3D Printing in Oral Dosage Form

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***Abstract*- The 3D printing process builds a three-dimensional object from a computer-aided design (CAD) model, usually by successively adding material layer by layer, which is why it is also called additive manufacturing. The term "3D printing" covers a variety of processes in which material is joined or solidified under computer control to create a three-dimensional object, with material being added together (such as liquid molecules or powder grains being fused together), typically layer by layer. In the 1990s, 3D-printing techniques were considered suitable only for the production of functional or aesthetic prototypes and a more appropriate term for it was rapid prototyping. As of 2019, the precision, repeatability, and material range have increased to the point that some 3D-printing processes are considered viable as an industrial-production technology, whereby the term additive manufacturing can be used synonymously with "3D printing". One of the key advantages of 3D printing is the ability to produce very complex shapes or geometries; including hollow parts or parts with internal truss structures to reduce weight, and a prerequisite for producing any 3D printed part is a digital 3D model or a CAD file. The most-commonly used 3D-printing process (46% as of 2018) is a material extrusion technique called fused deposition modeling (FDM).[4] While FDM technology was invented after the other two most popular technologies, stereo lithography (SLA) and selective laser sintering (SLS), FDM is typically the most inexpensive of the three by a large margin, which lends to the popularity of the process.**

***Index terms*- history, princle, objectives, application**

INTRODUCTION

Definition: 3D printing means the process which involves the formation of three-dimensional solid objects from a computerized or digital (ordinal) files. The process of spraying or the laying down of additives continues unless successive layers create an object. The thinly sliced horizontal cross-sections of the eventual object have been seen in every layer.

- Nowadays, Three-Dimensional Printing is one of the fastest developing branches of technology, art and science, and still broadens the applications.
- ISO defined 3D technology as: fabrication of objects through the deposition of a material using a print head, nozzle, or another printer technology. In this technique 3D model are used for preparing the parts in the process of joining materials layer by layer.

Terminology related to 3D printing

Drug product

A drug product means a finished dosage form; capsule, tablet, solution, emulsion, suspension, etc. containing active pharmaceutical ingredients. 3D printing can fabricate other regulated
products materials, which have well-defined quality purpose and regulation

HISTORY

- Additive manufacturing fabricating methods of 3D plastic model with photo hardening polymer were invented by Hideo Kodama of Nagoya Municipal industrial Research Institute, here the UV exposure area is controlled by scanning fiber transmitter or mask pattern.
- In 1984, Check Hull of 3D systems corporation developed a prototype systems based on a

process as a systems based on a process known as Stereo lithography.

- The Umbrella term additive manufacturing gained wider currency in the decade of the 2000s.
- The first 3D printing technique used in pharmaceutics was achieved by inkjet printing a
- binder solution onto a powder bed, binding therefore the particles together thanks to the semi-liquid binding solution.
- The process was continuously repeated until the final desired structure was obtained. This first happened in the early 90's at the MIT (Massachuset Institute Technology).
- FDA approved Spritam as the first 3D printed drug and in summers of 2016 Aprecia Pharmaceuticals released it in the market. Inkjet printing now a day has become the most used method for 3D printing.

Principle

The principle involved in 3D is "additive processes." In additive process an object is produced by establishing successive layers of material. It deposits a binder material onto a powder bed within inkjet printer heads layer by layer. It enables to produce complex shapes using less material than traditional manufacturing methods. It is an agile tooling used to describe the process to design and fabricate the AM of 3D printing methods to enable responses abruptly.

Why Should We Focus on This?

a. Save amount of money in the prototyping process of several companies
b. Cost refers to only in hundreds and changes can be made instantly on computer
c. Waiting tends to be only hours/days but not years/months in case of prototype
d. Easy availability of personally customized products
e. Useful in drug testing purposes which revolutionize pharmaceutical R&D
f. Synthetic models lower the risk of trial failure
g. Revolutionary method saves time and cost by eliminating outcast designs.

