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Exploring the Frontiers of 3D Printing: Current Trends and Emerging Applications

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Abstract:

The review focuses on how 3D printing has affected the pharmaceutical sector. It offers the flexibility to alter drug and dosage information as well as the required cost of drug production. Pharmaceutical manufacture uses a variety of 3D printing technologies, including hot melt extrusion, bioprinting, and stereolithography. Texts that are tailored to the requirements of the user can be created thanks to technology. Because it makes the process of producing active pharmaceutical substances easier, it also has numerous positive effects on medication development. In this discipline, using bioprintedorganoids for experimental observations is a significant first step. Dental implants and pacemakers are among the medical items that are manufactured using 3D printing. This overview outlines the development of 3D printing in the pharmaceutical sector as well as its potential for the future. It also discusses the legal aspects of 3D printing. There is also discussion on advancements in 4D and 5D printing. Using layers based on patterns, three-dimensional printing (3DP) is a novel technology that makes 3D items. The pharmaceutical business has witnessed a surge in the use of 3D printing technology, which is transforming the process of designing and producing novel medical devices and equipment. The technology gained a lot of attention when the FDA authorized Spiratam® (levetiracetam), the first commercially available 3D-printed tablet, in August 2015.

Key Words: 3D Printing, Stereolithography, Hot Melt Extrusion, Bioprinting, Pharmaceutical Industry, Medical Products.

Introduction:

Medical preparations have been made and manufactured for hundreds, if not thousands, of years. The fundamental procedure for making tablets and capsules hasn't changed in more than a century, despite advancements in manufacturing. Process analytical technology (PAT) and continuous production have been used in recent years to modernize the pharmaceutical manufacturing industry. However, the creation, production, and delivery of drugs have undergone significant changes since the advent of three-dimensional (3D) printing. Large-scale paper manufacture made possible by 3D printing allows for previously unheard-of levels of personalization for medication distribution and release. [1] By facilitating the development of digital processes, regulatory reviews, product modifications, and new drug development, this new strategy has the potential to completely change the pharmaceutical sector. Computer-aided design frequently provides information (CAD).In 1993, 3D printing was used for the first time in medicine. Improvements in patents and advertising show that this agreement spurred more funding and study in this area. six of the seven techniques for 3D printing. Physicians can theoretically utilize all six procedures, but the application of some is restricted by specific materials and products (e.g., barrel polymerization produces free radicals). [2] Because of its ease of use, fused deposition modeling, or FDM, is the approach most frequently employed in preliminary research and development projects. However, the uses of chemical filaments are limited due to difficulties in generating them with adequate and acceptable chemical characteristics. For self-dosing, extrusion-based 3D printing techniques like FDM, semi-solid extrusion, and direct powder extrusion are widely utilized.Large-scale production has embraced techniques including screen printing, melt extrusion deposition, and powder inkjet deposition, which are better suited for commercial production. [3]

The use of 3D printing technology in medicine offers a previously unheard-of chance to produce novel forms like pills and implants with odd shapes and negative effects. Without requiring the modification of specialized tools or equipment, the technology offers the freedom to create images and models based on CAD design. With minimal major changes to the manufacturing process, this capacity offers versatility in drug delivery, allowing control over the rate, shape, onset, and location of drug release. [4] Dosage forms can have different structures, from simple porous structures to layered or multidimensional structures with different geometries. The final 3D printing process allows drug release properties to be controlled by controlling the amount of processing, changing the design process and construction through testing and errors with no difference to what has been done previously. Lean and continuous processes ensure that the design process is always designed sequentially. This capability, combined with PAT application and online packaging, ensures fast delivery. Additionally, the 3D printer production line is digital in nature, supporting machine analysis and data generation to support management control. [5]

Personal-use 3D printing technology is currently undergoing early testing in demonstrations in Europe, China and Singapore. Although self-administration of drugs can be achieved through pre-planning or in-hospital planning, the regulatory framework for self- administration of drugs by 3D printing has not yet been clearly defined in these areas. Ensuring the quality of private property remains a major challenge. Both the United States Pharmacopoeia (USP) and the US FDA have established forums to discuss and develop standards to address these issues. For the large commercial sector of the 3D printing industry,the product complies with the usual approval rulesA number of Investigational New Drug (IND) applications for 3D-printed medications have been approved for human clinical trialsin China and the United States, in addition to the Spritam product that has been approved. [6]

