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APPLICATION OF 3D PRINTING IN PHARMACEUTICAL INDUSTRY

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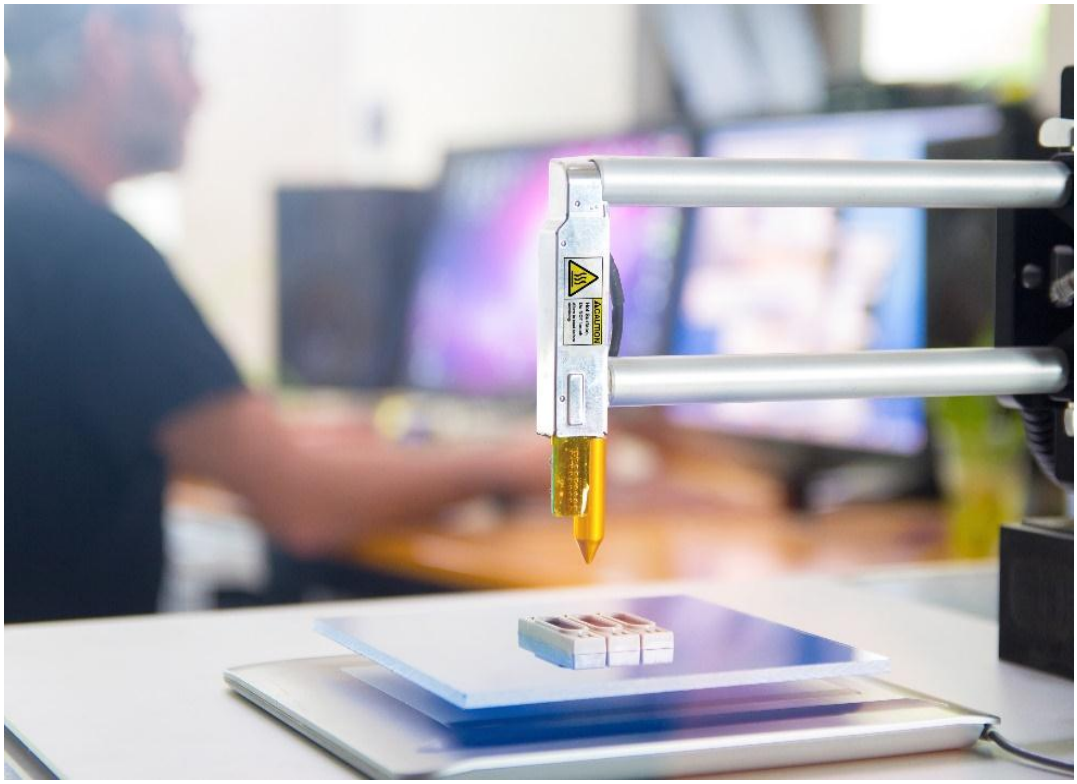
ABSTRACT

The pharmaceutical enterprise is shifting beforehand at a fast pace. Modern science has enabled the improvement of novel dosage varieties for focused therapy. However, the fabrication of novel dosage varieties at industrial scale is confined and the enterprise still runs on traditional drug shipping systems, specifically modified tablets. The introduction of 3D printing science in the pharmaceutical enterprise has opened new horizons in the lookup and development of printed substances and devices. The main advantages of 3D printing technological know-how lie in the manufacturing of small batches of medicines, every with tailor-made dosages, shapes, sizes, and launch characteristics. The manufacture of drug treatments in this way might also eventually lead to the thinking of customized medicines turning into a reality. This chapter gives an overview of how 3D printed technology has prolonged from preliminary unit operations to developed remaining products. The vast spectrum of purposes of third-dimensional printing (3D printing, 3DP) has attracted the interest of researchers working in numerous fields. In pharmaceutics, the essential concept at the back of 3D printing merchandise is to graph and advance transport structures that are suitable to an individual's needs. In this way, the size, appearance, shape, and charge of shipping of a broad array of drug treatments should be without problems adjusted. The goal of this chapter is to supply a compilation of the 3D printing techniques, used for the fabrication of oral drug transport systems, and assessment the applicable scientific tendencies in precise these with modified-release characteristics.

KEYWORDS: 3D print, personalized medicines, manufacturing, drug delivery, Computer-aided design.



➢ INTRODUCTION

There is a continuing motivation towards new concepts in drug design, better understanding of fabric properties, manufacturing technology and processes that assures prime quality of dosage forms. The range of physicochemical and biopharmaceutical characteristics of active pharmaceutical ingredients (APIs) must be considered and studied through each stage of development. Auxiliary substances must be examined furthermore so as to manufacture of the required dosage form.

