

3D Printing Technology in Pharmaceutical Formulation

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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 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 modelling, 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.

KEYWORDS: Additive manufacturing, 3D printing

INTRODUCTION

Three-dimensional printing (3DP) has become one of the most innovative technologies in the pharmaceutical field. Within the last decade, there has been a significant expansion in the manufacture of drug delivery and medical devices. Additive manufacturing (AM) includes a variety of processes in which a layer-by-layer process is used to fabricate a solid object. The 3DP techniques, which can be used in the pharmaceutical field and

are also covered under this editorial include Stereolithography (SLA), Selective Laser Sintering (SLS), inkjet-based 3DP, extrusion-based Fused Deposition Modelling (FDM) and Bioprinting. 3DP allows the potential for printing dosage forms on demand, with low cost and ease of use. AM is leading towards personalised medicine as the dosing and release characteristics of the drug delivery devices can be easily changed by altering the geometries of the 3D design using computer-aided design (CAD). The research outlined below and in this Special Issue addresses the current areas of research in bioprinting and 3D printing of drug delivery systems, focusing on the advantages and future directions in the use of AM in the pharmaceutical industry.[1]

liability, durability and cost issues. Cam-based valve systems offer reliable and durable functionality, the cam less valve trains can vary valve lift and more timings to a greater extent comparing to the cam-based types. Among various categories of cam less mechanisms, the electromagnetic actuator system is the most desired one.

What is 3D printing?

3D printing means the process which involves the formation of three-dimensional solid objects from a computerized or digital (ordinal) files.[2] 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.

History of 3D printing

✓ 3D Printing posed as a possible platform for personalized medicine in the 1990s. There are major achievements in 3D printed medical device, FDA's Center for Device and Radiological Health (CDRH) has reviewed and cleared 3DP medical devices.[4]

- ✓ The first 3D printing technique used in pharmaceuticals was achieved by inkjet printing a binder solution onto a powder bed, binding therefore the particles together. The process was repeated until the final desired structure was obtained. This first happened in the early 90's at the Massachusetts Institute of Technology invented and patented by Sachs et al.[5]
- ✓ In 1989, Scott Crump, filed a patent on another 3D printing technology: fused deposition modelling, where extruded polymer filaments heated into a semi-liquid state were extruded through a heated nozzle and deposited onto a build platform layer by layer to harden.[6,7]

3D printing procedure

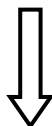
First, a virtual 3D design of an object using digital design software like On shape, Solid works, Creo parametric, AutoCAD, Autodesk etc. is created.[8,9,10]



This digital model is then converted to (STL) digital file format which stands for standard tessellation language or stereolithography.[8]



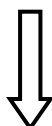
Triangulated facets give information regarding the surface of the 3D model that is present in the (STL) file.[8]



The (STL) file is converted into G file by slicing the design into a series of 2D horizontal cross-sections by the help of specialized slicer software, which is installed in the 3D printer (**Tables 1–2**).



Now the print head is moved in the x-y axis to create the base of the 3D object.



The print head is now allowed to move in the z-axis, thereby depositing the layers sequentially of the desired material, hence creating a complete 3D object.[8,9]

Maximum numbers of 3D printing technologies are compatible with (.STL) file format. Some errors might occur during the conversion of the 3D model to STL digital file; therefore, software like Magics can be employed to correct the errors during conversion. File formats other than.

STL like additive manufacturing file format (AMF) and 3D manufacturing format (3MF) are used as STL does not have information regarding the type of material, its colour, texture, properties, and other features.[11]

Sr no	Year	Major development
1	1980	Dr. Hideo Kodama filed first patent for RP technology
2	1984	Stereo lithography apparatus (SLA) was invented by Charles Hull
3	1986	Carl Deckard invented apparatus for producing parts by selective sintering
4	1989	Patent was granted to Carl Deckard for SLA
5	1990	Fused deposition modelling (FDM)

Table 1. Historical development in the field of 3D printing

3D PRINTING TECHNOLOGY USED	FORMULATION	API	REFERENCE
Stereolithography (SLA)	Hydrogels	Ibuprofen	12
Selective layer sintering (SLS)	Facial mask	Salicylic acid	13
	Tablets	Paracetamol	14
Fused deposition modelling (FDM)	Drug delivery device	Progesterone	15
	Caplets	Caffeine	16
	Tablets	Hydrochlorothiazide	17
Inkjet 3dprinting	Implant	Levofloxacin	18
3D printing machine	Multidrug implant	Rifampicin	19
Thermal inkjet printing	Solution	Salbutamol sulfate	20