Advantages7:

1. Accurate and precise dosing of potent drugs which are administered at small doses.
2. Reduces cost of production due to lesser material wastage.
3. Narrow therapeutic window.
4. Medication can be tailored to a patient in particular based on genetic variations, ethnic differences, age, gender and environment.
5. High drug loading ability when compared to conventional dosage forms.

Disadvantages7:-

1. The 3D printing technology is currently limited by size limitations. Very large objects are still not possible when built using 3D printers.
2. As with all new technologies, manufacturing jobs will decrease. This disadvantage can have a large impact to the economies of third world countries especially China, that depend on a large number of low skill jobs.
3. Human errors (placing wrong spool of the base material in printer)
4. Final product should undergo validation
5. How 3D Printers Works8-12?

It starts with making a virtual design of the object we want to create. This bears a computer-aided design (CAD) file, which creates 3D modeling application, 3D scanner which can make a 3D scanner which can make a 3D digital copy of an object. American Society for Testing and Materials developed standards that classify the AM process into seven categories.

- Vat photopolymerization
- Material jetting
- Binder jetting
- Material extrusion
- Powder bed fusion
- Sheet lamination
- Directed energy deposition

Vat polymerization

- Commonly used technology is stereo lithography (SLA).
- SLA is used for created models, prototypes, patterns, and production parts using photochemical process by which light causes chemical monomers to link together to form polymers.

- This technology employs a vat of liquid ultraviolet (UV) curable photopolymer resin and an UV laser to build the layers on object.

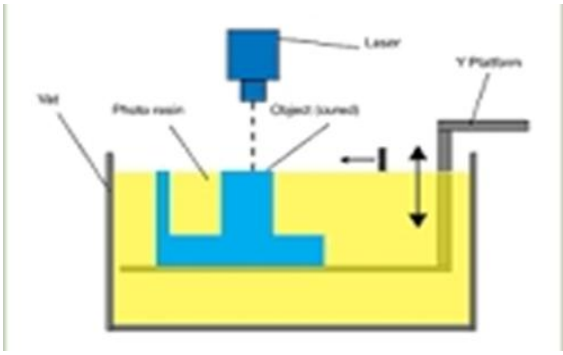


Fig 1: Vat polymerization

Material jetting

- This process resembles to inkjet paper printer it is the only AM technology that can combine different print materials with in the same 3D printed model in the same print job.
- Completely processed models can be covered and used instantly without additional post processing.
- Material applied in the form of droplets through small diameter nozzle and layer by layer, which hardened by UV light

Material extrusion

- Commonly used technology is fused deposition modeling material applied using a filament or wire estruses to nozzle, which turns the flow on and off and gets heated and melts the material and moves horizontally and vertically by computer-aided manufacturing.
- The melted material forms as layer and hardens immediately and results 3D object. In the case of complex shape, support material is also extruded .
- The sacrificial material is later removed by hot water, water jet, or a solvent. Mainly used filaments are acrylonitrile butadiene styrene and polylactic acid (PLA).

Binder jetting

- It combines the principles of selective laser sintering (SLS) and material jetting. This includes powder-based material and a liquid binder.
- The powder is spread in build chamber and a binder is applied through nozzles that glue the powder particles in the shape of a programmed 3D object.

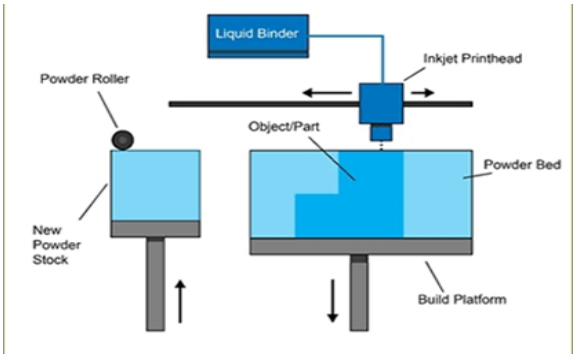


Fig 2: Binder jetting

Powder bed fusion

- Commonly used technology is SLS.
- This technology uses a high power laser to fuse small particles. The laser selectively fuses the powdered material by scanning the layers generated by programmed 3D object on the power bed.
- The SLS process uses an infrared laser beam to selectively scan powder material slightly above its normal temperature.
- After scanning, it maintains the thickness and then deposition of new layer of material is applied on top and then the process is repeated until the object is completed.
- This is an advantageous technology over SLS and SLA because, no need of any support structure.