Within last decade the patient-centric drug development has been under considerable attention. It had been focused on novel dosage forms and technological processes. Growing demand for customized devices combined with an expansion of technological innovation drives the most important progress in personalized medicine expressed e.g., by the assembly of small series of individually-selected doses and tailor-made prostheses meet the anatomical needs of patients. Within many discoveries introduced into pharmaceutical and biomedical market, three-dimensional printing (3DP) is believed to be the foremost revolutionary and powerful. This method is recognized as a flexible tool of precise manufacturing of varied devices. It is a technology for developing novel dosage forms, tissues and organs engineering additionally as disease modeling.

Nowadays, three-dimensional printing is one in all the fastest developing branch of technology, art and science, and still broadens the applications. The term three-dimensional printing was defined by International Standard Organization (ISO) as: "fabrication of objects through the deposition of a fabric employing a print head, nozzle, or another printer technology". In contrast to commonly used subtractive and formative manufacturing methodologies, this system is one in all the methods of additive manufacturing (AM) during which the parts are prepared from 3D model data within the process of joining materials layer by layer. The sensible approach of AM is named rapid prototyping (RP)[1] and its advantages include the reduction of prototyping time and costs, easy modifications of a product at a designed level, the chance of producing of small objects, individualized product series or structures impossible to be formed with subtractive techniques.[2]

The application of 3D printing within the science and engineering has grown since 2012. the number of scientific papers recorded in Web of Science Core Collection containing a term "3D printing" or "3D printed" within the title increased from 59 in 2012 to 1573 in 2017. Moreover, the number of citations of those papers within the same period grown from 209 to 12,411. Narrowing the searching results to the category of pharmacy/pharmacology gives no end in 2012, however 77 records were found up to 2017, which also shows a good interest within the 3DP methods in pharmaceutical sciences.

This review is geared toward the latest development and achievements within the field of pharmaceutical and biomedical research from the literature items that are published within the last 3 years. The novel approaches within the formulation of solid dosage forms for individualized therapy are particularly focused, however transdermal drug delivery moreover as biomedical applications of additive manufacturing technique including implants, surgical models, bio printed materials and bio robotics are mentioned. The parallel development of additive manufacturing employed in pharmaceutical technology and bioprinting is summarized and compared with a special effort made to entails the evolution of bioprinting. because of the very fact that the pharmaceutical applications of additive manufacturing are on the first stage of development and implementation not many regulatory is out there however the important issues that are introduced by the FDA in 2017 are mentioned.

➢ History of 3D printing

The concept of 3DP has developed from early 70′ of the twentieth century when Pierre A. L. Ciraud described the technique of application of powdered fabric and subsequent

solidification of every layer thru the motion of excessive strength beam.[3] In this case meltable substances such as plastics or metals can be theoretically used for object preparation. In early 80′ in a patent entitles: BA molding manner for forming a three-dimensional article in layers^, Ross Householder described an idea of sand binding by using unique substances and Carl Deckard developed a technique of solidification of powdered mattress by means of laser beam known as selective laser sintering (SLS).[4] The first commercially handy science created by Chuck Hull was once stereolithography (SLA). This approach was based on photopolymerization of liquid resin by means of ultraviolet light. At the cease of 80's Scott Crump filed a patent for fused deposition modelling (FDM) – a approach which used thermoplastic cloth for object preparation. In the 90's Emanuel Sachs - MIT scientist with co-workers patented B Three-dimensional printing techniques^ primarily based on joining the chosen areas of powder by using binding fabric. The most vital achievements in 3D printing in pharmaceutical and biomedical functions are introduced.

- **3D Printing procedure**

First, a digital 3D format of an object the use of digital diagram software program like Onshape, Solidworks, Creo parametric, Autocade, Autodesk etc. is created.[2,4,5]

↓

This digital mannequin is then transformed to (.STL) digital file layout which stands for widespread tessellation language or stereolithography.[6]

↓

Triangulated sides supply records related to the floor of the 3D mannequin that is current in the (.STL) file.[7,8]

↓

The (.STL) file is transformed into G file through cutting the format into a sequence of 2D horizontal cross-sections by using the assist of specialized slicer software, which is established in the 3D printer.