The rise in IND applications suggests that, due to their special qualities that make prescription medications difficult or expensive to create, 3D printed drugs may soon be used in clinical settings. The use of self-medication will continue to be investigated or restricted until quality criteria, recommendations, and standards are developed by medical researchers, the medical community, government agencies like the FDA, and standards groups like the USP. Pharmaceutical equipment for use in medicine will continue to be developed, both commercially and privately. As a digital process, 3D printing is used for manufacturing and designing drugs as well as for the production of quantitative procedures from CAD. [7] The useof 3D printed goods will probably rise as the pharmaceutical and medical industries adoptthis technology, much as electronic media will someday rival or be published alongside traditional printed prints. Teaching patients about community health services can alter their behavior, enabling more individual consumption by lowering patient prescriptions and dosages. A new business ecosystem can be created by combining 3D printing with other technologies like blockchain, cloud computing, electronic medical records, real-time PAT, and the Pharm 4.0 framework. The ecosystem can increase the capacity for health care, distribution, production, and product design. Additionally, 3D printers can be managed and controlled from a single hub. Due of its compact size, the 3D printer can be used for a variety of purposes, including emergency situations. 3D printing, a technology with many unique advantages, has the potential to revolutionize healthcare. [8]

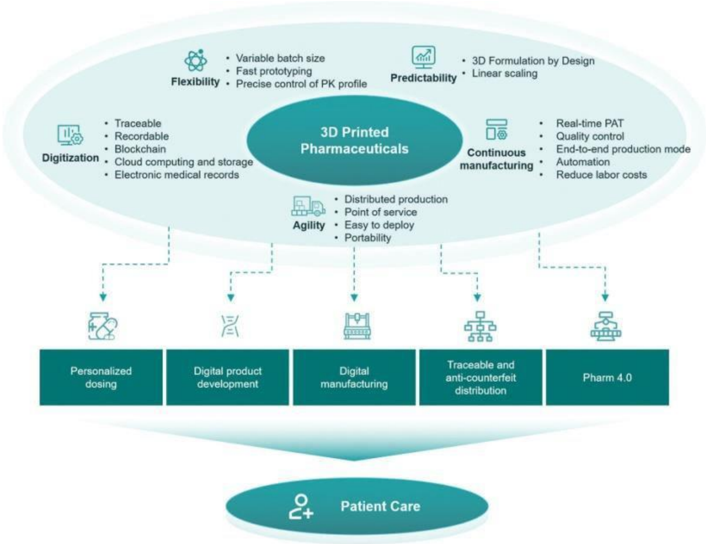


Figure 1 3D Printing in Pharmaceutics

- **Technology classification for 3D printing**

3D printing is a term that frequently refers to additive manufacturing, product freeform technology, or fast prototyping combined. Technologies based on computer-aided and computer-aided design (CAD) software are referred to by both of these words interchangeably. The American Society for Testing and Materials (ASTM) developed standard designs for a range of goods, machinery, and equipment in order to create the first standards for 3D printers. Layering and deposition procedures. ASTM divides this technology into seven categories: extrusion equipment, powder bed fusion, aircraft equipment, adhesives, polymerization, energy deposition, and paper lamination. Figure 2 shows various types of 3D printing technology. [9]

1.Stereolithography
2.Material Extrusion
3.Binder jet printing
4.Powder bed fusion
5.Selective Laser Sintering
6.Vat polymerization
7.Targeted Deposition of Energy
8.Extrusion of semi-solids
9.Utilizing bioprinting
10.Lamination of sheets

