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Review Article

Recent Trends, Opportunities and Challenges in 3D Printing Technology for Personalize Medicine

Mule Shrikrishna T.^{1*}, Bhusnure O.G.¹, Waghmare S.S.² Mali Mamta R.³,

Department of Pharmaceutical Quality Assurance, Channabasweshwar Pharmacy College(Degree), Kava Road, Basweshwar Chowk, Latur, Maharashtra, India- 413512

ABSTRACT

The scrutiny of medical devices industry as well as pharmaceutical industry for its application in health care industry on different platform is captured the 3D printing technique. 3D printing technology withstand for a very long duration only because of the approval of medical devices, 3D printed tablets and also with the advent of USFDA guideline on technical consideration. This technology is specific to devices utilizing preservative manufacturing. Many thoughts are triggered by 3D printing this technology and for successful delivery of intended product which is necessarily take into a consideration. In this review paper expectation limitations of some regulatory companies, Advantages, disadvantages, what type problems are arises while establishing this setups for drug product production, method, application, and manufacturing risk are represented. It also gives information about the current status of 3D printing technology in research and development of drug products. For the fabrication of novel solid dosage form a number of 3D printing technology have been developed. This review is mainly focused on describing different technology used for the application of 3D printing in pharmaceutical industry.

Keywords: - 3D printing technology, recent trend, Opportunities, personalize medicine, challenges, future.

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*Address for Correspondence:

Mule Shrikrishna T, Department of Pharmaceutical Quality Assurance, Channabasweshwar Pharmacy College(Degree), Kava Road, Basweshwar Chowk, Latur, Maharashtra, India- 413512

Introduction:-

Drug delivery is nothing but it is the one type of technique used for accurately transport a pharmacologically active component inside the body for getting a therapeutic efficacy in a safe way. By regulating the release profile of pharmaceutical product the safety as well as efficiency can be achieved which helps in balancing the pharmacokinetics of a drug molecule.¹

3D printing technology play an essential role in case of multiple active ingredient dosage forms, in that formulation can be as a multi layered printed or single tablets with sustained release profile. In 3D printing technology material layers are made under the control of computer to design and develop a 3D product therefore this technology is known as an additive manufacturing technology. Now a days, different types of 3D printing techniques, like fused deposition, stereo lithography and inkjet printing have been utilized in many pharmaceutical industry.²

Recently, all over the drug development process 3D Printing could be broaden, variation is observed from preclinical

development and clinical trials to frontline medical care. This technology has large number of advantages as compared to conventional dosage form such as because of its fast operating system production rate is higher, production cost is reduced ,acceptance of active pharmaceutical ingredients with less water soluble peptides , proteins as well as drug which are having narrow gauged therapeutic window, precision and accuracy can be achieved along with high drug-loading capacity in case of small doses.³

History:-

The principle of 3D “additive processes” is in this process by establishing the successive layer of material an object is developed. Binder material is placed layer by layer on powder bed in inkjet printer heads. This process allows to produce complex shapes with the help of using less material than traditional manufacturing methods. This technique suddenly enables responses.⁴

In 1990s 3D Printing technology provides a platform for personalized medicine. 3D printing medical devices are analyzed and cleared with the help of FDA's Center for

Device and Radiological Health (CDRH). In the field of aerospace, bioengineering, automobiles and tissue engineering as well as in pharmaceutical industry 3D printing technology is more developing. 3D printing and risk based approaches are measured by FDA.⁵

Advantages of A 3D Printed Drug Delivery:-

- Spatial circulation of API in dosage form can be regulated.
- Drug loading capacity is higher as compared to conventional dosage forms.
- Easy to disintegrate.
- This technology gives accurate solution to evaluate pharmacy demand.
- Precision & accuracy of the dosing of potent drugs can be achieved.
- To improve patient adherence in case of multi drug therapy with multiple dosing regimen, treatment can be customized.
- This process is workable can be completed in a single run.

Current trends

As compared to other sector 3D printing technology in healthcare has played a secondary role. The healthcare only accounted for 1.6 % of all investment made \$700 million it is assumed by 3D printing industries.⁶

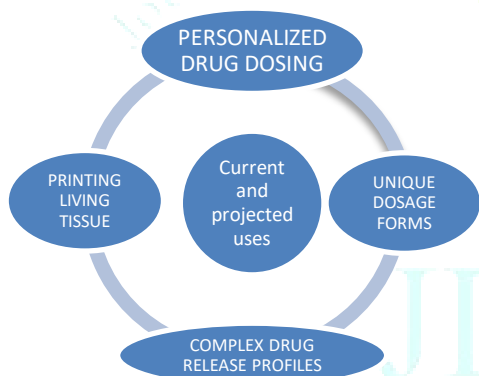


Figure 1: Current trends and projected uses of 3D printing technology ⁷

Personalized Medicine

Definition:

Medicine used in the treatment to the personal characteristics of each patient that not only gives the potential to identify the disease but also enhance our capability to treat disease, at an initial stage and to cure it effectively.⁸

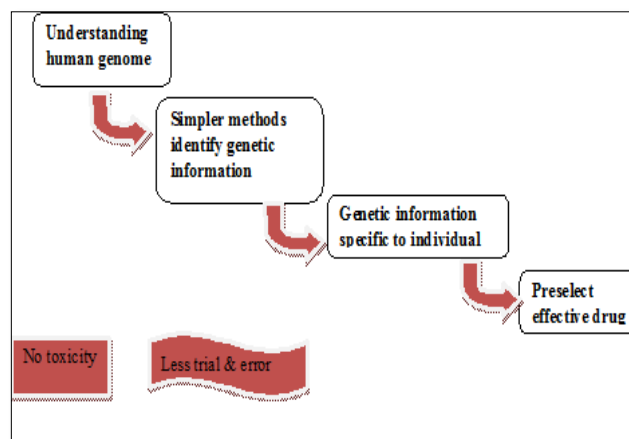


Figure 2: Initial stage of personalize medicine⁹

The main aim of drug development is to prevent the the risk of adverse reactions, and this can be achieved with the help of 3D printing of personalized medicine.

However, some impossible method is also there that are generally used to make personalized solid dosage forms like tablets. With the use of well-traditional processes equally mixing, wet granulation and milling of powder ingredients Oral tablets are prepared directly via compression process. Conventional method for the manufacturing of personalized medicine is not used because of its capacity of customized dosage form formulating is reduced along with its complex geometries, new drug release profiles as well as stability.¹⁰

Formulation of three dimensional printing personalized medicine is completely novel formulation and equivalently pills that involves different active ingredients, either as a complicated multilayer printed or single blend printed tablet.¹¹

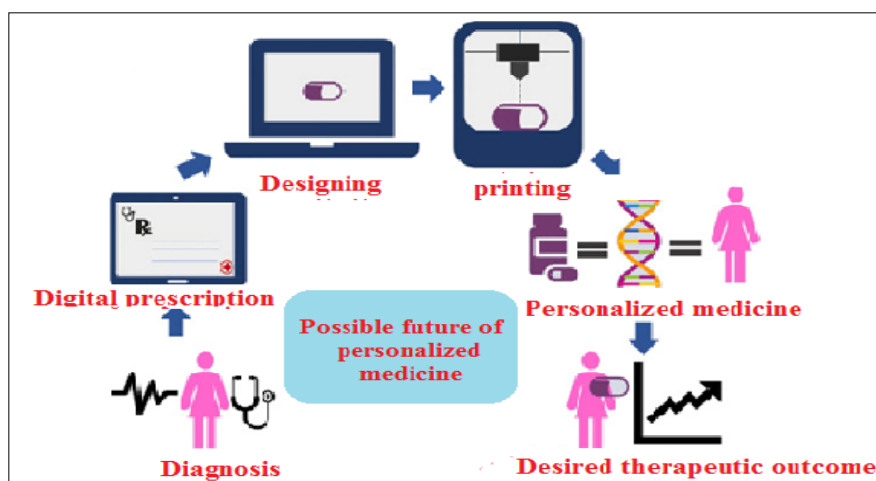


Figure 3: Personalized medicine using by 3D printing¹²

Benefits:

- In customized pharmaceutical life dangerous adverse effect are removed.
- Reduction in cost.
- Failures are immediately recognized.
- For particular background response is agreeable.
- Efficacy of the drug is enhanced.

Need For Personalized Medicine: ¹³

- Symptoms are same but illness will be different.
- Medical interventions works in few patient but not in other.
- Drugs that are taken not enough i.e. 40% of drugs
- Advanced genomics is helpful in diagnosis of patient in effective and precise manner.
- Adverse and allergic reactions can be avoided.

Advantages ¹⁴

- Decreased disease burden.
- concentrate on prevention
- Reduce the duration and seriousness of illness
- Decreased healthcare cost.
- Benefits are enhanced and risks are decreased.

Disadvantages

- Incorrect diagnostic outcome.
- Quantitative and multiple genetic variations.
- Still not extensively available.
- In case of personalized medicine patients are not decided.

Dosage Forms for Personalized Medicine:

- Personalized medicine grip a tremendous promise to upgrade health care since it is also known as precision medicine.
- In this form of medicine information used from patient's genotype to start a inhibitory measure against the progression of disease.
- Accurate therapy is selected for pathogenesis of disease.
- As reported by "National Cancer Institute" personalized medicine consolidates information regarding person's genes, proteins, prognosis and cure disease.

