WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES

SJIF Impact Factor 7.421

Volume 8, Issue 1, 673-684 Review Article ISSN 2278 – 4357

REVIEW OF RECENT ADVANCEMENT IN 3D PRINTING AND HOW THE 3D PRINTING IS BOON FOR PHARMACEUTICAL AND MEDICAL SCIENCE

***Mahadev Govindrao Tate and Priyanka Shailesh Gala**

India.

Article Received on 15 Nov. 2018,

Revised on 05 Dec. 2018,
Accepted on 25 Dec. 2018

DOI: 10.20959/wjpps20191-13010

***Corresponding Author**

Mahadev Govindrao Tate

India.

ABSTRACT

The 3D printing technology was first introduced by Charles Hull in the early 1980s.[5] Although the technology was developed in the 1980s, 3D printers were not widely available commercially until the earl 2010s.[13] In it's most setup, 3D printing uses computer-aided drafting technology and programming to produce a 3D object by layering material onto a substrate. 3D printing is used in many fields such as architecture, medicine and even pharmaceutical manufacturing. A variety of 3D printing technologies have been used to produce novel dosage forms which are among the most renowned and distinct outcomes. This review highlights the overall 3D printing process, it's mechanism, advantages limitations and challenges.

INTRODUCTION

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 modeling. The current achievements of 3D printing include multifunctional drug delivery systems with accelerated release characteristic, adjustable and personalized dosage forms, implants and phantoms corresponding to specific patient anatomy as well as cell-based materials for regenerative medicine.

In medical imaging, 3D printing is mainly used to produce various anatomical models of the human body. The physical interaction with these 3D-printed models allows the physicians and surgeons to enhance the visualisation of lesions, planning of surgical procedures and communication with patients. 3D printing technology have brought a revolutionary change in medical imaging and healthcare, and its adoption is slowly taking place in many hospitals around the world. By segmenting, or creating thresholds in the image based upon density, users can create volumes of interest and selectively reconstruct specific anatomical structures or display them in different colors when printed. Segmentation in these programs often involves manually shading 2D anatomical features slice-by-slice to identify the correct volume of interest through which the CAD software "interpolates" the region.[15] The main component of the 3D bioprinting is the bioink, which is crucial for the development of functional organs or tissue structures. The bioinks used in 3D printing technology require so many properties which are vital and need to be considered during the selection.[17]

Three-dimensional (3D) printing is a transformative technology that has the potential to greatly impact the field of orthopaedic spine surgery. Three-D printing has been used in surgical planning for complex spine surgeries since the 1990s.[24]

Need of 3D Printing Technology in Pharmaceutics

1) The conventional manufacturing unit operation involving milling, mixing, granulation and compression can result in a dispartate qualities of the final product with respect to drug loading, drug release, drug stability and pharmaceutical dosage form stability.

2) As the lack of stability face the problems of altered pharmacokinetics.

Types of 3D Printing

1) Inkjet Printing

Home inkjet printers work by forming small ink droplets on paper. In the same fashion, drug inkjet printers form small liquid droplets and deposit them onto a substrate.[11] Inkjet printers prepare the ink formulation, which consists of binders and medications, and spray the ink droplets at precise velocity, motion, and size onto a non powder substrate. Spraying the ink droplets onto a liquid film that encapsulates the uniform ink droplet. These matrices may be used for delivery of small hydrophobic molecules, growth factor, antibodies, micro particles, and nanoparticles. Inkjet printing has used for printing structures out of sol-gel, conductive polymers, ceramic, metal, and nucleic acid or protein materials. The two main types of inkjet printing are continuous and drop-on-demand (DOD).[3]

Ex-Rifampicin, steroidal Anti-inflammatory drugs, Acetaminophen.

2) Powder-Based Printing

The powder substrate differentiates inkjet and powder based 3DP. The inkjet printer head sprays the ink onto the powder, which is laid as a foundation. This ink acts as a binder and /or active ingredient. When it contacts the powder, it hardens and creates a solid. The inkjet head continues to spray the liquid onto the powder through subsequent layers until a solid forms. After it is dry, the solid object is removed from the surrounding unprinted loose powder substrate.[11] In this method layers of solid particles, typically 200micro meter in height with particle sizes ranging between 50 and 100 micro meter, are bound together by a printed liquid material to generate 3D model.[3] As a powder based 3D printing technique, inkjet printing does not require photopolymerizable materials or liquids with modified viscosities. Powders from polymer, ceramic, or glass materials can be combined with liquid binding materials to generate a 3D model, which has significantly expanded the technique's application in areas like art design and industrial modeling.