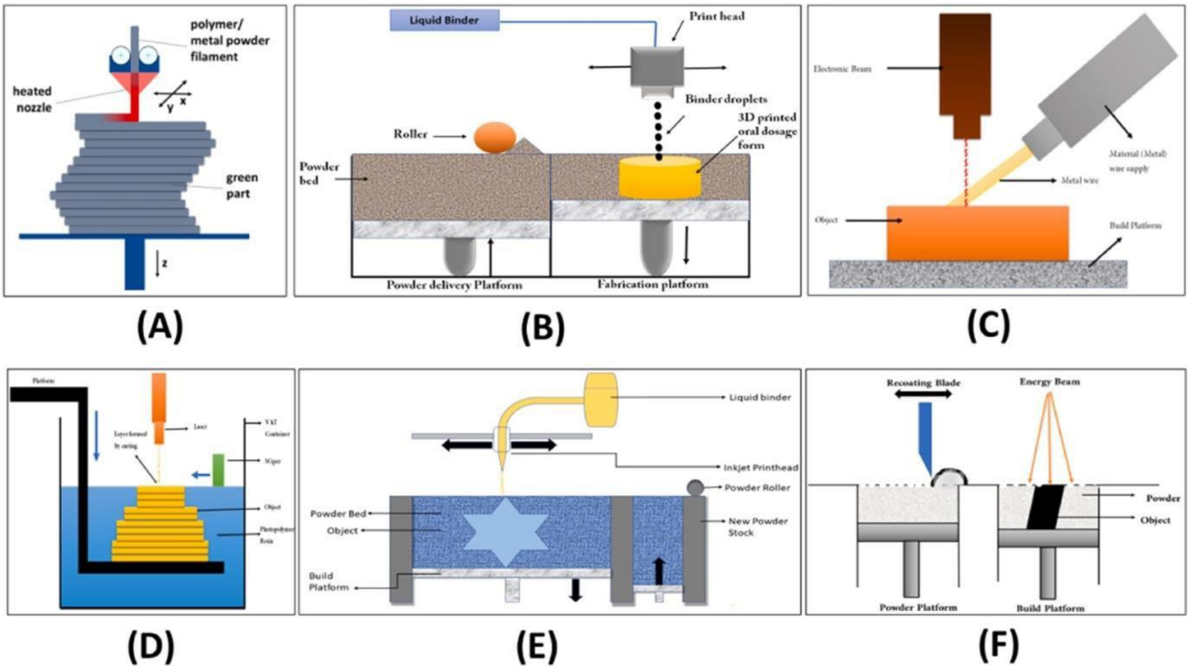


Figure 2The following are many 3D printing technologies: (A) Material Extrusion; (B) Binder Jetting; (C) Vat Polymerization; (D) Directed Energy Deposition; (E) Sheet Lamination;and (F) Powder Bed Fusion.

1. Stereolithography

SLA is one of the most sophisticated 3D printing techniques available. In order to start the polymerization process, the substance is exposed to intense light, such as ultraviolet radiation. This process occurs in the x-y axis, and when the material becomes lighter, the bed moves towards the y-axis, creating a complete process. SLA is a type of reduction polymerization that uses thermosetting photopolymer, which hardens when exposed to light, allowing the creation of high-quality products with smooth edges. [10] Although SLA has advantages such as good surface quality and good properties, it also has disadvantages such as brittleness and low photopolymer effect. But its ability to produce consistent, high-quality products makes it valuable in the automotive and medical industries, tissue engineering, and medicine. Recent applications include the developmentof modified tablets and specialized dental medications that continue to be used in neurosurgery, back surgery, and the treatment of heart disease. Material Extrusion [11]

2. Material Extrusion

Material Extrusion, commonly known as Fused Filament Fabrication (FFF), is an easy-to-use and inexpensive 3D printing method. The device consists of dispersing molten, semi-solid or softened material through a nozzle. Thermoplastic material in filament form is heated above its glass transition temperature and extruded to form a layer. The resolution and breadth of printed lines are determined by the primary parameters, which are layer thickness and extrusion head diameter. [12] The final surface has to be enhanced when steps like painting or sanding are completed. Because extrusion technology is so adaptable, it may be used to produce practical items and models at a low cost, with minimal need for specialized equipment. These technologies, which are widely utilized in the biomedical industry to simulate tissue, include partial extrusion, bioprinting, and fused deposition models. [13]

3. Binder Jet Printing

Binder Jet Printing was developed by Sachs et al. delayed release of tablets. The process will spread a layer of powder and then spray glue to form the powder mixture. This layering process creates 3D models without the need for a support structure, as the powder itself provides physical support. Benefits include recycling of unused powder, mixing with a variety of materials and adhesives, and the ability to create color. High- quality metal, ceramic, and plastic parts can be produced quickly and affordably with adhesive spraying. [14]

4. Pink Bed Fusion

The 3D printing method known as "Pink Bed Fusion" makes use of powders, binders, sintering methods, powder removal, and maybe post-processing. The most widely used technology in this category is selective laser sintering (SLS), which melts a thin layer of tiny powder with a laser. To guarantee layer fusion and minimal porosity, this procedure needs a combination and volume of powder. Three-dimensional printing (3DP) is the term for the method of using lasers to print using adhesive. [15] Binder chemistry and rheology, powder particle size and shape, deposition rates, and post-processing methods are important ideas in 3DP. The primary benefits of powder bed fusion include excellent printing quality, great resolution, and suitability for intricate patterns. Tissue engineering, aerospace, and electronics are three industries that frequently use this technique, which uses the powder bed as a support framework in place of additional support. However, there are drawbacks to utilizing adhesives, including increased porosity, slowness, and high cost. [16]

5. Selective Laser Sintering

Selective Laser Sintering (SLS) is an additive manufacturing process that creates 3D objects from a bed of powder. Lasers are used to selectively melt the powder in a specific pattern and bind the particles together into a layer. After a layer is sintered, a new layer of powder is laid on top and the process is repeated to create a 3D model. SLS has many advantages over fused deposition modeling (FDM) and extrusion processes, with higher resolution (up to 100 μm) and the absence of solvents and long time after drying.[17]Although traditionally used in tissue engineering to create scaffolds and pharmaceutical products, SLS's ability to create high-density materials using a variety of materials (polymers, metals, ceramics, and composites) gives it diversity and useful productivity. Factors affecting SLS quality and performance include laser power rate, scanning speed, strategy, coating, and bed temperature. Despite some disadvantages such as slow commercialization and high mass cost, SLS is still a popular choice for the production of practical, high-quality products. [18]