Opportunities:- ¹⁵

- Quick pre-symptomatic estimation of new drugs
- Novel formulations for increased drug delivery
- Personalized/Precision medicine
- Regional manufacture
- Custom-built products
- smaller manufacturing runs
- Physical testing
- Job appointment (new)
- Expedition to novelty

Types of 3D printing:-**1) FDM – fused deposition modeling**

Fused Deposition Modeling, is generally used for designing, prototyping and manufacturing applications. It works on an "additive" principle by put down the material in layers. From the coil a metal wire or plastic filament is released and after the particular time interval food material to an extrusion nozzle responsible for changing the flow of material. With the help of heated nozzle material is melted and by analytical controlled mechanism it can be uplift in horizontal as well as vertical and regulated by a computer-aided manufacturing (CAM) software package. By using extruding limited choker of thermoplastic material the model is produced to form the layers this material is hardened after the extrusion from nozzle. Extrusion head is changes by employing the stepper motors. Iterative testing is simplify due to the fast modeling. ¹⁶

Advantages:

- Economical 3D printer have acceptable resolution for many application
- Different materials are utilized for more costly models use a different material.
- Plastic material is used hence it is cheaper in cost.
- Printing cost is less and available extensively.
- Friability and uniformity of drug is high.

Disadvantages:

- For support leave marks removing and sanding is require.
- For thermoplastic material Warping, limited testing grant expected.
- Due to high temperature of process starting material might deteriorate.
- It requires advanced filaments for the preparation in advance.

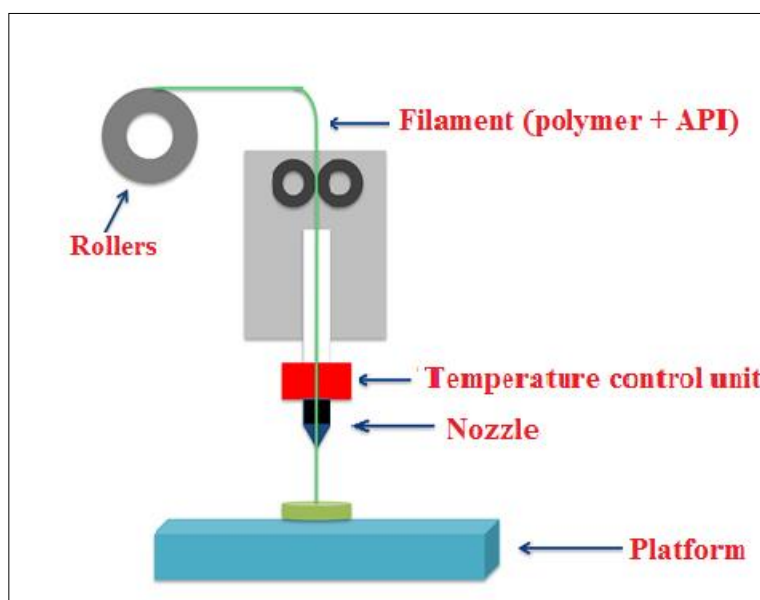


Figure 4: Fused Deposition Modeling (FDM)¹⁷

Table 1: Capabilities of FDM

| Features of Material | Solid (Filaments) |
|--------------------------------|--|
| Material | Polycarbonate, Thermoplastics, and Elastomers; Poly phenyl sulfone |
| Best particle size | 36.00 x 24.00 x 36.00 in |
| Minimum feature size | 0.005 in. |
| Minimum layer thickness | 0.0050 in. |
| Tolerance | 0.0050 in. |
| Build speed and Surface finish | Build speed is stagnant and exterior finish is rugged. |
| Functions | Adjustment of tooling is fast, mini parts, presentation models, Patient and food applications, utilization of heat is high |

2. SLA - Stereolithography

In this technique utilize an ultraviolet laser as well as a container of liquid radioactivity correctable photopolymer "resin" to fabricate parts' sheet one at a time. After that parts are absorbed in a chemical bath to clean surplus resin and in ultraviolet oven are afterwards improved. Approving structures are connect the part to the escalator platform, overcome the changes because of the gravity and side pressure is resist due to the control of the cross sections in area from the re-coater blade. Exposures to the ultraviolet laser light prevented. By this overall process a three dimensional part is build. In the stereolithography machine give rise a supports are naturally while preparing the 3D Computer Aided Design. It may be utilized manually.¹⁸

Advantages:

- Size of object is Deci-micron sized layer and submicron.
- Suitable to all other types of 3D printing technology, high accuracies as well as resolution.

Disadvantages:

- Post- printing curing.
- Cost of equipment is high.
- Time consuming.