Sheet lamination

- It is used to produce colored objects in high detailed resolution.
- The precision of the results depends mostly on the thickness of the layered materials used.
- It involves material in sheets which can be a polymer which bound together with external.

Directed energy deposition

- Mostly used in the high tech industry and rapid manufacturing applications.
- This process enables the creation of parts by melting material as it is being deposited. In this focused thermal energy is used to fuse materials.
- The device attached to multi-axis robotic arm and consists of nozzle deposits powder on

surface and get melts by an energy source and finally forms a 3D dimensional solid object.

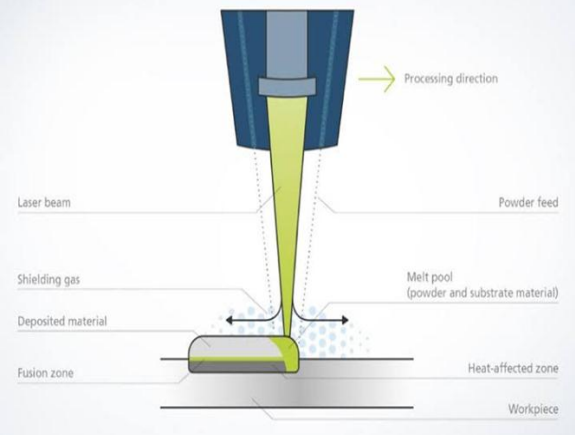


Fig 3: Directed energy deposition

AIM

The use of 3D printing technique in manufacturing of oral dosage form for treatment of various diseases.

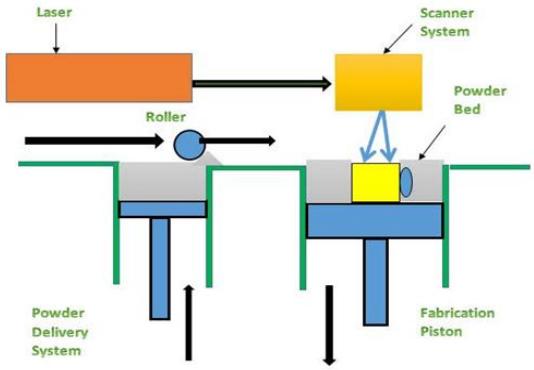
OBJECTIVES

- To understand the advantage and disadvantage of 3D printing in pharmacy sector.
- To promote the knowledge and interest in 3D printing.
- To realize the future development of 3D printing in pharmacy.
- To learn about printer type and feature.
- To compare and contrast printing technologies used in pharma industrial sector.

TYPES OF 3D PRINTING

1. Selective Laser Sintering

- Selective laser sintering is a quick manufacturing process based on the use of powder coated metal additives, a process generally used for rapid prototyping.
- For scanning and aligning particles in predetermined sizes and shapes of the layers a continuous laser beam are used as heating source.
- The geometry of the scanned layers corresponds to various sections of the models established by Computer-aided design or from files produced by stereo-lithography.
- After scanning the first layer, the scanning of second layer continues which is placed over the first, repeating the process from the bottom to the top until the product is complete.
- To fuse small particles of plastic, metal, ceramic or glass powders into a mass that has the desired three dimensional shapes, this technology uses high power laser.
- Scanning the cross section or layers generated by 3D modeling program on the surface of powder bed, laser selectively fused the powdered material so that the powder bed is lowered by one layer thickness.
- Then a new layer of material is applied on top and the process is repeated until the object is completed.



4: Selective Laser Sintering

2. Fused Deposition Modeling

- Fused Deposition Modeling Printers are much more common and inexpensive than the Selective Laser Sintering type.
- Fused deposition modeling printer uses a print head similar to an inkjet printer. However, instead of ink, beads of heated plastic are released from the print head as it moves, building the object in thin layers.
- As each layer of plastic cools, it hardens, gradually creating the solid object as the layers build. Depending on the complexity and cost of a Fused Deposition Modeling printer, it may have enhanced features such as multiple Print heads.
- Fused Deposition Modeling printers can use a variety of plastics.
- In fact, 3D Fused Deposition Modeling printed parts are often made from the same

thermoplastics that are used in traditional injection molding or

- Machining, so they have similar stability, durability, and mechanical properties.