Table 2. Pharmaceutical preparations that were developed by 3DP technology

Methods of 3D Printing

Fused Deposition Modelling (FDM)

FDM is one of the most commonly explored additive manufacturing methods due to the low cost of printers, print quality and ability to use drug-loaded filaments through hot-melt extrusion (HME). In this issue, the most common way of incorporating drug into the system was by creating drug-loaded filament created through HME with Chew et al. being the only exception, choosing to soak the polymer filaments in a drug-loaded solution. The articles within the Special Issue that used the FDM method of printing are outlined in this section. Current implants are made with non-biodegradable polymers, which require surgical removal from the body after use. 3DP allows tailored dosage forms to be created specific to the patient and their condition, using biodegradable

polymers, which can be broken down in the body into products that can be easily excreted. Dimensions of already marketed implants were used to create the hollow 3DP implants using filaments made from HME. Polylactic acid (PLA) and Poly(vinyl alcohol) (PVA) filaments were used to print hollow implants with a PVA window. presented a novel approach to the fabrication of gastro-retentivefloating tablets (GRFT) by using HME in order to create drug-loaded filaments that can be used on an FDM printer to create 3D printed tablets. GRFT has the ability to stay above the normal gastric content of the stomach for a prolonged period of time allowing them to overcome common issues with oral dosage forms such as unpredictable gastrointestinal transit and emptying times and metabolic degradation. Theophylline was used along with hydroxypropyl

cellulose (HPC) matrix to create drug-loaded filaments using HME.[21]

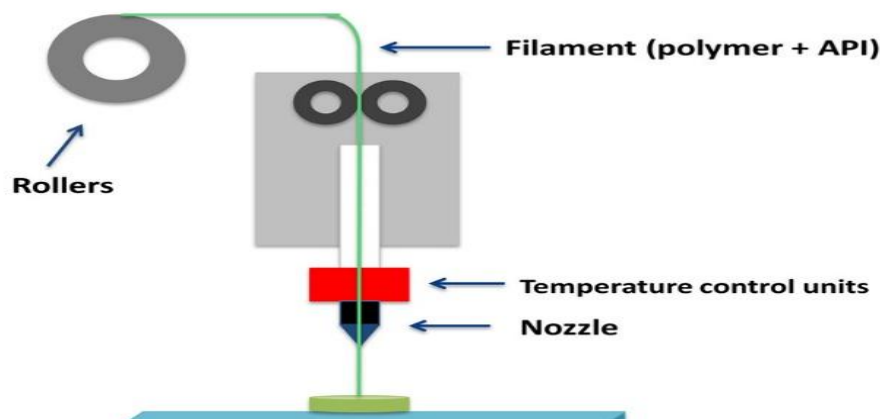


Figure : Fused deposition modelling (FDM)

Stereolithography

Stereolithography (SLA) is a laser-based printing method that was the first commercially available solid freeform fabrication technique. The fabrication of a 3D object by SLA is based on the controlled solidification of a liquid resin by photopolymerization.[22] A movable platform is located in the vessel filled with liquid photopolymer. First, the lifting platform starts near the surface of the liquid photopolymer, and after the proper laser is applied, the platform is lowered into a vessel to a depth equivalent to the thickness of the new polymerized layer. This process is repeated until a solid 3D product is obtained. SLA has high resolution which allows creating a complex structure, and it also minimizes the heating during the printing process, and thereby it is highly applicable to thermo-labile drugs.[23] The choice of photopolymer is essential, as it should be a liquid that quickly solidifies upon illumination with ultraviolet (UV) light and, also, it must be approved for human use. Accordingly, the lack of Food and Drug Administration (FDA)-approved photosensitive polymers and the low drug loading significantly limit the pharmaceutical applications of