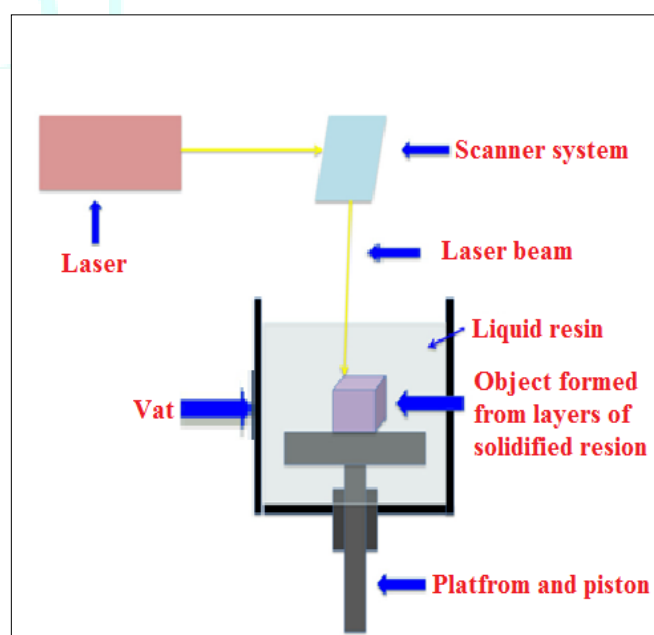


Figure 5: Stereolithography (SLA)¹⁹

Table 2: Capabilities of SLA

| | |
|--------------------------------|---|
| Material Type | Liquid (photo polymer) |
| Material | Mainly photo curing polymers which arouse polypropylene, ABS, PBT, rubber; expansion of ceramic-metal alloys. |
| Best particle size | 59.00 x 29.50 x 19.70 in |
| Minimum feature size | 0.004 in |
| Minimum layer thickness | 0.0010 in. |
| Tolerance | 0.0050 in. |
| Build speed and Surface finish | Build rate is medium and outer finish is mild. |
| Functions | Fast tooling pattern, more detailed parts, Snap fits, Presentation models, utilization of heat is high. |

3. SLS - Selective laser sintering:-

In SLS powder particles are crushed from a powder bed with the help of laser. At the time of printing a 3D structure is formed. For example Paracetamol Orodispersible tablets which is formulated by this method. This technique is used for industrial manufacturing of metallic, bricks and plastic objects. SLS manufacturing technique helps to blend a small sized powder particle with the help of a high power laser [for example- a carbon dioxide laser] to blend small particles into a mass that has 3D. The laser discriminatory merge powdered material by scanning cross-sections which is developed from a 3D digital confession of the part (for example - from a scan data or CAD file) on the outer side of a powder bed.²⁰

Full melting, partial melting, or liquid-phase sintering these are the physical actions. Materials having up to 100 %

density execute material properties identical to traditional method of manufacturing. In some cases huge numbers of parts can be packed inside the powder bed.²¹

Advantages:

- High porosity and internal microstructure.
- Easily reproducible and Manageable.

Disadvantages:

- It requires Post -printing finishing procedure. .
- Speed for sinteration is restricted.
- Due to use of more energy inputs leads to degradation starting materials.