↓

Historical development in the field of 3D printing (table adapted from Ref.[9]

↓

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 cross in the z-axis, thereby depositing the layers sequentially of the preferred material, subsequently growing a whole 3D object.[22]

Maximum numbers of 3D printing applied sciences are like minded with (STL) file format. Some mistakes would possibly show up throughout the conversion of the 3D mannequin to. STL digital file; therefore, software program like Magics (Materialise) can be employed to right the blunders at some point of conversion. File codecs different than. STL like additive manufacturing file layout (AMF) and 3D manufacturing layout (3MF) are used as. STL does now not have statistics related to the kind of material, its color, texture, properties, and different elements.[18]

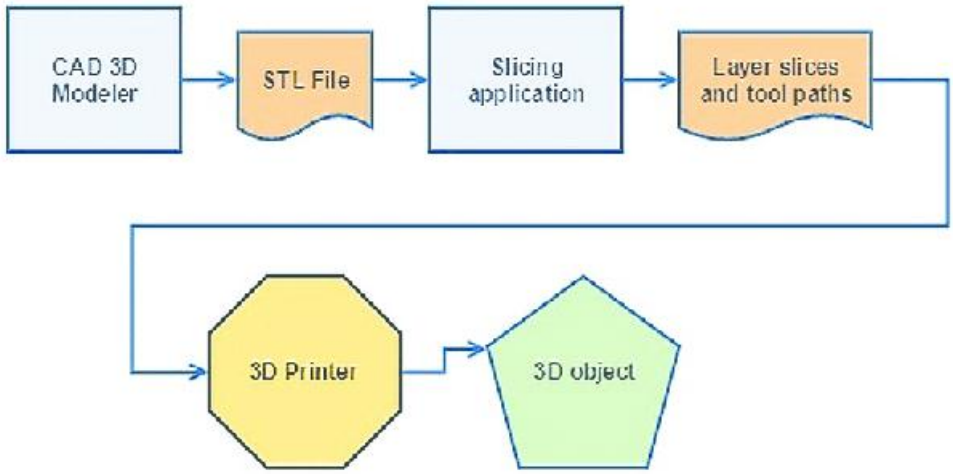


Fig. 3D: Printing process.

Year major development

1980 → Dr. Hideo Kodama filed first patent for RP technology

1984 → Stereo lithography equipment (SLA) was once invented with the aid of Charles Hull

1986 →Carl Deckard invented equipment for producing components through selective sintering

1989 → Patent was once granted to Carl Deckard for SLA

1990 →Fused deposition modeling (FDM)

1992 →First SLA desktop used to be produced the use of 3D system

1993 →3D printing patent used to be granted to E.M Sachs

1996 →Clinical utility of biomaterials for tissue regeneration

1999 → Luke Massella acquired first 3D printed bladder which was once an amalgamation of 3D printed biomaterials and his very own cells

2000 → MCP applied sciences added the SLM technology

2002 → Miniature purposeful kidney used to be fabricated

2003 →Term organ printing was once coined

2004 → Dr. Bowyer conceived the RepRap idea of an open-source, self-replicating 3D printer

2005 → First coloration 3D printer used to be added with the aid of Z Corp

2007 → Selective layer customization and on-demand manufacturing of industrial parts

2009 →Organovo, Inc., introduced the launch of information on the first utterly bioprinted blood vessels

2011 → 3D printing used to be utilized in gold and silver

World's first 3D printed car, robotic aircraft used to be introduced

2012 → Extrusion-based bioprinting for a synthetic liver

3D printed prosthetic jaw used to be implanted

2013 →Solid Concepts produced a 3D printed steel gun

2014 → Implementation of multi-arm bioprinter to combine tissue fabrication with printed vasculature

2015 → First 3D printed tablet was once permitted with the aid of US FDA

Organovo introduced the launch of facts on the first totally bio printed kidney.

Historical improvement in the area of 3D printing.

Table 1: Pharmaceutical preparations that have been developed with the aid of 3DP technology.

3D printing technology used	Formulations	API	Ref.
Semi-solid extrusion (SSE)	Bi-layered tablets (polypill)	Guaifenesin	[12]
	Multiactive tablets (polypill)	Nifedipine, Glipizide, and captopril	[13]
Stereolithography (SLA)	Hydrogels	Ibuprofen	[14]
	Facial mask	Salicylic acid	[15]
Selective layer sintering (SLS)	Tablets	Paracetamol	[16]
	Drug delivery device	Progesterone	[17]
Fused deposition modeling (FDM)	Caplets	Caffeine	[18]
	Tablets	Hydrochlorothiazide	[19]
	Oral films	Aripiprazole	[20]
Binder jet printing	Tabular devices	Methylene blue and alizarin yellow (dyes)	[21]
	Cubic tabular devices	Pseudoephedrine	[22]
	Tablets	Chlorpheniramine meleate and fluorescein	[23]
	Orodispersible tablets	Levetiracetam	[24]
Inkjet 3D printing	Implant	Levofloxacin	[25]
3D printing machine	Multidrug implant	Rifampicin and isoniazid	[26]

Inkjet 3D printing	Nanosuspension	Folic acid	[27]
Thermal inkjet (TIJ) printing	Solution	Salbutamol sulfate	[10]
Inkjet 3D printing	Nanoparticle	Rifampicin	[11]