SLA, although it is widely used in tissue engineering.[24] Electron beam melting (EBM) and selective laser melting (SLM) are also similar to SLS. However, unlike sintering technology, both EBM and SLM completely melt metal powders during the layer-by-layer process. The SLM method uses energy from a laser beam to fuse the powder particles by heating it beyond the melting point while EBM uses a high-power electron beam in a vacuum. EBM can provide higher throughput and more uniform thermal field distribution than SLS, but its accuracy and surface quality are lower.[25] EBM and SLM are widely used in drug-loaded implants. In addition to the 3DP technologies described above, there are many other 3DP technologies available, including multi-jetting modelling, selective heat sintering, and laminated object manufacturing. Those 3DP technologies are not currently used for pharmaceutical manufacturing, but some of them have a high potential for pharmaceutical applications in the future. Therefore, a great advance in material sciences and the emergence of new adequate materials will facilitate more broad applications of various 3DP technologies.

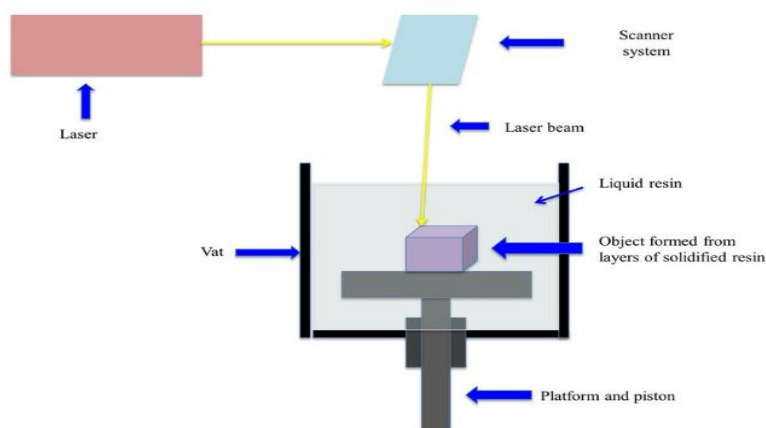


Figure : Stereolithography (SLA) Printer.

Selective Laser Sintering (SLS)

Similarly to SLA, this method of AM works with lasers but powder materials are fused together, whereas SLA works with a resin. Awed et al., utilised SLS 3DP, for the first time, to produce small oral dosage forms with modified release properties. They fabricated single miniprinters using paracetamol as a model drug and dual miniprinters where paracetamol is combined with ibuprofen. For the single miniprinters, ethyl cellulose (EC) was employed as the main polymer matrix. In the case of dual miniprinters one layer contained EC for sustained release whereas the second layer

containing Kollicoat IR (a graft copolymer comprised of PEG: PVA, 1:3) for immediate release. In order to assess the effect size has on dissolution properties, miniprinters of two different diameters, 1 mm and 2 mm, were developed. The single miniprinters exhibited slow paracetamol release, which was reduced when increasing the diameter. For the dual miniprinters, the diameter does not affect the paracetamol release profile. This work demonstrates the possibility to use SLS 3D printing to combine multiple Active Pharmaceutical Ingredients (APIs) with distinct release properties in a single dosage form.[26]

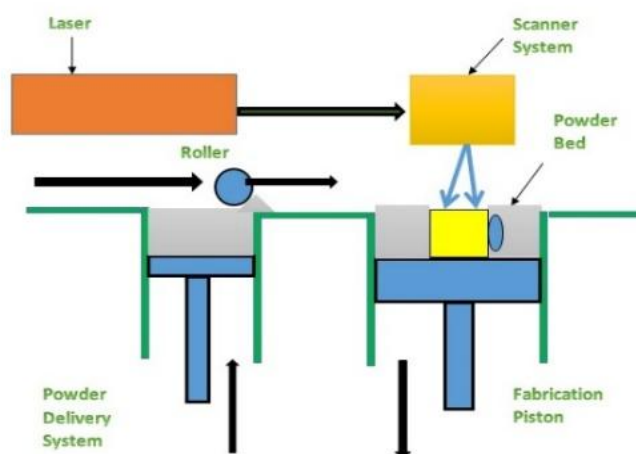


Figure : Selective Laser Sintering (SLS)