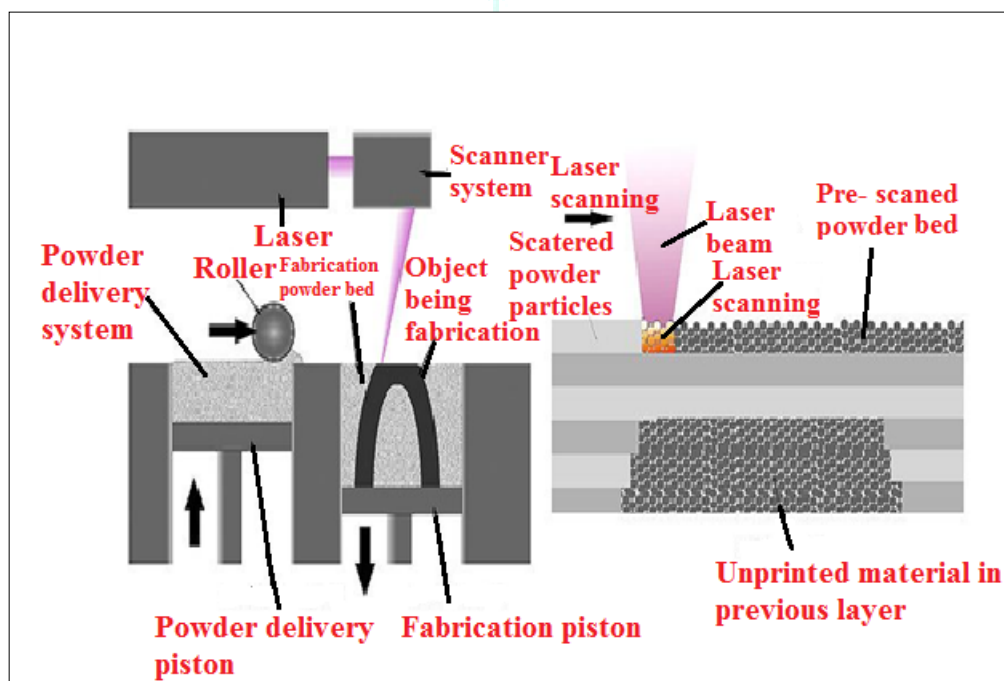


Figure 6: Selective laser sintering (SLS)²²

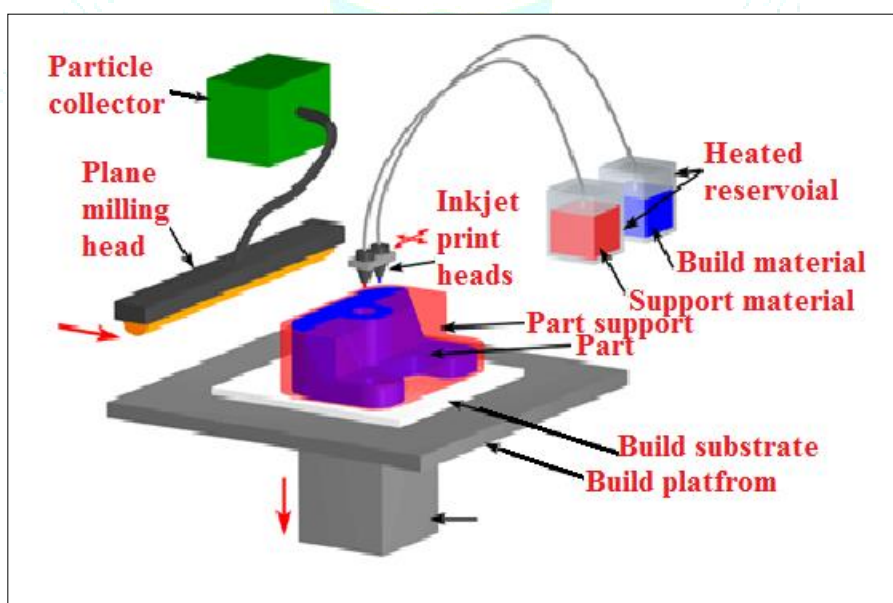
Table 3: Capabilities of SLS

| | |
|--------------------------------|---|
| Material Type | Powder (Polymer) |
| Material | Elastomers; composite; Thermoplastics material such as Nylon, Polyamide, and Polystyrene. |
| Maximum particle size | 22.00 x 22.00 x 30.00 in |
| Minimum feature size | 0.005 in |
| Minimum layer thickness | 0.0040 in. |
| Tolerance | 0.0100 in. |
| Build speed and Surface finish | Build momentum is rapid and finish of exterior is medium . |
| Functions | Pattern of tooling is speedy, Less detailed parts, Parts with snap-fits, more heat is used. |

4. Ink Jet Printing:-

In this technique for plastic habit material single jet is used uses and melted liquid is withstand in a container along with suitable supportive material . In the flowing heads liquid material is deliver which flow small droplets of the materials and this is lifted in X-Y fad is necessary to form a layer of the

object. By quickly lowering the temperature material is harden. The ink jet machine is also known as a Thermo-Jet Modeler (TM) in which in a broad head composition having proper hundred nozzles. A hair-like matrix of build material gives support for extends which can be easily plane off once all the matter is complete. Ink jet machine is very fast as compare to the Solid-scape access.

**Figure 7: Ink Jet Printing²³****Table 4: Capabilities of Ink jet printing:-**

| | |
|------------------------------|--|
| Material Type | Liquid |
| Material | Natural as well as synthetic waxes, acrylic established thermo polymeric Plastic, Fatty Esters |
| Best particle size | 12.00 x 6.00 x 6.00 in. |
| Minimum feature size | 0.005 in. |
| Minimum layer thickness | 0.0005 in. |
| Tolerance | 0.0010 in |
| Surface finish & Build speed | Plane exterior finish and build rate is slow |
| Functions | Medical devices, Parts are more detailed; Rapid assembly pattern is very fast. |