➢ **Types of 3D printing technology**

I) Fused deposition modeling (FDM)

The method entails the resolution of the favored polymer, which is melted and compelled thru a movable heated nozzle. Along the whole three axes (i.e., x-y-z), the polymer is laid down layer by way of layer, which on solidification offers the specific structure as was once designed by way of pc aided sketch models. Multiple dosage varieties like implants, zero-order launch drugs etc. that encompass polymer as a phase of their system can be made with the aid of this approach.[9,21,30,31]

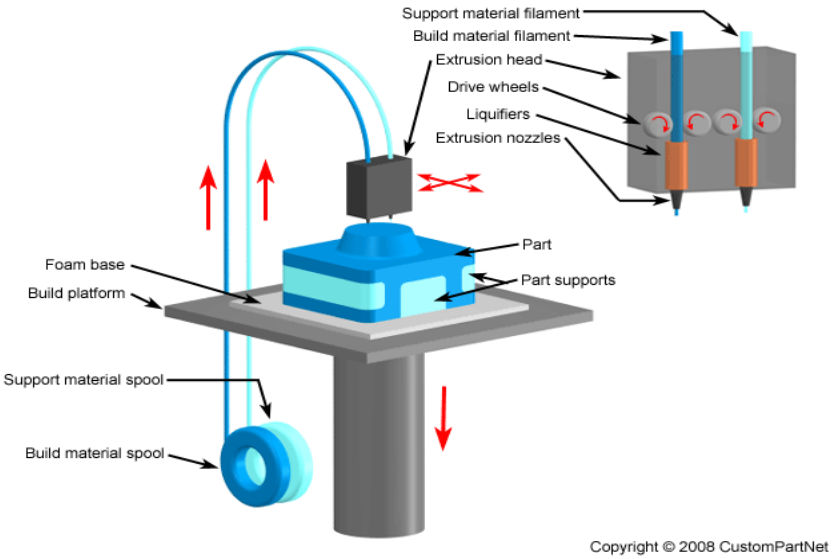


Fig. Fused deposition modeling for 3D printing.

Ⅱ) Thermal inkjet (TIJ) printing

It entails the heating of ink fluid with the aid of the assist of micro-resistor, thereby developing a bubble of vapor that nucleates and upon growth forces the ink to drop out of the nozzle. Dispensing of extemporaneous preparation/solution of drug onto 3D scaffolds is a region the place this method can be employed.[22,23]

Fig: Thermal inject printer.

Ⅲ) Inkjet printing

It is a powder-based 3D printing that makes use of powder as a substrate on which layer by means of layer specific mixtures of energetic components and ink is sprayed which is of various droplet dimension that finally solidifies into stable dosage structure.[9,19,24,25,26,27,32]

Fig. Inject printer used in pharmaceutical industry.

Ⅳ) Direct-wise

It encompasses a pattern-generating machine that strikes as per the preparation of computer-controlled translational stage so that layers after layers are put on in order to gain a 3D microstructure.[33,34]

Ⅴ) Zip dose

This science presents a personalized dose in extra to the shipping of an excessive drug-load with excessive disintegration and dissolution degrees by using manufacturing fantastically porous cloth.[35]

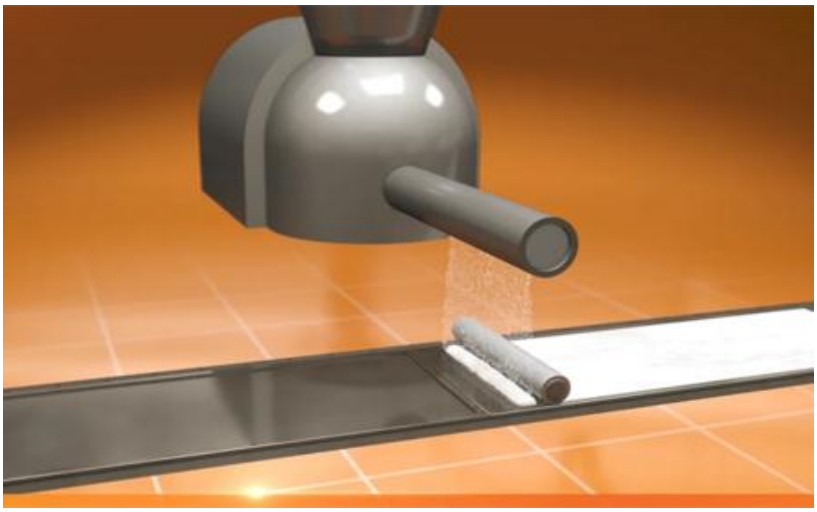


Fig: Zip dose technology.