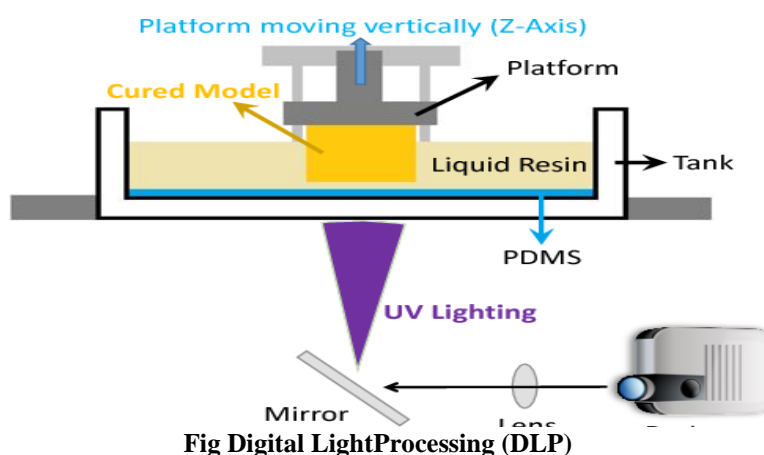
Digital Light Processing (DLP)

DLP is another method of 3DP, which is similar to SLA. Is a resin-based method, however, rather than using a laser-focused UV beam, DLP uses UV light from a projector to cure each layer of the 3D printed product. Madzarevic et al., prepared

ibuprofen tablets through DLP 3DP technology. Eleven formulations were prepared following the D-optimal mixture design from Design Expert software. It was noticed that an increase of water content leads to an enhancement of printing time. Two artificial neural networks (STATISTICA 7.0

and MATLAB R2014b) were used in order to evaluate how the components and the printing parameters affect the ibuprofen release. The data obtained from these two software were compared with the one obtained experimentally. The drug

release predicted with STATISTICA 7.0 was quite similar to the one obtained experimentally. This study described that suitable ANN allows to recognise the input-output relationship in DLP printing of pharmaceuticals.[27]



Thermal Ink-Jet Printing

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.[28] It is used in the preparation of drug-loaded

biodegradable microspheres, drug-loaded liposomes, patterning microelectrode arrays coating, loading drug eluting stents.[29,30] It is also an effectual and applied method of generating films of biologics without negotiating protein activity.[31]

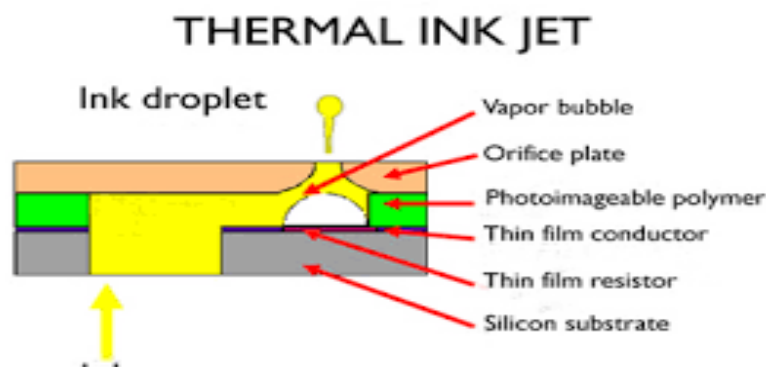


Fig. Thermal Ink-Jet Printing

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.[32,33]

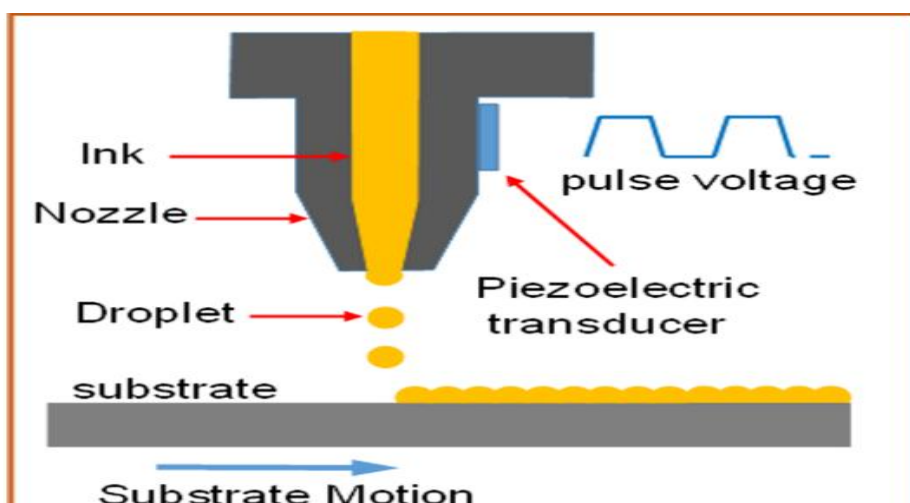


Fig. 4.6 Inkjet Printing

Powder Based 3D Printing

This method custom powder jetting/powder bed to feast thin layers of powder and instantaneously applying liquid binder drops with inkjet printers.[34]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.[34,35]