5. Laminated Object Manufacturing (LOM):-

In 1991 the first trading Laminated Object Manufacturing (LOM) system was developed by Helisys of Torrance, CA. Core mechanism is the main factors of the system that have a cover upon a physique platform .The plate is bind to the

layer down by using heated roller and each part of plate layer is cut with the help of a laser. By cutting, mounting, and bonding layers of adhesive-coated sheet material on top of the previously mentioned parts are produced. The process is reproducible before the part is accomplished. ²⁴

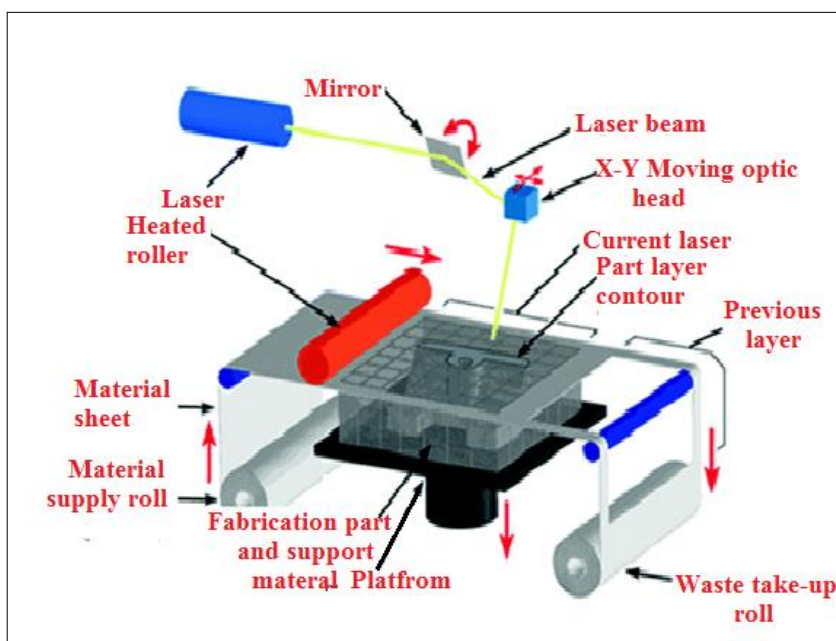


Figure 8: Laminated Object Manufacturing (LOM)²⁵

Table 5: Capabilities of LOM

| | |
|------------------------------|--|
| Material Type | Paper, plastics (Sheets) |
| Material | Paper; Composites; Thermoplastics such as PVC. |
| Best particle size | 32.00 x 22.00 x 20.00 in. |
| Minimum feature size | 0.008 in. |
| Minimum layer thickness | 0.0020 in. |
| Tolerance | 0.0040 in. |
| Surface finish & Build speed | Coarse outer finish and build rate is sobriety. |
| Functions | Detailed parts are very few, quick tooling patterns. |

How does a 3D printing works?

In 3D printing solid objects are formed from a digital file. This technology was developed in the 1980 but the 3D printer did not become publicly available till 2009.

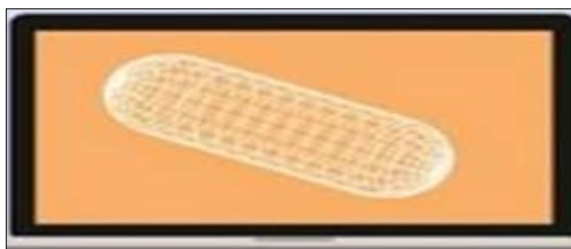
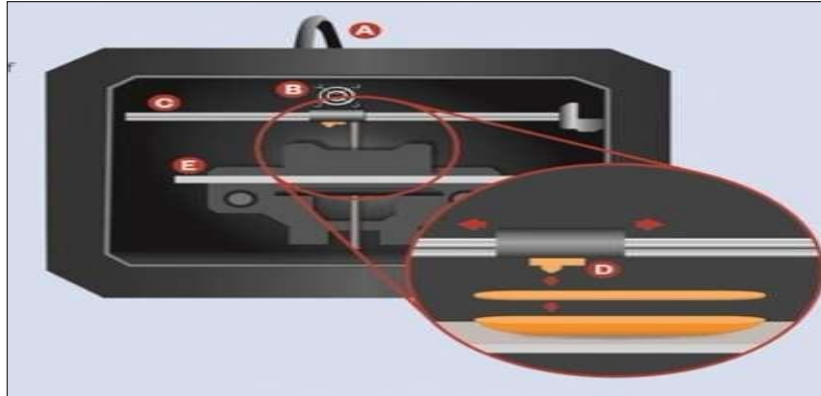