6. Reduction Polymerization

Reduction Polymerization covers a variety of 3D printers that use vats or tanks of liquid photopolymer, all of which are processed by a laser beam or other illuminated location.Stereolithography (SLA), solar polymer printing (DPP), digital light processing (DLP), lithography-based ceramic manufacturing (LCM), two-photon polymerization (2PP), and extended optical interface (CLIP) are the primary methods for decreasing polymerization. [19] When using cube polymerization, the design platform is submerged in a tank filled with liquid photopolymer resin, and the product is fixed layer by layer by the laser or projector of choice. Because UV lasers can penetrate resin and give strong adherence, they are employed extensively. This adaptable method is renowned for its excellent surface quality and high precision.; This makes it suitable for the creation of patterns, models and end uses. [20]

7. Directed Energy of Deposition

In the Directed Energy Deposition (DED) manufacturing method, a material (wire or powder) is melted and deposited onto a substrate using concentrated energy, such as a laser or electron beam. DED is appropriate for the synthesis of other metals and alloys as well as high-performance superalloys since the exposed material combines with the substrate and solidifies. DED doesn't rely on a powder bed like other additive manufacturing techniques like selective laser melting (SLM). [21] Rather, it melts feedstock prior to deposition, allowing for uses including part reconditioning, fracture filling, and large-scale, low-complexity assembly production. Numerous benefits of DED include its fast construction speed, expansive work area, superior mechanical qualities, controlled microstructure, and controllable material composition. However, it also has drawbacks, including less complexity, poorer accuracy, and lesser field quality. DED is mostlyutilized in materials including titanium, Inconel, stainless steel, and aluminum as well as in the aerospace, automotive, and medical industries. [22]

8. Semi-Solid Extrusion

A gel or paste-like substance is extruded in layers onto a forming plate using a semi-solid extrusion technique, which resembles the usage of a syringe. The paste is chilled and hardened to make the pattern, just like in FDM. The technology is applicable to a wide range of materials, including hydrogels, resins, and even culinary items like cheese and chocolate. It allows for accurate and controlled material creation. [23] In pharmaceutical applications, semisolid extrusion can be used to produce coated tablets by mixing the drug, polymer, and solvent in semisolid form. Key applications include the production of double-layer tablets and polypellet tablets. Its versatility and ability to use a variety of materials make it particularly useful in biomedical and pharmaceutical applications. [24]

9. Bioprinting

Bioprinting or bioadditive manufacturing is a type of 3D printing that uses biological chemicals to create products layer by layer. This technique is often used in tissue engineering, regenerative medicine and pharmaceutical research to create living tissue for transplantation and various biological applications. Bioprinting has the ability to create functional biological processes, making it an important technology for the advancement of science and medicine. [25]

10. Lamination Of Sheet

Sheet Lamination, which was developed by Helisys in 1991, is not the same as 3D printing in that paper—such as paper, plastic, or metal—is used instead of powder or filament. A piece of material is shaped using a laser or other cutting instrument while it is positioned on a building platform. [26] The sheets are then glued together layer by layer to create the final product. Sheet lamination has many advantages, including the ability to use many materials and not requiring semi-molten material or photopolymer curing. It is particularly suitable for Laminated Object Manufacturing (LOM) production, where many parts are put together to form a product. This technology differs from other 3D printing methods due to its unique approach to processing and layering. [27]

- **Energy Consumption**

3D printing is a revolutionary manufacturing technology that has led to significant advances in medicine. Although it is generally considered an environmentally friendly process due to the use of good materials, it has some negative effects on the environment, especially regarding energy consumption and energy use. Many 3D printers use plastic, which emits harmful chemicals, and energy consumption, especially from non-renewable materials, can contribute to climate change. [28] Therefore, it is important to create a sustainable 3D printing technology. Key points include energy consumption and associated CO2 emissions during standby and operating phases. Elbadawi et al. The energy consumption of six desktop 3D printers in standby mode and during printing was analyzed. The standby power consumption is 0.03 to 0.17 kWh, while the power consumption for printing 10 prints is 0.06 to 3.08 kWh. High temperature causes high energy consumption. Carbon emissions per 10 units range from 11.60 grams CO2e to 112.16 grams CO2e. [29]

Significant research showing that reducing printing heat can reduce energy needs and CO_2 emissions suggests that developing materials for high-temperature printing can improve the safety environment. Additionally, using renewable energy sources such as photovoltaic technology to power a 3D printer can further reduce CO_2 emissions. And it has many applications in many fields. Traditionally, soft lithography has been the primary method for producing these materials, including creating features in elastomers such as polydimethylsiloxane (PDMS). Although effective, this approach has limitations,especially when creating complex 3D models and tracking non-planar surfaces. It overcomes the plane limitation of soft lithography. [30]