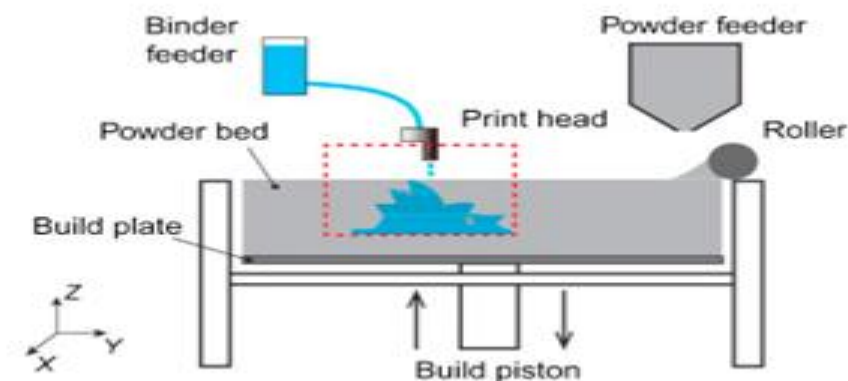


Fig .Powder Based 3D Printing

Embedded 3D Printing (e-3DP)

Embedded 3D printing is a novel form of AM in which a viscoelastic ink is extruded into a solidifying reservoir using a deposition nozzle at a predefined path. Rycerz et al., presented one of the first examples in using e-3DP in the pharmaceutical field to fabricate chewable oral dosage forms with dual drug loading. The two drugs used were paracetamol and ibuprofen, which were suspended in locust gum solution and an embedding medium of

a gelatin-based matrix material. These were printed at an elevated temperature of 70 °C and then solidify at room temperature. The dosing of the printed dosage forms were varied by specifically altering the printing patterns. The rheology, printing speed and the needle size of the embedded phase were examined. This proof of concept study showed the potential for e-3DP to be used to print oral dosage forms thatcould include various

materials, allow personalised dosing and geometry

for novel oral dosage forms in paediatrics.[36]

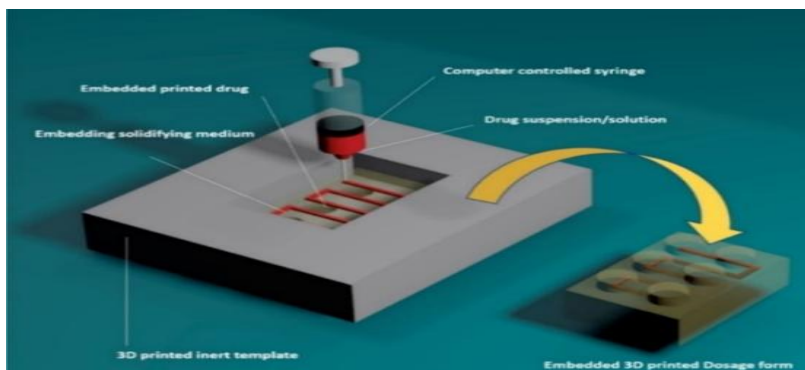


Fig. Embedded 3D Printing (e-3DP)

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 overcoming a difficulty in swallowing.[37] Spritam-R (Anti-epilepsy drug) is an oral dispersible tablet, marketed by Aprezia 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 tab.[38]

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.[39]

APPLICATIONS OF 3D PRINTING

- ✓ Potential use in improving process, modifying performance for industrial design, aerospace, medical engineering, tissue engineering, architecture, pharmaceutical.
- ✓ 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.[40]