Ⅵ) Vat photopolymerization

It is light-induced polymerization the place substances like photopolymers, radiation-curable resins, and liquid are accumulated in vats, which are successively cured into layers, one layer at a time by using irradiating with a mild source, thereby supplying a 2D patterned layer. This entails strategies such as stereolithography (SLA), digital mild processing (DLP), and non-stop direct mild processing (CDLP).[36,37,38]

Depending on the orientation of mild supply and the floor the place polymerization of the photoactive resin occurs, SLA can be divided into two specific configurations:

1. Bath configuration (free floor approach)
2. Bat configuration (constrained floor approach).

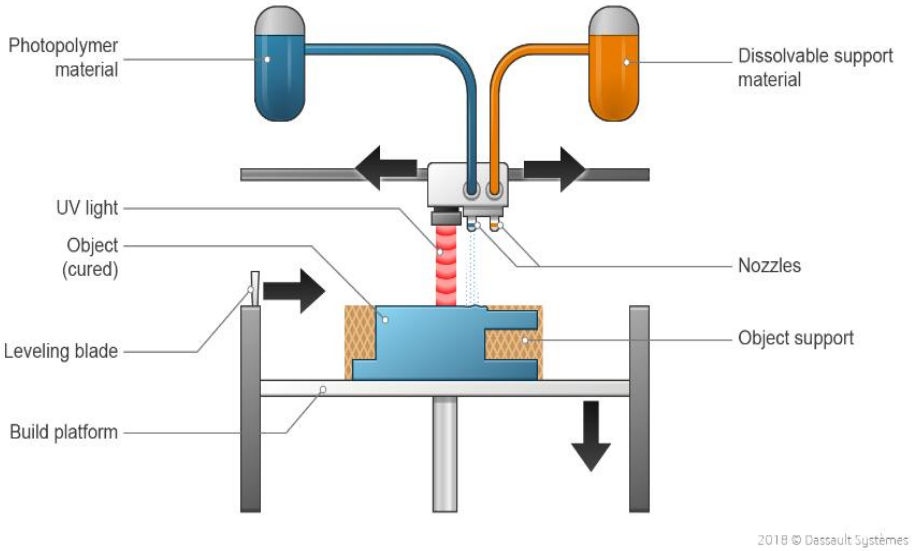


Fig: Photopolymerization technique.

- **Advantages of 3D printing in the pharmaceutical field**

1. **Enhanced productivity:** 3D printing works extra rapidly in distinction to normal techniques specifically when it comes to fabrication of objects like prosthetics and implants with an extra advantage of higher resolution, repeatability, greater accuracy, and reliability.[39]
2. **Customization and Personalization:** One of the pioneer advantages of this science is the liberty of fabrication of personalized scientific tools and products. Customized implants, prosthetics, surgical tools, fixtures can be a brilliant boon to sufferers as properly as medical practitioner.[40]
3. **Increased fee efficiency:** Objects produced by using 3D printing are of low cost. It is an benefit for small-scale manufacturing gadgets or for agencies that produce pretty complicated products or components due to the fact nearly all substances are less expensive.[41,42]
4. By eradicating the use of pointless resources, manufacturing fee can additionally be reduced. For instance, 20-mg drugs ought to be probably formulated as 1-mg capsules as per want.[19]
5. 3DP permits managed dimension of droplets, complicated drug launch profiles, electricity of dosage and multi-dosing.[43,44,45]

➢ **Disadvantages of 3D printing**

1. In inkjet printing, desirable go with the flow of ink can solely be accomplished with ink that has unique viscosity.[46]
2. Ink method cloth need to have the property of self-binding however need to know not bind to different
3. printer elements. In some formula when the ink does now not possess ample self-binding property or it binds with different factors of printer then the resultant system does no longer have required hardness.[47,48]
4. Rate of drug launch might also get affected due to binding of ink with different printer substances.[49,50]