Selective Laser Sintering (SLS)

SLS is another powder based 3D model fabrication method developed by Carl Deckard and Joseph Beaman. Powder based 3DP technique is used to build 3D bone scaffolding. This new advancement in bone reconstruction happens in vivo. The scaffold holds the cells together and mimics ghe natural bone extracellular matrix.

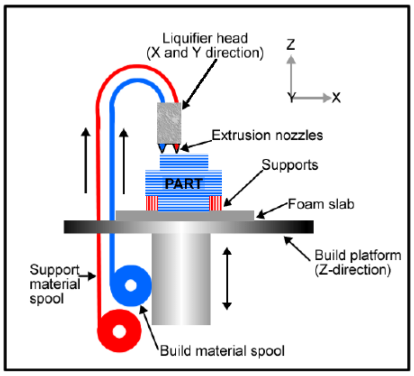
Ex- carbon dioxide and Nd:YAG, to sinter polymer powders to generate a 3D model, rather than using liquid binding materials to glue powder particles together.

INK Formulations and Printing Substrates

The ink formulations covered a wide range of compounds, including poly(lactic-co-glycolic acid) inks, ethanol-dimethyl sulfoxide, surfactants (eg. Tween 20), kollidon SR, glycerine, cellulose, propylene glycol, methanol, acetone, and others.[11] The composition of these ink formulations could be valuable for a compounding pharmacy at which the inks need to be reconstituted.

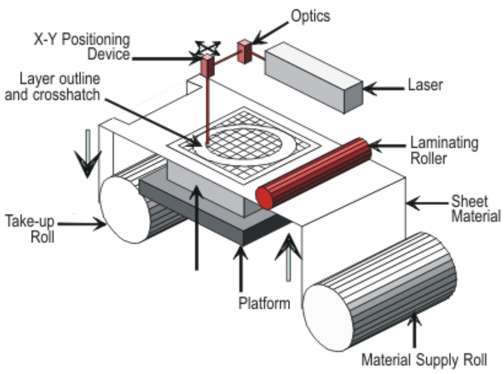
Types of 3D Printers

1) Fused Deposition Modeling (FDM).



Developed by scott Crump of Stratasys, FDM is one of the most widely used manufacturing technologies for rapid prototyping today. FDM fabricates a 3D model extruding thermoplastic materials and depositing the semi molten materials onto a stage layer by layer. In FDM thermoplastic filaments, the material used to build 3D models, are moved by two rollers down to the nozzle tip of the extruder of a print head, where they are heated by temperature control units to a semi molten state.[3] As the print head traces the design of each defined cross-sectional layer horizontally, the semi molten materials are extruded out of nozzle and solidified in the desired areas. The stage then lowers and another layer is deposited in the same way. These step are repeated to fabricated a 3D structure in a layer-by-layer manner. A notable advantages of FDM is that it can create objects fabricated from multiple material types by printing and subsequently changing the print material, which enable more user control over device fabrication for experimental use.

2) Laminated Object Manufaturing (LOM)



LOM, developed by Helisys, generates a 3D model by stacking layers of defined sheet materials such as paper, plastic, and metal. After the first layer of a sheet material is loaded onto a stage, a laser (carbon dioxide laser have been used) or razor traces the designed cross-section to define the pattern on the layer.[3] After the excess material of the sheet is removed, a second layer covers the previous layer and the laser of knife tracing will define the next pattern based on information in the STL file. The LOM process does require a heating step during production, either on the support stage or on the roller, to ensure that the adhesive acts to bound the sheets together. Another limitation of LOM is that the materials applicable for method use are limited by their ability to be formed into sheets and to be integrated with adhesive.