Medical applications of 3D printing

Bioprinting of tissues and organs

One of the critical medical issues is the failure of organs and tissues as a result of accident, congenital defects, and the current resolution for this problem is organ transplant from dead or living donors. However, only few fortunate people receive organs and the rest die due to donor shortage. Moreover, the procedures for organ transplants are so expensive that it is out of reach of common people. Another problem with transplant surgery is that donors with tissue match are difficult to find.[41,42]

The solution to this problem lies in the fact that the required tissue or organ should be fabricated using the patient's own body cells, which would decrease the risk of tissue or organ rejection; moreover, the requirement for immunosuppressant will also be greatly reduced.[41,43]

In the conventional method of tissue engineering from a small tissue sample, stem cells are isolated, amalgamated with growth factor, and then multiplied in the laboratory. Then the cells are seeded onto scaffolds that direct cell proliferation and differentiation into a functioning tissue.

Placement of cell with accuracy, digitally controlled speed, drop volume, resolution, concentration of cells and diameter of printed cell are some of the additional advantages that 3D bioprinting offers over traditional tissue engineering.[43,44]

Depending upon the porosity, the type of tissue, and required strength, various materials are present to make the scaffolds. Among all materials,

hydrogels are said to be the most suitable for

building soft tissues.[44,45]

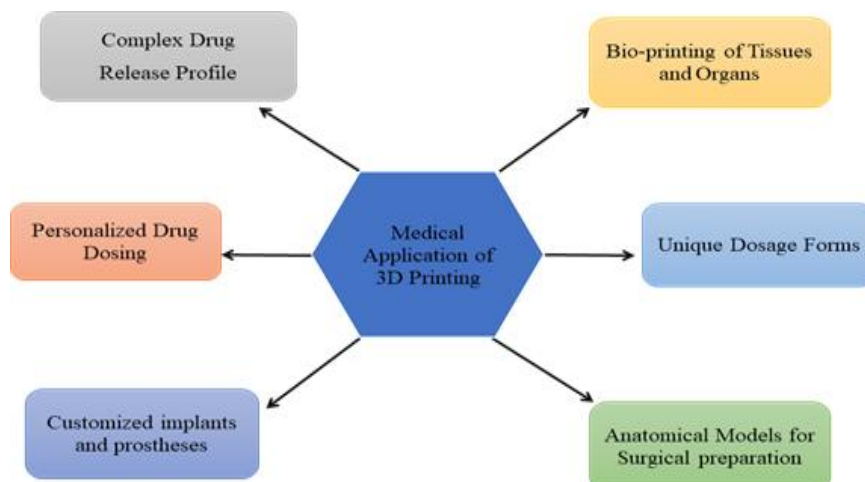


Figure 6.1 : Medical Application of 3D Printing

Unique dosage forms

Infinite dosage forms can be created using 3D printing. Inkjet-based 3D printing and inkjet powder-based 3D printing are the two main printing technologies employed in the pharmaceutical industry. Microcapsules, antibiotic printed micropatterns, mesoporous bioactive glass scaffolds, nanosuspensions, and hyaluronan-based synthetic extracellular matrices are some of the novel dosage forms formulated using 3D printing.[44]

Personalized drug dosing

Increasing the efficacy of drugs and at the same time reducing the chances of adverse reaction should be the aim of drug development, which can be achieved by using 3D printing to fabricate personalized medications.[42,45,46]

Oral tablets are prepared by mixing, milling, and dry and wet granulation of powder ingredients, which are eventually compressed to form tablets; till today, tablets are the most popular dosage form because of the ease of preparation, good patient compliance and accurate dosing and because they are painless. However, no method is available that can prepare personalized solid dosage forms like tablets.

In the traditional way of preparing tablets, drugs can easily undergo degradation if proper guidelines are not followed, leading to altered therapeutic value of the final product. Moreover, these conventional methods cannot be used to prepare customized dosage forms that possess long-lasting stability, novel drug release profile, and detailed geometries.[47]

Drugs with narrow therapeutic index can easily be prepared using 3D printing; and, by knowing the patient's pharmacogenetic profile and other characteristics like age, race etc., optimal dosage can be given to the patient.[44]

Preparation of entirely new formulation is another vital potential of 3D printing for instance fabrications of pills that have a blend of more than one active pharmaceutical ingredient or dispensed as multi-reservoir printed tablets. Hence patients suffering from more than one disease can get their formulation ready in one multi-dose form at the healthcare point itself, thereby providing personalized and accurate dose to the patient with better or best compliance,[47]