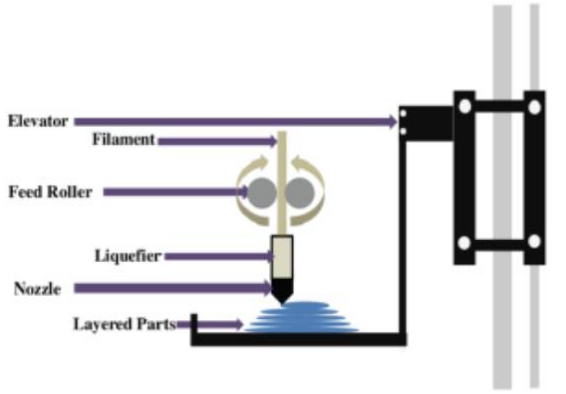


Fig 5: Fused Deposition Modeling

3. Hot melt extrusion

- Hot melt extrusion is the process of melting polymer and drug at high temperature and the pressure is applied in the instrument continuously for blending.
- It is a continuous manufacturing process that includes several operations such as feeding, heating, mixing and shaping.
- In recent years, it has proved that Hot Melt Extrusion has the ability to improve the solubility and bioavailability of poorly soluble drugs.

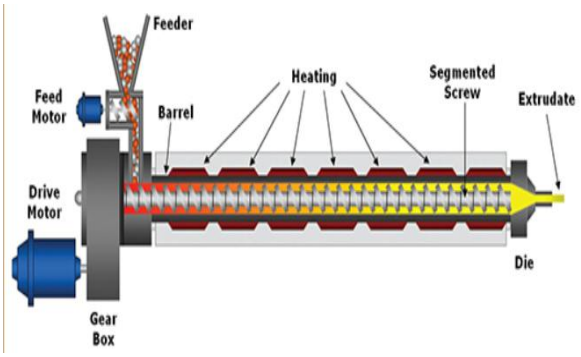


Fig 8: Hot melt extrusion

6. Extrusion 3D Printing

- In this technique the material is extruded from the automated nozzle on to the substrate and it does not require any higher support material.
- It is only used to fabricate tablet containing Guaifenesin as expectorant.
- The materials that can be extruded are molten polymers, suspensions.

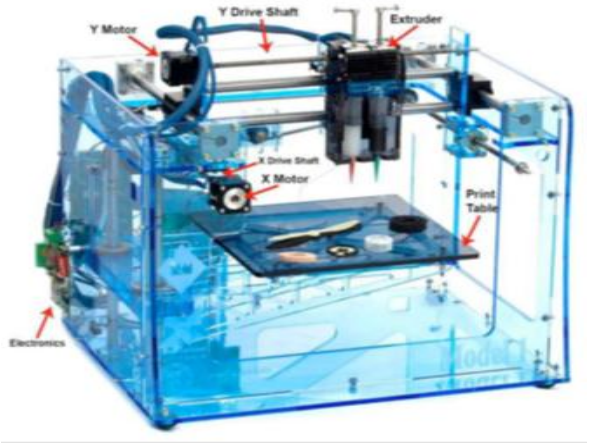


Fig 9: 3D printer used in 3D Printing

Table 1: Fabrication of dosage forms by 3D printing technology.19

3D PRINTER MATERIALS

Polymers used in 3D printing for medical purposes:

1. Acrylonitrile Butadiene Styrene

- One of the most widely used material since the inception of 3D printing.
- This material is very durable, slightly flexible, and lightweight and can be easily extruded, which makes it perfect for 3D printing.
- It requires less force to extrude than when using Poly Lactic Acid, which is another popular 3D filament.
- This fact makes extrusion easier for small parts. The disadvantage of acrylonitrile butadiene styrene is that it requires higher temperature. 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. Poly Lactic Acid

- Poly lactic acid derived from corn and is biodegradable another well-spread material among 3D printing enthusiasts.
- It is a biodegradable thermoplastic that is derived from renewable resources.
- As a result Poly lactic acid materials are more environmentally friendly among other plastic materials.