➢ **Medical applications of 3D printing**

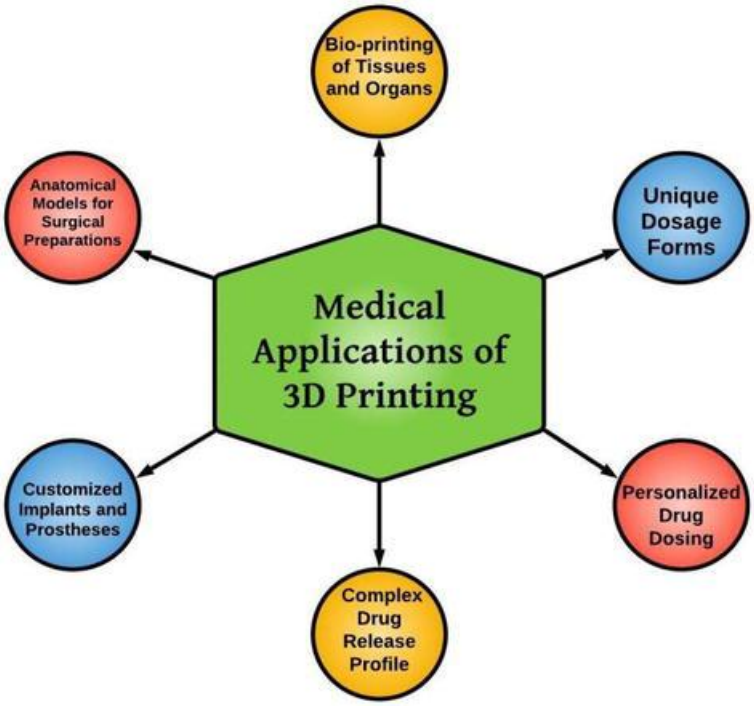
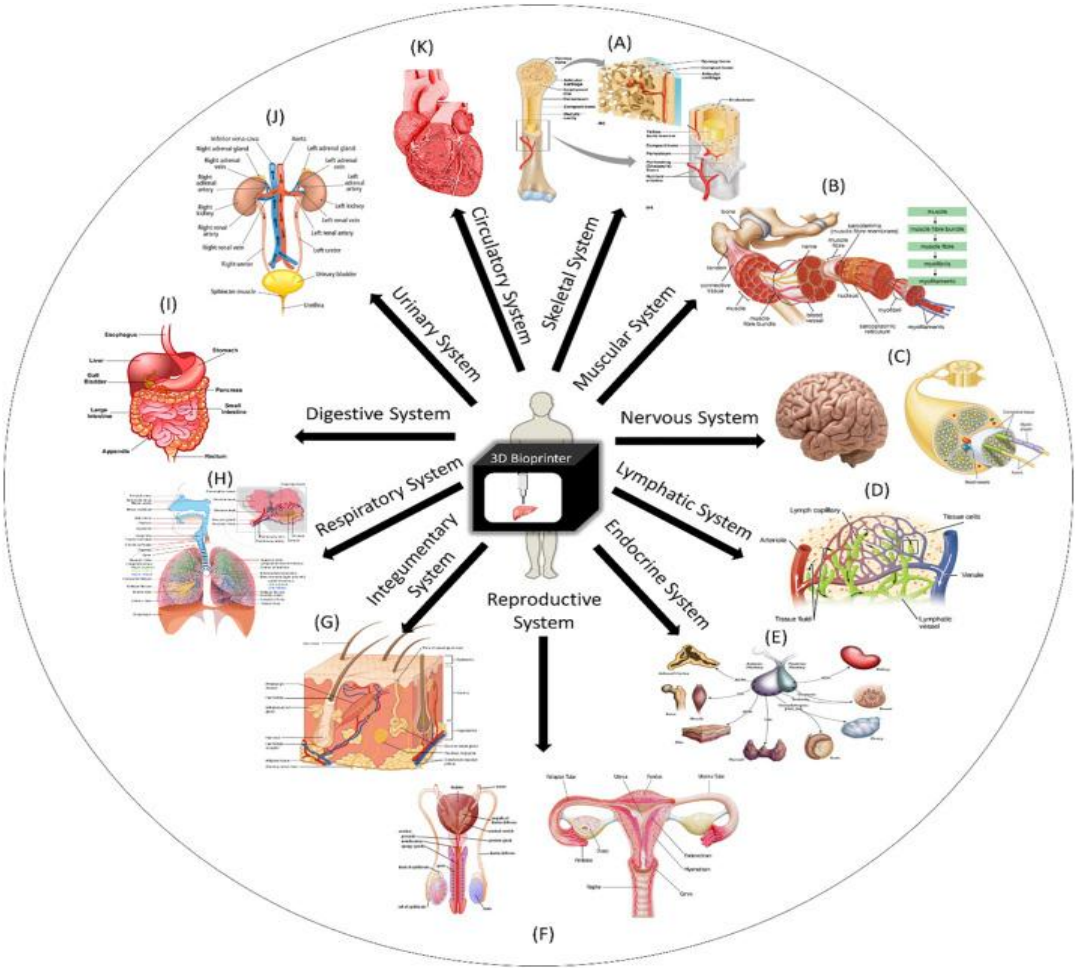


Figure: Different medical applications of 3D printing technology.

i) Bioprinting of tissues and organs

One of the essential scientific troubles is the failure of organs and tissues as a end result of accident, congenital defects, ageing and so forth (Figure 1) and the present day decision for this trouble is organ transplant from lifeless or dwelling donors. However, solely few lucky human beings get hold of organs and the relaxation die due to donor shortage. Moreover, the processes for organ transplants are so high-priced that it is out of attain of frequent people.