- **Drug discovery via 3D printing**

Various 3D printing methods have unique capabilities in the fabrication of microfluidic devices, with advantages in resolution, configuration, and integration. 3D printing in microfluidics enables the combination of microfluidic properties and functional materials to have more applications in biomedicine, medical care, bioprocessing, fuel cells, and drug synthesis. [31] The new drug market is estimated to cost approximately $5 billion. 3D printing is flexible, efficient and effective for the production of small quantities of customized drugs, accelerating the drug development process. middle. For example, researchers at the University of Glasgow used fused deposition modeling (FDM) to produce polypropylene tubes and used this new method to make ibuprofen. This approachallows APIs to be created as needed, providing flexibility and support for testing with a variety of reactions and conditions. Additionally, on-demand 3D printing of intravenous drugs facilitates API synthesis in situations where traditional methods are not possible, such as in clinical settings where drugs are required. [32] Formulation development. The technology allows for early collection of information on excipient content, performance and compatibility, which can reduce drug development time and cost. Additionally,advances in bioprinting are helping to create animal and human tissues for acute and chronic toxicity and metabolism studies, reducing the need for animal testing and further reducing construction costs. "Organs on a chip" are replicas made with 3D printing that imitate the structure and functionality of human tissue. For instance, Harvard University researchers created a cardiac microphysiological device using 3D printing to examine how medications affect heart cells. Along with individualized treatment and drug testing, bioprinting has also resulted in the construction of numerous organs, such as the stomach,pancreas, and small intestine. [33]

- **Formulation and Development in 3D Printing**

Traditional pharmaceutical manufacturing methods face many problems, including problems with collisions and accidents that can lead to inconsistencies in drug transportation, drug release, and sustainable development process. How much data is produced at predetermined doses, which is not easy, especially when it comes to mixing drugs. The production process is complex and requires extensive facilities, trained personnel and high production costs. [34] Additionally, 75-85% of adverse drug reactions result from inappropriate use of drugs and drug combinations.The complexity of the human body, genetic variables, and variations in pharmacokinetics and pharmacodynamics are the causes of this variance in medication response. Address these issues. Personalized medicine should become less of a "one size fits all" approach. With its much-needed flexibility, 3D printing, which was first introduced over three years ago, promises to transform the pharmaceutical production industry. The technology was initially introduced as a possible replacement for the tablet production process in 1996. [35] Using computer-aided design (CAD), the method entails building a three- dimensional physical object layer by layer from a digital design. In addition to being helpful and time-saving, 3D printing can provide drugs in the desired form. Table 1 lists the various tablet varieties made with 3D printing. This has the potential to enhance therapeutic results and lower the frequency of adverse medication reactions. [36]

Table 1A variety of tablets were created by utilizing 3D printing technology.

Tablets	Drug	3D Printed Technology
Single Layer	Prednisolone	FDM 3D Printing
	4-aminosalicylic acid (4-ASA), 5-aminosalicylic acid (5-ASA, mesalazine)	FDM 3D Printing
	Fluorescein	Fused Filament
	Ropinirole HC1	3D Printing
	Fenofibrate	FMD 3D Printing
	Acetaminophen	Inject Printing
	Haloperidol	Hot Melt inject
	Paracetamol	Hot Melt Extrusion
Bi-layered	Guaifenesin	sintering
Multi layered (polypill)	Nifedipine, glipizide, captopril	SSE
	Captopril, nifedipine	SSE

• 3D Printing's Benefits for the Pharmaceutical Sector

The pharmaceutical industry's adoption of 3D printing technology holds the potential to transform drug manufacture through the transformation of distribution hubs, including hospitals, neighbourhood pharmacies, and patient homes. Mass or individual production is replacing traditional industrial production as a result of this change. The following are some of the main benefits of this change: [37]

1. The global pharmaceutical industry was valued at approximately $1.2 trillion in 2017, of which $283 billion worth of products required refrigeration and transportation. These logistics costs can be reduced by manufacturing drugs closer to the point of care. [38]
2. **Personalized Medicine**: With 3D printing, personalized medicine can be created according to the needs of the patient. This modification may improve treatment outcomes and reduce adverse drug reactions that often result from inappropriate drug use and combinations. [39]
3. **Manufacturing on demand:** 3D printing can produce medicines on demand, reducing the need for large inventories and enabling rapid responses to specificpatient requests. This capability is particularly useful for rare or orphan diseaseswhere the number of patients is small and the need for specific drugs is limited. [40]
4. **Enhanced convenience**: This device provides the best performance in the production of drugs of different types, sizes and distributions. This change enables the development of complex drug formulations and treatment combinations that are difficult to achieve with traditional production methods. [41]

5. **Low Costs:** 3D printing can reduce the overall cost of pharmaceutical production by reducing the need for extensive facilities, trained personnel, and lengthy production processes. Additionally, the ability to produce chemicals in small quantities reduces waste and improves resource use. [42]
6. **Improve drug safety:** 3D printing can improve the safety of drug formulations by controlling the content and structure of dosage forms. This control helps maintain the effectiveness and safety of the drug throughout its shelf life. [43]
7. **Accessibility:** Illicit production can improve access to medicines, especially in remote or underserved areas. Regional organizations can reduce inequalities in access to healthcare by ensuring essential medicines are easily accessible to those who need them. [44]
8. **Environmental Benefits:** 3D printing can reduce the environmental impact associated with industrial production by reducing the need for transportation and storage space. Additionally, precision in the design process allows for less waste and efficient use of raw materials. It is effective and tailored to the individual needs of the patient. [45]