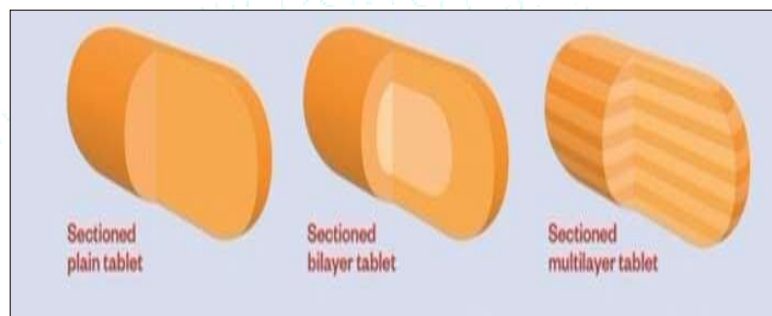
Figure 9: schematic diagram computer aided design ²⁶

1. A digital modeling program such as CAD (computer aided design) or animation modeling software is used for designing.
2. After completion of design the file is sent to the 3D printer. Similar to the inkjet printer the 3D printing makes passes on the build plates, finished product is formulated by loading layer upon layer of material.

- a) **Filament guide tube:** Drug and polymer material is poured through the tube.
- b) **Extruder:** Drug polymer blend is melted.
- c) **Gantry :** It allows the extruder to run from side to side and front to back
- d) **Extrusion nozzle:** A melted filament is passing via nozzle.
- e) **Build plate:** once the layer is finished it runs downward, since the additional layer is build by using helping nozzle helping the nozzle.



3. By fusing the various layers Single 3D objects are designed.



The main components of a 3D printer: ²⁷

A 3D printer includes a set of components that operate in concert to produce the desired output from the input differential file; the basic components of a 3D printer are listed below:

1. Print Bed (Tray)

Printed bed is nothing but the one type of flat surface where the 3D models are layered at the time printing. Perverting is avoided during the layering procedure by using heated print beds.

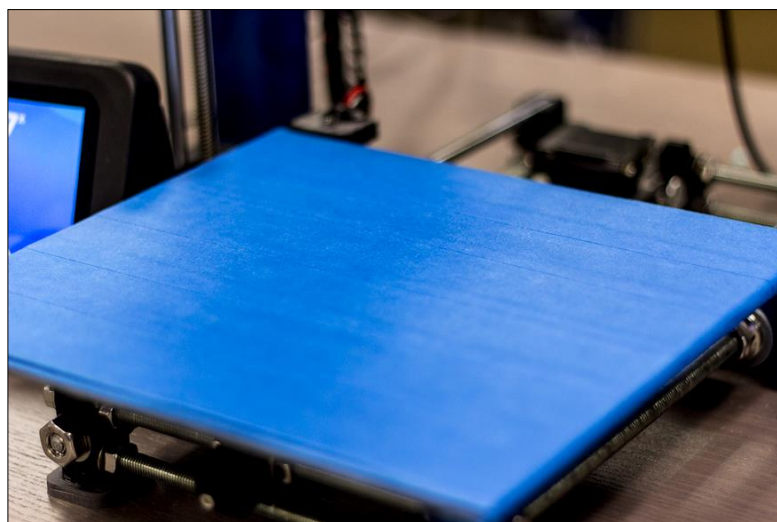


Figure 10: Print bed

2. Extruder:

It is the plunge out part. The main function of The extruder is to pass the plastic filament inside the 'hot-end'. Extruders are repeatedly integrated inside the hot-end in some types it can be different, the filament is send over tube is called a Bowden cable, into the hot-end. In some types of printer a binal extruder is utilized. This type of extruder has ability to print two different materials at the same time.

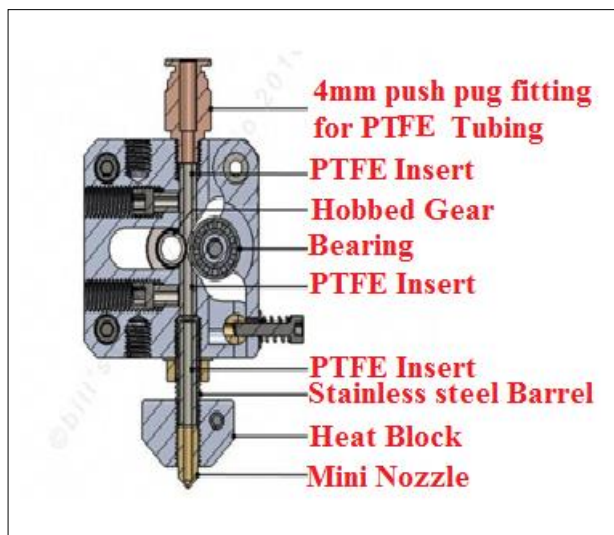


Figure 11: Extruder

3. Hot-end:

Due to the heat cause the hot-end is formed, a plastic material is poured between the temperature sensor and an extrusion edge for the deposition of fused material, sometime due to the extruder it is diverted. The slot crack size may ranges between 0.2mm and 0.8mm. The print accuracy is depends upon the size of nozzle. smaller the nozzle, the more appropriate the printing.