Mechanism of 3D Printing

Prepare a 3D model to
be 3D printed

↓

↓

Dividing a 3D models into X-Y-Z
Planes by using different softwares

↓

↓

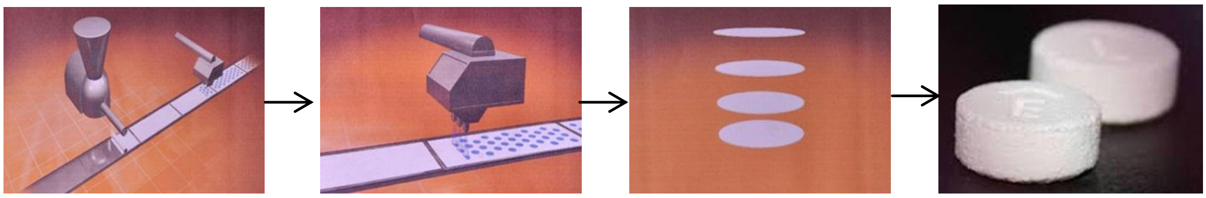
3D printer first follows
Instructions in CAD file to build
foundation of object moving
Printed along X and Y plane

↓

↓

The printer then continue to
follow instructions moving
Printhead along Z axis to built
Object vertically layer by layer.

Three-dimensional printing, also known as additive manufacturing, is a fabrication process whereby a 3D object is created layer-by-layer by depositing a feedstock material such as thermoplastic polymer. The most common 3D printing technology is called the Fused Deposition Modelling (FDM) which utilises thermoplastic filaments as a starting material, then extrudes the material in sequential layers above its melting temperature to create a 3D object. These filaments can be fabricated using the Hot-Melt Extrusion (HME) technology. The advantage of using HME to manufacture polymer filaments for FDM printing is that a homogenous solid dispersion of two or more pharmaceutical excipients.



The HME and FDM technology can be combined into one integrated continuous processing platform. This article reviews the working principle of Hot Melt Extrusion and Fused Deposition Modelling, and how these two technologies can be combined for the use of advanced pharmaceutical applications. Hot-melt extrusion is a continuous manufacturing process that includes several operations such as feeding, heating, mixing and shaping into one continuous process. Recent years, this technology has gained much interest in the pharmaceutical industry, especially for the production of oral dosage forms and drug delivery systems. HME is a continuous process where heat and pressure are applied to melt or soften materials through an orifice to produce new products of uniform shape and density. There are two types of hot-melt extruders: the single-screw extruder and twin-screw extruder. The filaments are suitable to be used in FDM 3D printers for the fabrication of tablets. The 3D printed tablets also possess excellent mechanical strength.[12]

CASE STUDY

1) 3D Printing is very useful in treatment of Spinal tuberculosis. Most of the people know Tuberculosis as a disease of the lungs but that not always the case some time Tuberculosis manifested in spine.

As a case study 32 years old woman in India suffering with spinal tuberculosis and Indian physicians were successful to treat this. Surgeons at Medanta - the medicity in Gurgaon, India replaced the woman’s damaged first, second, third vertebrae with a 3D printed titanium implant in a 10- hour surgery, closing the gap between her skull and spine and allowing her to stand and walk normally again. It was the first time such a procedure had been performed in India, and among the first in the world, following similar operations in china that first look place in 2014 and a surgery that was performed a year ago in Australia.

CT and MRI Scans helped create a replica of the spine so that the gaps between vertebrae could be measured to ensure that the final printed vertebrae would fit perfectly.

These technique have opened a new avenue wherein any type of complex reconstruction can be done in the spine with less collateral damage.[1]

2) The 3D printed drugs receive the approval from U.S.FDA. Pennsylvania-based Aprecia Pharmaceuticals said its 3D-Printed spritam (Levetiracetam) tablets are used to treat epilepsy. In case of epilepsy the quick response of drug important and the drug which are made by using 3D Printing technology like Levetiracetam shows rapid disintegration with the sip of liquid. Aprecia said it used some off the shelf 3D Printer parts but mostly developed its own technology to create the drugs, layer by layer at its East Windsor, N.J. manufacturing facility. The new process, which it calls zip dose, stitches together multiple layers of powdered medication using an aqueous fluid to produce a porous, water soluble matrix that rapidly disintegrates.

Applications

1) Personalized Drug Dosing

A Doctor or Pharmacist would be able to use each patient's individual information such as age gender and contraindications to produce their optimal medication dose rather than relying on standard set of dosages. 3D printing may also allows pills to be Printed in a complex construct of layer using a combination of drug to treat multiple ailments at once. The idea is to give patients one single pill that offers treatment for everything they need.