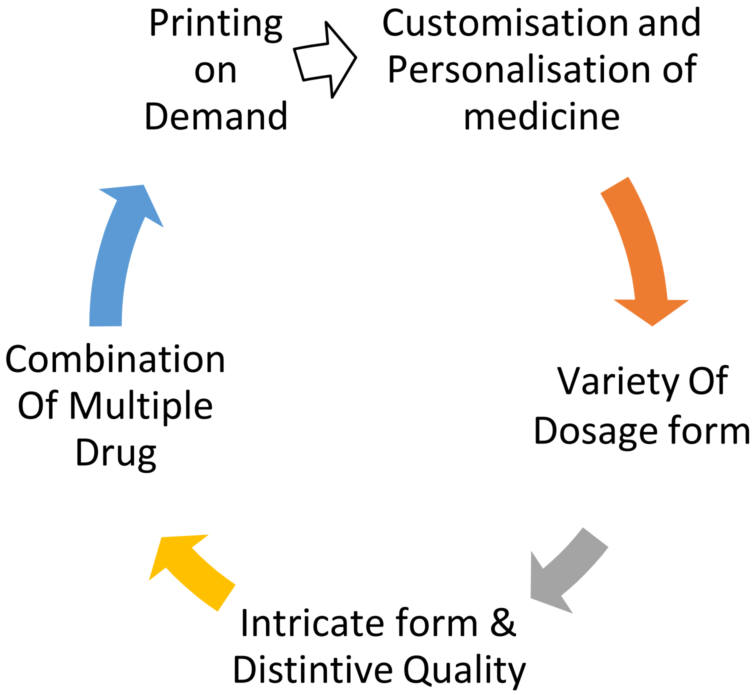


Figure 3 Advantages of 3D Printing

1. Customisation and Personalisation of medicine

Conventional pharmaceutical formulations have been used for decades; direct compression and encapsulation are the most common applications. This process is cost-effective for mass production but is often time-consuming, labor-intensive and chemically inefficient. Also, different people will respond differently to the same drug. Revolutionary technologies suchas 3D printing can solve these limitations by increasing the personalization of medicines. The technology allows doctors to adjust medication based on age, gender and medical condition to make it more effective. [46] It also makes it easier to compile personal information into small pieces, or even a package, to be used directly at the medical center. Dosage may vary depending on the patient's age and gender, and caregivers or patients often split or crush tablets to adjust the medication. This practice can lead to problems with injection accuracy, transfer, and drug excretion, especially with enteric-coated tablets. Hospitals can addressthese issues by using 3D printing technology to customize medications based on patient needs. According to research, the medication can be printed with a shell made of methacrylic polymer to generate enteric-coated capsules. [47] In visual broadcasting, geometry is also crucial.

The surface area and volume ratio of various prints can be changed to modify the drug release profile. Doctors can use this method to modify dosage based on patient age, which is particularly helpful when treating younger patients who require lower dosages. The drug's form can also be changed based on the patient's compliance, in addition to the dosage. In general, 3D printing offers a multitude of options and versatility for modifying the amount, form, and dimensions of the paper. [48]

2. Variety Of Dosage form

Three-dimensional (3D) printers can be used to create patient-oriented designs. This new technology allows the development of oral prescriptions tailored to patients' specific needs. Physicians can now create different types of drugs and combinations as needed, from solid, dosage forms that are chewable or orodispersible to different geometric elements including size, color, soft texture, and pictures. [49] 3D printers have been successfully used to generate patient-friendly formulations, such as orodispersible films and instant-dissolving pills. With 3D printing, there is practically no limit to the amount of paper and information that can be printed in different sizes and shapes. One study assessed the acceptability of various colors, sizes, and forms according to patient application ease and preferred eating patterns. Tablets in the shape of a tortoiseshell scored highest. [50]

3. Intricate form &Distintive Quality

Contemporary methods often fall short when processing large amounts of data with reduced doses and complex geometries. However, advances in technology now allow the use of 3D printing to easily create printed articles with unique features. As many studies have shown, technology has the ability to create images and designs that gain popularity. 3D printing has been used to make tablets as small as 10-15 mg, which is helpful for pre-clinical development and first-in-human (FIH) trials. By using this alteration, scientists can create tablets with different forms and sizes according to the pharmacokinetic and pharmacodynamic profiles in animal models. Lowering the dosage also aids in minimizing adverse effects, and creating updated release data is made simpler by the intricate picture. [51]

4. Combination Of Multiple Drug or Polypharmacy

Polypharmacy is a growing concern, especially for patients with multiple diseases who require more than one medication and more than one medication. Multiple or multiple drug formulations in a single dosage form are needed to improve medication compliance and reduce medication errors. This can be achieved by creating multiple drugs using 3D printing, which allows for easy and precise spatial distribution of drugs. For example, researchers developed a 3D-printed cardiotonic tablet consisting of five multiple-release drugs, such as pravastatin, atenolol, ramipril, hydrochlorothiazide, and aspirin. [52]