Another hassle with transplant surgical operation is that donors with tissue healthy are challenging to discover.[7,51]



The answer to this trouble lies in the reality that the required tissue or organ must be fabricated the use of the patient's personal physique cells, which would reduce the hazard of tissue or organ rejection; moreover, the requirement for immunosuppressant will additionally be noticeably decreased.[7,52] In the traditional approach of tissue engineering from a small tissue sample, stem cells are isolated, amalgamated with increase factor, and then extended in the laboratory. Then the cells are seeded onto scaffolds that direct mobile phone proliferation and differentiation into a functioning tissue. Placement of mobile phone with accuracy, digitally managed speed, drop volume, resolution, attention of cells and diameter of printed phone are some of the extra benefits that 3D bioprinting presents over standard tissue engineering.[2,53] Depending upon the porosity, the kind of tissue, and required strength, a range of substances are current to make the scaffolds. Among all materials, hydrogels are stated to be the most appropriate for constructing tender tissues.[2,54]

No doubt that organ printing is nevertheless in the section of improvement however various researches have validated its thought with proof. Scientists have constructed an synthetic ear, cartilage and bone, and coronary heart valve via the assist of 3D printers.[2,47,55] Wang et al. used 3D bioprinting technological know-how to credit score special cells inside more than a few biocompatible hydrogels to produce an synthetic liver.[56]

As with the growing activity of researcher and academician and with substantial workable of this technological know-how it can perhaps unfold new possible therapeutic capsules thereby substantially slicing lookup value and time.[57]

ii) Unique dosage forms

Infinite dosage types can be created the usage of 3D printing. Inkjet-based 3D printing and inkjet powder-based 3D printing are the two important printing applied sciences employed in the pharmaceutical industry. Microcapsules, antibiotic printed micropatterns, mesoporous bioactive glass scaffolds, nanosuspensions, and hyaluronan-based artificial extracellular matrices are some of the novel dosage varieties formulated the usage of 3D printing.[58]

Table 2: List of Active and Inactive ingredients used in 3D printing.

Active pharmaceutical ingredients	Inactive pharmaceutical ingredients
Vancomycin	Glycerin
Ofloxacin	Methanol
Folic acid	Acetone
Dexamethasone	Surfactants (like Tween 20)
Theophylline	Kollidon SR
Acetaminophen	Ethanol-dimethyl sulfoxide
Paclitaxel	Propylene glycol
Tetracycline etc.	Cellulose etc.

Ⅲ) Personalized drug dosing

Increasing the efficacy of tablets and at the equal time decreasing the possibilities of damaging response ought to be the goal of drug development, which can be performed by using the use of 3D printing to fabricate personalized medicines.[7,26,59]

Oral capsules are organized by using mixing, milling, and dry and moist granulation of powder ingredients, which are sooner or later compressed to shape tablets; until today, capsules are the most famous dosage structure due to the fact of the ease of preparation, correct affected person compliance and correct dosing and due to the fact, they are painless.

However, no approach is reachable that can put together customized stable dosage varieties like tablets.

In the regular way of getting ready tablets, capsules can without difficulty endure degradation if applicable hints are no longer followed, main to altered therapeutic cost of the closing product. Moreover, these traditional techniques can't be used to put together custom-made dosage varieties that possess long-lasting stability, novel drug launch profile, and designated geometries.[60]

Drugs with slim therapeutic index can without problems be organized the use of 3D printing; and, through understanding the patient's pharmacogenetic profile and different traits like age, race etc., most reliable dosage can be given to the affected person.[61]

Preparation of absolutely new formula is some other critical workable 3D printing for occasion fabrications of drugs that have a combination of greater than one lively pharmaceutical ingredient or allotted as multi-reservoir printed tablets. Hence sufferers struggling from extra than one ailment can get their system equipped in one multi-dose shape at the healthcare factor itself, thereby imparting customized and correct dose to the affected person with higher or fine compliance.[62]

Ⅳ) Complex drug launch profile

In most traditional compressed dosage forms, a easy drug launch profile which is a homogenous combination of lively substances is observed. Whereas in 3D printed dosage forms, a complicated drug launch profile that lets in fabrication of complicated geometries that are porous and loaded with a couple of pills throughout, surrounded with the aid of barrier layers that modulate release, is discovered.[63] One instance is the printing of a multilayered bone implant with a awesome drug launch profile alternating between rifampicin and isoniazid in a pulse launch mechanism. 3D printing has additionally been used to print antibiotic micropatterns on paper, which have been used as drug implants to eradicate Staphylococcus epidermidis.[64]

