacturing sophisticated structures for the delivery and personalized medicine.
- In Healthcare industry to create dental implants.
- On fabricating an organized release multi-drug implant for bone tuberculosis remedy.
- Helps in Organ printing, biomaterials and cell-laden materials.[35]

## RISK ASSESSMENT DURING 3D PRINTING PROCESS

Risk determination is an important step in 3D printing technology. Mainly it was performed to prevent failure of quality assurance parameters such as assay, content uniformity, appearance, etc. Risk factors are identified with the process and process variables to conform the quality of product which was manufactured in industries.

### Risk factors are checked in these conditions

- Software controls should be employed, if a particular printer cannot print a particular pattern.
- Layer thickness variability has to be controlled by real – time layer thickness monitoring.

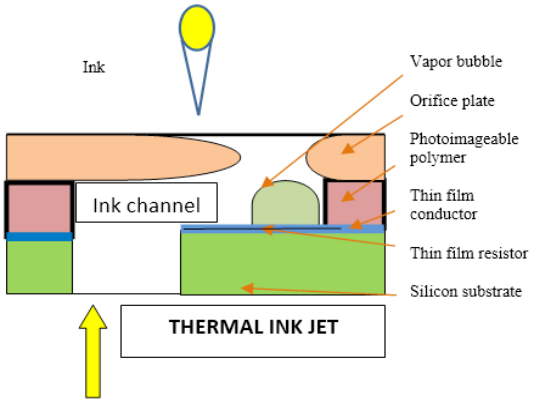


**Figure 1:** Thermal Ink Jet.

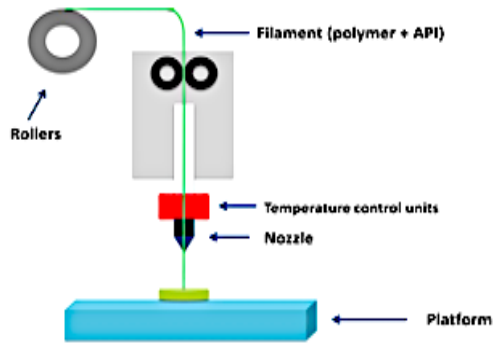


**Figure 2:** Fused deposition modeling (FDM).

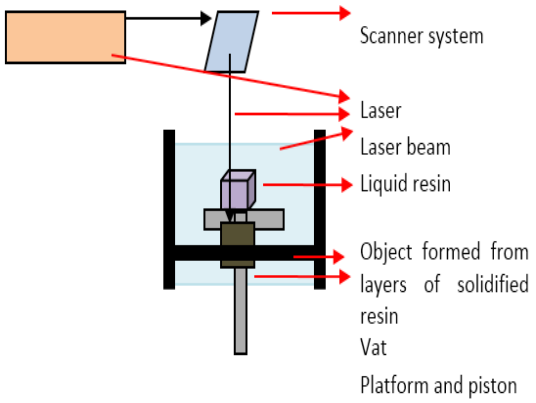


**Figure 3:** Stereolithography (SLA) Printer.

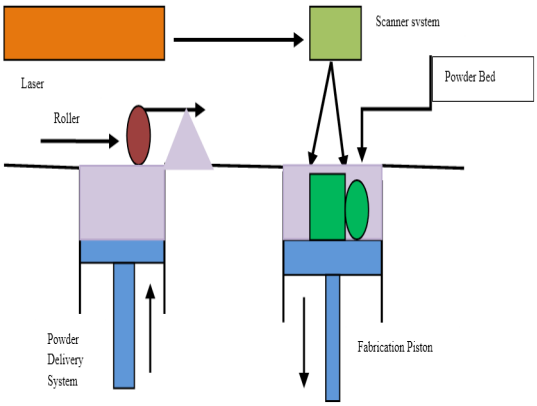


**Figure 4:** Selective laser sintering (SLS).

- Controlling the temperature and moisture content of the production place caused to improper layering, mainly it was a result of changes in environmental conditions.
- Improper location throughout printing might be avoided by tracking print head height and print head speed can prevent the inaccurate position in the printer.
- Monitoring the powder aqueous content and powder molecule size distribution can prevent the uneven layers.
- Ensuring the particle size distribution and monitoring inkjet flow can reduce or eliminate the print head clogging.
- Binder surface tension or binder viscosity variation leads to inconsistent agglomeration.

## DISCUSSION

3D printing is an advanced layer-by-layer system that can create sophisticated, personalized objects on demand. Drug delivery systems' 3D printing acts as an enticing method for the development of personalized products. The concept of 3D-printed drug formulation has evolved rapidly since a few years and was directed by patient-centric medicine to enhance therapy. The first FDA approval of drug produced by 3D printing technology resulted in an exceptionally rapid development of studies on oral, oromucosal and topical dosage forms. This promising technology offers flexibility in formulation, which with conventional technological processes is difficult to achieve. Additional processing allows the preparation of different dosage formulations with high accuracy of API (Active Pharmaceutical Ingredient)- excipients ratio, in completely new way compared to traditional pharmaceutical manufacturing. The added value in 3D printing is also opportunity to create multifunctional drug delivery systems, multidrug devices and drug formulations for personalized therapy with rapid release characteristics. Future research should therefore emphasize the production of pediatric and geriatric dosage forms in individual dose and dimensional specific drug formulations to ensure optimal therapeutic index. Increasing volumes of drug development trials show obvious advantages of this technique, but maximum effectiveness will be reached by leading complicated novel dosage forms on an industrial scale. 3D printing technology has the ability to open doors for pharma companies in product development, production and distribution.

## CONCLUSION

3D printing technology can make complex formations as cost and time efficient. It may improve its applications in Pharmaceutical Research and Biotechnological fields. 3D printing involves wide technical range in pharmaceutical field with novel drug delivery system, generation of new excipients, improvements of drug compatibility and customized dosage forms. In future 3D printing can be regulated and followed by pharmaceutical and all other sectors with needed level of safety and security concerns.

## ACKNOWLEDGEMENT

Nil.

## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest. The article does not contain any studies with animals or human participants performed by any of the authors.

## ABBREVIATIONS

**3D:** Three dimensional; **FDA (US):** Food and Drug Administration (United States); **CDRH:** Center for Device and Radiological Health; **3DP :** Three dimensional Printing; **FDM:** Fused deposition modeling; **2D:** Two Dimensional; **SLS:** Selective laser sintering; **API:** Active Pharmaceutical Ingredient.

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**Cite this article:** Ponni RT, Swamivelmanickam M, Sivakrishnan S. 3D Printing in Pharmaceutical Technology – A Review. Int. J. Pharm. Investigation. 2020;10(1):8-12.