5. Printing on Demand

On-demand medication production is another benefit of 3D printing., especially drugs with poor solubility or short shelf life. Technology makes it easy to create medicine instantly, allowing the right dose to be taken. For example, some antibiotics need to be replaced, and some medications, such as nitroglycerin, use desiccants. In one study, the exact dose of dipyridamole was released upon request and had a shelf life of up to six weeks after exposure to the open source. The on-demand capabilities of 3D printing enable community pharmacies, private clinics, hospitals, etc. It can be used in a variety of medical settings, from primary to advanced, including disaster areas, emergency medical centers, and urgent care centers. Rapid drug development may be useful in these cases. [53]

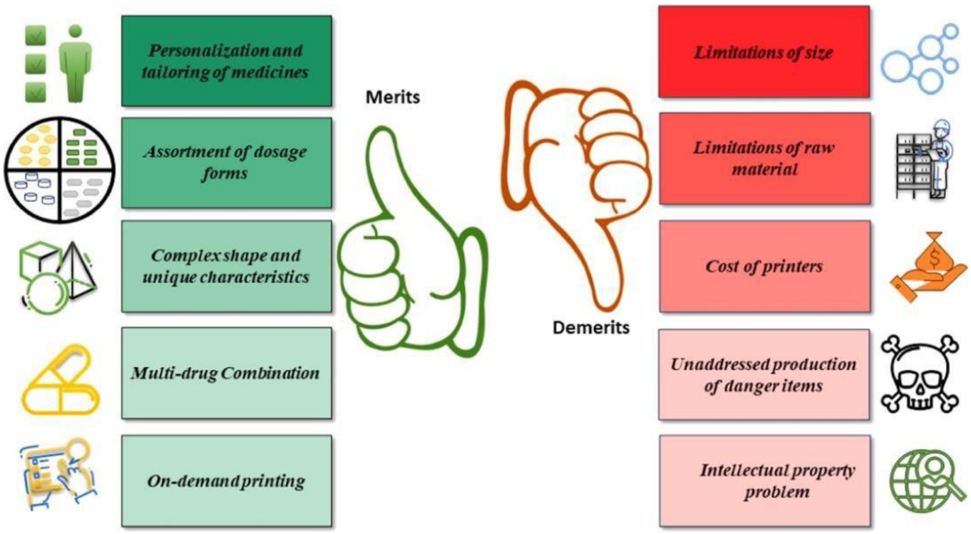


Figure 4Variours Advantages of 3D printing

- **3D printing's uses in the biomedical and pharmaceutical fields**

1. Biomedical Applications

3D printing is widely used in many biomedical fields, such as creating bodies for dentistry and orthopedic applications. It was also used to make noses, hearts, bones, retinas and pacemakers. Use advanced computed tomography (CT) and magnetic resonance imaging (MRI) CAD programs to create detailed top-down images of complex physiological processes. These images are then converted by a 3D printer to create hard-to-manufacture artificial objects with high performance and accuracy. [54]

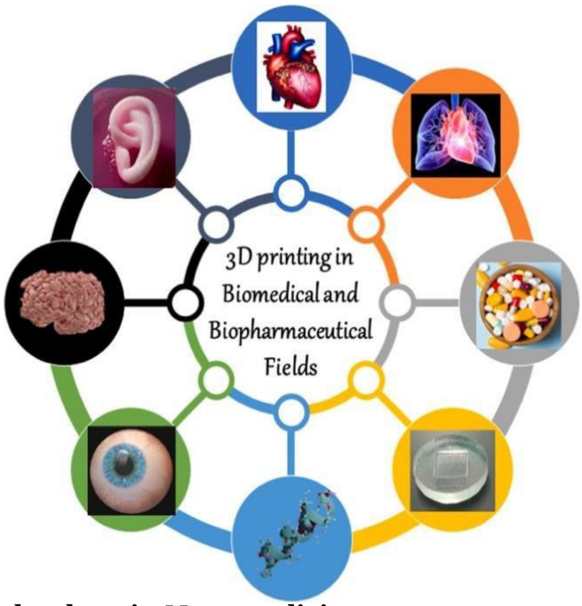
Issues with organ and tissue scarcity, tissue engineering, and stem cell synthesis are common in the field of organ transplantation. One way to produce the full body for layer-by-layer alteration might be through 3D printing. Three-dimensional (3D) tissue models are printed using biomaterials including collagen, hydrogels, and other substances. As bioinks, stem cells cultured in hydrogel matrices can be employed. The strength, porosity, and network structure of printed materials, as well as their robust regeneration potential, all influence their attributes. When building the hollow structures needed in intricate systems where blood vessels and nerves must be inserted into the framework, layer-by-layer 3D printing is especially useful. The human heart and heart valves are two examples of organs that have been 3D printed. In order to print organs using inkjet technology, a combination of biomaterials (hydrogel) produced from the fatty acids in human tissue was utilized. It takes about three to four hours to press a seed with clear veins. The printed model is immersed in food and exposed to oxygen for a few days in order to simulate the function of a real human heart. In order to enable customized surgery, a 3D kidney model that depicts the renal tissuein the tubule area has been provided. [55] In a similar vein, liver transplant models are being created using 3D printing. Scientists from the Human Genome and Stem Cell ResearchCenter at the University of São Paulo have demonstrated the ability of mini-livers composed of blood cells and 3D-printed liver organoids to function similarly to human hearts. A different research team at the University of Michigan has demonstrated that lung airways composed of bioresorbable materials can be created by 3D printing and CT scans for surgical therapy. Researchers at Boston Children's Hospital have also looked into the idea of printinga 3D bladder; they created a 3D bioprinted bladder for patients with bladder cancer. The cornea is also being considered for use. This tissue may be utilized to restore tissues and organs that have been harmed in accidents or by birth defects. [56] Replacing broken, wounded, defective bones can be accomplished with 3D printed limbs, cartilage, and joints.