In a lookup regarding drug launch profiles, chlorpheniramine maleate was once 3D printed onto a cellulose powder substrate in quantities as small as 10–12 moles to display that even a minute extent of drug ought to be launched at a distinctive time. This find out about displayed

accelerated accuracy for the launch of very small drug doses in contrast with conventionally manufactured medicinal drugs.[65]

V) Customized Implants and Prostheses

By the assist of MRI, CT scan, and X-ray and its translation into. stl 3D print files, implants and prostheses of any viable form can be made.[1,7,66] Standard as nicely as complicated surgical implants and prosthetic limbs can be made as per want in time as much less as 24 hours. Spinal dental and hip implants have been fabricated so some distance however their validation is a time-consuming process. Previously, in order to obtain a preferred structure and dimension that matches perfectly, surgeons had to craft metal and plastic portions and operate bone grafting or use drill machines to adjust the implants.[2,7] This additionally stands right in neurosurgery instances due to the irregu[1] lar structure of the cranium whose standardization is a complicated procedure.

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

a. First 3D printed titanium mandibular prosthesis was once implanted efficaciously at BIOMED Research Institute in Belgium.[1]
b. Dental, orthopedic, maxillofacial, and spinal implants are manufactured through a company named Layer Wise.[67]
c. Invisalign braces is every other profitable industrial use of 3D printing.

By the usage of silver nanoparticles, chondrocytes, and silicon, a prosthetic ear was once made out of 3D printing technological know-how that used to be capable to notice electromagnetic freiquencies. The have an impact on of this technological know-how is so significant in the area of listening to aids that nowadays 99% of custom-made listening to aids are made the use of 3D printers, because, as everyone's ear canal has a exceptional shape, this science is capable to supply best fit for every receiver and, moreover, the gadgets can be produced correctly and price effectively.[7]

VI) Anatomical fashions for surgical preparations

In order to have profitable scientific procedures, understanding about patients' specific anatomy earlier than clinical surgical operation is necessary due to variants in character and complicated human anatomy. 3D printed fashions have helped appreciably in this respect, making them a quintessential device for surgical techniques.[1,68] One of the most complex

constructions of human physique is the head, whose 3D printed neuro-anatomical fashions are of exquisite assist to neurosurgeons. Sometimes, it is very hard to attain exact facts about the connections between cranium architecture, cerebral structure, cranial nerves, and vessels from radiographic 2D.

➢ 3D Printing in pharmaceutical sector

Images solely and even a mild error in the clinical technique can be fatal. Here comes the function of 3D models, which are extra sensible and grant in element comparison and distinction between a ordinary intelligence shape and a Genius with deformity or lesions, which propose the surgeons greater protected methods to follow.

- For liver transplant, Japan's Kobe University Hospital had used 3D printed models by means of the use of reproduction of patients' personal organ, to discover out how to exactly craft a donor liver with least tissue loss.[1]
- 3D printed mannequin of calcified aorta for surgical planning of plaque elimination was used with the aid of surgeons.[69]
- To find out about aerosol drug transport to lungs, airways of untimely children was once reconstructed the usage of 3D printing science.[70]

➢ CONCLUSION

3D printing science is a treasured and conceivable device for the pharmaceutical sector, main to personalized remedy centered on the patients' needs. It affords several advantages, such as increasing the price effectivity and the manufacturing speed. 3D printing has revolutionized the way in which manufacturing is done. It improves the format manufacturing and reduces lead time and tooling value for new products. 3D printing has already mounted itself as an innovative platform for the fabrication of medical units and drug products. 3D printing has proven top notch flexibility in producing dosage types for customized regimens to patients. This technological know-how will solely develop in addition and shape the future of healthcare and patient centric drug transport.

The introduction of additive manufacturing into a clinic reduces the time and fees of scientific cure and improves the success charge of surgeries. It may also additionally lead to the development of new surgical procedures, mainly regarding these unstable and rarely performed. Moreover, 3D printing of notably mimetic models of organs for surgical coaching can ease and shorten operation time and limit the intraoperative complications. The use of

residing cells allows formation of biomaterials for reproducing vascularized tissues that can be used for implantation, drug screening as nicely as disorder modelling and cancer research. The improvement of biorobots opens a new scope of the improvement of sensors relying on physiological changes experienced with the aid of cells or even synthetic immune system. Giving all the advantages, additive manufacturing wishes to various challenges in phrases of layout parameters control, device performance, biocompatibility of printed cloth and sterilization. Furthermore, the fragile nature of printed objects, especially cell-based blended with complicated nature of manufactured buildings requires well-planned procedure. However, all advantages for sufferers and usual healthcare system supplied by using the implementation of 3D printing makes the amount of required lookup main to organizing the process of custom-made merchandise manufacturing reasonable.

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