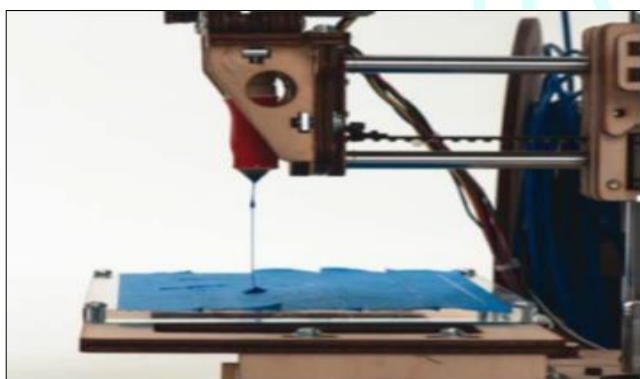


Figure 12: Hot End

4. Filament

The filament manufactured by using printer as a 3D solid matter. It is used as a absorption material. Similar to the inkjet ink, a 3D printer fed melted filament

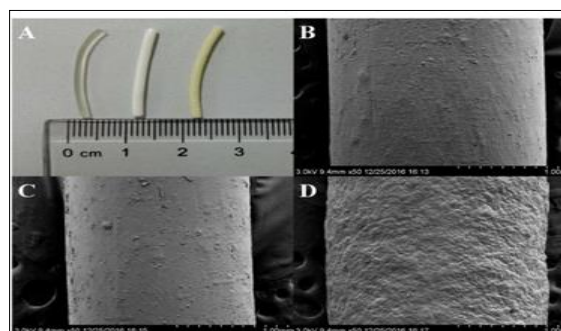


Figure 13: HME fabricated filaments ²⁸

Applications of 3D Printing Using Particular Technologies in Particular Areas

1. Aerospace

Advanced techniques are carried out by NASA engineers carry. In a heated chamber of manufacturing level in Stratasys 3D Printer about 70 of the parts combine the migrant to built a analog, directly against computer designs⁰.²⁹

2. Architecture industry

Smooth, detailed constructive model is utilized in Poly-Jet 3D printing technique and it is used as a designing material. In case of manufacturing-grade thermoplastics FDM Techniques build strong parts.

3. Automobile industry

Fused deposition modeling) authorize certificate to build both advanced models and functional prototypes from polycarbonate, ABS, and poly-phenylsulfone.³⁰

4. Consumer products Consumer electronics:

With the help of thin walls i.e 0.6mm or less Poly-Jet techniques can generate models, in case of small devices is gently packed with small segment.³¹

5. Dental industry

The fresh adopter of CAD/CAM techniques is APEX Dental Milling Center for manufacturing the dental parts direct from CAD design symbolism. While maintaining the high quality code it can administer faster delivery times.³²

Challenges in 3D Printing Technology

3D printing technology still under the advance stage and have significant application during drug delivery. Since it go throughout the different challenges like improvement in instrument performance for its all over use, optimization convert, selections of applicable excipients, panel treatment method, etc., to enhance 3D printed products achievement and to strengthen the application of this products range in novel drug delivery systems. From the safety point of view deep-seated flexibility may be a dominant source of blameworthiness and quality oriented to 3D printing products can be carried out by considering various critical parameters i.e. line quickness of the print head, printing gap, intermission time between two printing layer, printing rate, distance between the nozzles together with the powder layer, etc.³³



Figure 14: Global challenges of 3D printing technology³⁴

Future Prospects

3D printing technology offers new opportunities for the pharmaceutical research and development with biotechnological applications. This approach is used in different ways like fabrication as well to engineer number of new dosage forms, drug release rate can be optimized. 3D printing gives a novel personalized medicine possibility dimension. Production of personalized 3D printed oral tablets is more childish against researcher as well as the idea of. 3D printed drug products achieve limited shelf half life. It is an opportunity to traditional compounding pharmacies. In future it may causes modernization in garage biology. This technology is so novel, but there is a lack of control, security and safety of three dimensional printing. In future these difficulties can be affected.

Conclusion:

In pharmaceutical field 3D printing technology has become a useful technique for designing and development of personalized medicine depends upon needs of the patients needs. 3D printing technology is a novel drug designing process along with built in flexibility of the product. This technology is most suitable for the designing and developing a personalized /customized medicine. The biggest challenge of various regulatory authorities is solved by utilizing the 3D printing technology mainly because of its manufacturing style and formulation. In the recent years future 3D printing approach will be used mainly to formulate different new dosage forms.

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