- The other great feature of Poly lactic acid is its biocompatibility with a 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 and it is another example of support 3D materials.
- This material is well spread in food industry for packaging. It is also used to pack CD discs and to produce trays in medicine naturally this filament has bright white color and it is also biodegradable so there is no adverse effect when it is put in tight contact with a human or animal body.
- High Impact Polystyrene filaments have curling and adhesion problems, which can be reduced by using a heated bed during the printing.
- High Impact Polystyrene material that can also be used as support structure during the printing and then dissolved in a colorless liquid hydrocarbon Solution.

APPLICATIONS OF 3D PRINTING 22-23

3D Printing has been applied in medicine from long times when first it used to make dental implants and custom prosthetics. The current medical uses of 3D Printing can be organized into several broad categories: tissue and organ fabrication; creating prosthetics, implants, and anatomical models; and pharmaceutical research concerning drug discovery, delivery, and dosage forms.

Bio Printing Tissues and Organs

- Organ printing takes advantage of 3D printing technology to produce cells, biomaterials, and cell-laden biomaterials individually or in tandem, layer by layer, directly creating 3D tissue-like structures.
- Researchers have used 3D printers to create a knee meniscus, heart valve, spinal disk, other types of cartilage and bone, and an artificial ear. Customized Implants and Prostheses

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.
- This approach has been used to fabricate dental, spinal, and hip implants.

Anatomical Models

- 3D-printed neuroanatomical models can be particularly helpful to neurosurgeons by providing a representation of some of the most complicated structures in the human body.

3D-Printed Dosage Forms and Drug Delivery Devices

- In pharmaceutical industries various techniques have been used and the 3D printing is one of them in pharmaceutical research and fabrication due to the précis control of droplet size and dose, high reproducibility, and ability to produce dosage forms with complex drug-release profiles.
- Complex drug manufacturing methods can also be standardized through use of 3D printing to make them simpler and more viable.
- 3D printing technology could be very important in the development of personalized medicine, too.

Unique Dosage Forms

- The primary 3D printing technologies used for pharmaceutical production are inkjet-based or inkjet powder-based 3D printing.
- These technologies offer the ability to create limitless dosage forms that are likely to challenge conventional drug fabrication.

Personalized topical treatment devices

- Nose-shaped masks, loaded with salicylic acid, used for anti-acne treatments, have been developed in a short and efficient manner.
- The face of the patient was scanned and the taken image was projected to the AutoCAD

program, through which the nose section was selected.

3D Printing for cancer treatment

- Chemotherapy has widely applied in cancer treatment but chemotherapy can cause side effect. Chemotherapeutic drugs have poor solubility in aqueous media; thus, they are administering through a different route.
- Currently, the construction of patches loaded with 5-fluorouracil, poly (lactic-coglycolic) acid, and PCL have been efficaciously printed and implanted directly into pancreatic cancer.

3D printed polypill

- The concept polypill described that a combination of several drugs in a single personalized tablet. It provides advantages over poly medicated patient such as elder person.
- Different polypills using 3D extrusion printing have been successfully created. As an example, captopril, nifedipine, and glipizide, to treat hypertension and type 2 diabetes.
- The formulation rapidly disintegrated with a sip of liquid.

CONCLUSION

This project concludes that the use of 3D printing for medical purposes today is beyond the limit. The rapidly evolving 3D printing technologies and the rise of pharmaceutical sector have huge potential in dosage form personalisation required by patients. It will be a revolutionary force in manufacturing technology and has a set of potential profit to society. Several 3D printing technologies have been used to manufacture solid dosage forms for oral drug delivery. PB 3D printing technologies have evolved with several patent applications and an FDA approved product to be introduced to the market. It is highly efficient, reliable, time saving, and ecofriendly technique. It has applications in wide variety of fields too.

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