2) Printing of Living Tissue

While it's not likely that this will possible on a full scale anytime soon, experts project that science is less than 20 years away from a fully functioning 3D printed heart. But for now 3DP is still challenged by intricate nature of vascular networks. Some tissue would be much easier to print such as flat structures like human skin the most difficult area in organ printing are the heart, liver and kidney.[1]

3) Drug Release Profiles

3DP makes it possible to print personalized drug that facilitate targeted and controlled drug release by printing a binder on to a matrix powder bed in layer this creates a barrier between active ingredients.

4) Forensic Applications

3DP has had meaningful impact on medical imaging in the field of forensic science, allowing for anatomically correct recreation of bodily injuries from CT and MRI scans.[3] 3DP technique were used to recreate skull fragments from a blunt force head injury and aid in weapon identification and determination of the mechanism of injury leading to death.

5) Surgical Preparations

3DP has facilitated advancement in Individualized patients care, allowing for development of patient specific treatment plans via the printing of patient patient anatomy. 3D printed models have been used to gain insight into a patient's specific anatomy prior to performing a medical procedure. Namely this methodology has been applied in recreating a calcified aorta with 3D printing to develop a procedure for plaque removal presurgery, using a 3D model of bone growths on a shoulder to aid in surgical organization of their removal, constructing a premature infant's airway to study aerosol drug delivery to the lungs and stimulating presurgical tumor removal from a skull and deep tissue.[3]

6) This is mainly focus on encapsulation technologies, orally disintegrating tablets, printed antibiotics, micropatterns, printed dosage form on porous substrates, printed mesoporous bioactive glass scaffolds, nanosuspension and multilayered drug delivery devices.

7) The evolution of radiographic imaging has allowed surgeons to better prepare and plan surgical approaches. As cross-sectional imaging has rapidly advanced in the last decade, high-resolution 3D images can routinely be obtained which help visualize complex vascular anatomy.[16]

8) The use of 3-D printing in different areas of urology along with their potential use.

→ Resection planning of genitourinary organs

→ Prostate biopsies

→ Determining detailed and accurate imaging before surgeries like PNL
→ Operation decision on both blunt and sharp traumas
→ Culture models in order to create organs
→ Tactile anatomical models to medical students, surgical assistants.

Advantages

1) The 2D radiographic images such as X-ray, MRI, CT Scans can be converted to digital 3D printed files.
2) High production rate due to its fast operating system.
3) Ability to achieve high drug loading.
4) Reduction of material wastage which can save in cost production.
5) Dissolution time of 3D printed drug is less.
Ex- Levetiracetam (2-3 min)
3D printed Aprecia (25 sec)
In disease like epilepsy quick response is required.
6) Drugs produced through 3D printing technology are very precise.
7) Accuracy for very small doses as compared with conventional manufacturing.
8) 3DP technologies may replace current additive technologies and decrease the overall cost of manufacturing because they may reduce the use of unnecessary resources.

Disadvantages

1) Precise ink viscosity must be required for proper flow with inkjet printing.
2) Mechanical properties of the formulation being Printed.
3) A need exists for proper postprinting processes that will not interact with the finished printed process.
4) Parameters such as speed and rate of printing must be taken into account and may not be suitable for all drug candidates.
5) High Cost is the primary limitation of 3D printing.

Challenges

1) 3D printed organs are often talked about as the ultimate goal in medical 3D printing and companies such as 'organovo' have already made an impact on pharmaceutical research with their 3D printed liver and kidney tissue.
2) We may not yet be at the point where we can 3D print full human organs and transplant them into patients, but the fact that we can even talk about such a thing as a feasible

possibility show just how quickly and dramatically this technology in changing the industry.

3) Personalized implantation.

CONCLUSION

Inkjet printing and powder-based printing technologies used for drug development and fabrication. Advantages of the 3D printers to create pharmaceutical dosage forms include precise control of droplet size and complex drug profile. Use of 3D printing technology may offer an important benefits to patients who need medications that have narrow therapeutic indices. 3D printing has found an increasing application in all fields of medicine but especially in plastic surgery, orthopedics and dentistry.

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