Complex drug release profile

In most conventional compressed dosage forms, a simple drug release profile which is a homogenous mixture of active ingredients is observed. Whereas in 3D printed dosage forms, a complex drug release profile that allows fabrication of complex geometries that are porous and loaded with multiple drugs throughout, surrounded by barrier layers that modulate release, is found.[48] One example is the printing of a multilayered bone implant with a distinct drug release profile

In a research concerning drug release profiles, chlorpheniramine maleate was 3D printed onto a cellulose powder substrate in amounts as small as 10–12 moles to demonstrate that even a minute quantity of drug could be released at a specified time. This study displayed improved accuracy for the release of very small drug

doses compared with conventionally manufactured medications.[42]

Sr.No	Active Pharmaceutical Ingredients	Inactive Pharmaceutical Ingredients
1.	Vancomycin	Glycerine
2.	Ofloxacin	Methanol
3.	Folic acid	Acetone
4.	Dexamethasone	Surfactant (like Tween 20)
5.	Theophylline	Kollidon SR

Table 3 - List of Active & in-Active ingredient used in 3D printing

Customized implants and prostheses

By the support of MRI, CT scan, and X-ray and its translation into 3D print files, implants and prostheses of any possible shape can be made.[45,49,50]

Standard as well as complex surgical implants and prosthetic limbs can be made as per need in time as less as 24 hours. Spinal dental and hip implants have been fabricated so far but their validation is a time-consuming process. Previously, in order to achieve a desired shape and size that fits perfectly, surgeons had to craft metal and plastic pieces and perform bone grafting or use drill machines to modify the implants.[44,49] This also stands correct in neurosurgery cases due to the irregular shape of the skull whose standardization is a complex procedure.

Some examples of commercially and clinically successful 3D printed implants and prostheses are as follows:

- A. First 3D printed titanium mandibular prosthesis was implanted successfully at BIOMED Research Institute in Belgium.[48]
- B. Dental, orthopedic, maxillofacial, and spinal implants are manufactured by a company named Layer Wise.[45]
- C. Invisalign braces is another successful commercial use of 3D printing

By using silver nanoparticles, chondrocytes, and silicon, a prosthetic ear was made out of 3D printing technology that was able to detect electromagnetic frequencies. The impact of this technology is so extensive in the field of hearing aids that today 99% of customized hearing aids are made using 3D printers, because, as everyone's ear canal has a different shape, this technology is able to provide perfect fit for each receiver and, moreover,

the devices can be produced efficiently and cost effectively.[49]

6.6 Anatomical models for surgical preparations

In order to have successful medical procedures, knowledge about patients' specific anatomy before medical surgery is essential due to variations in individual and complex human anatomy. 3D printed models have helped extensively in this respect, making them a vital tool for surgical methods.[45,48]

One of the most complicated structures of human body is the head, whose 3D printed neuro-anatomical models are of great help to neurosurgeons. Sometimes, it is very difficult to gain detailed information about the connections between skull architecture, cerebral structure, cranial nerves, and vessels from radiographic 2D images only and even a slight error in the medical procedure can be fatal. Here comes the role of 3D models, which are more realistic and provide in detail comparison and contrast between a normal brain structure and a brain with deformity or lesions, which suggest the surgeons more safe procedures to follow

- For liver transplant, Japan's Kobe University Hospital had used 3D printed models by using replica of patients' own organ, to find out how to precisely craft a donor liver with least tissue loss.[48]
- 3D printed model of calcified aorta for surgical planning of plaque removal was used by surgeons.[45]
- To study aerosol drug delivery to lungs, airways of premature infants was reconstructed using 3D printing technology.[45]

7. 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.

8. Disadvantages of 3D Printed Drug Delivery

- ✓ 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 adaptations and ink formulations effects.

9. Current challenges in drug development

- ✓ The overall challenges for pharmaceutical industries are paramount regarding successful infusion of new drug molecules or medicaments into the market.[50] The rate of approval of drugs is very limited; hence it becomes necessary for scientists to identify suitable drugs promptly using preclinical or clinical studies during early phase of drug development process. In low cost, there are multiple formulations to support flexible bioavailability with easy administration. But drug solubility and stability are a big concern for materializing new drug into a novel formulation,[51]

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