This technology is also used in dental procedures to create new teeth to replace decayed teeth or togrow new teeth after root canal surgery has failed. Therefore, 3D printing is widely used in biomedical engineering. [57]

2. Biopharmaceutical Applications

Ink is an important component of 3D printers. Protein inks are particularly attractive for 3D printing because they have many advantages over other materials, such as biocompatibility, biodegradability, customization, and the ability to create complex patterns. Proteins have been 3D printed into a variety of structures with great potential for tissue engineering, disease modeling, and drug screening. Advances have been made in assembling short peptides and polymers into functional structures. [58]

Food proteins including milk, eggs, and egg protein are examples of proteins utilized in 3D printing, along with keratin and fibrin. The building blocks of biological processes, proteins are utilized to make scaffolds that have the appearance and functionality of living structures. The process of producing biopharmaceuticals is extensive, multifaceted, and tightly regulated. [59]



- **3D Printing Technology in Nanomedicine**

Treatments for several disorders, such as brain tumors, infectious diseases, and multidrug resistance (MDR), could benefit greatly from the application of nanomedicine. They are also suggested for the management of recurring and metastatic cancers, which frequently show resistance to conventional therapies. For instance, medium hydrophobic composites were made with diameters of roughly 200 and 20.59 µm, and the contact angles of the nanofiber layer and the 3D printing layer were 64.4° and 92.2°, respectively. [60] These composites are appropriate for cell adhesion, development, and migration because of their tensile strength of

6.12 ± 1.26 MPa and water absorption capacity of almost 95%.Using cellulose nanocrystals (CNCs) with an extrusion-based 3D printer, create viscoelastic hydrogels. To ascertain the rheological characteristics and printability of the hydrogels, they tested them at CNC concentrations ranging from 0.5 to 25 weight percent. The best printing resolution and accuracy, together with a high degree of CNC assembly (72–73%) following printing, are found in hydrogels containing 20 weight percent CNC. [61]

Small, spherical structures called nanocapsules can contain both hydrophilic and hydrophobic medications. They are composed of a polymer shell and a hollow center. Nanometer preparations have been printed using a variety of 3D printers, including stereolithography (SLA), fused deposition modeling (FDM), selective laser sintering (SLS), liquid inkjet printing, and pressure-assisted microinjectors. Rup et al. Make core-shell capsules with two-step 3D printing. The top and bottom layers of the capsule, which were comprised of PCL, a thermoplastic polymer, were designed using a CAD program. The nanocapsules were then densely packed using FDM.The second phase involved loading oils (linalool, limonene, trivalent alkynes, and farnesol) into the capsule's main layer using an inkjet printhead. This results in microcapsules that include nanocapsules and range in size from 200 to 800 microns. 3D printed capsules have a temperature stability of up to 80 degrees Celsius. Numerous elements have a role, such as the storage conditions, pharmaceutical goods, and the 3D printing method employed. [62]

- **Safety of 3D printed drugs**

A number of elements, including the substance, storage, and the 3D printing technique, affect the complicated question of drug safety when it comes to pharmaceuticals printed utilizing these machines. Pharmaceutical items' stability can be impacted by 3D printing in a number of ways. Certain 3D printing procedures, for instance, involve heat and shear, which might break down medication molecules. Other processes employ solvents, which can seep out of the drug and compromise its stability. Further jeopardizing safety is the porous aspect of 3D printed goods, which leaves them open to microbial and moisture contamination. For instance, it can produce goods with controlled release qualities that boost medication absorption and lessen adverse effects. Additionally, by producing goods with unique shapesor geometries, 3D printers can enhance chemical distribution and absorption. The advantages of 3D printing for medication production are substantial, even though the safety of this technology is still being studied. Personalized medicine is going to be a big part of the future, thanks to this technology. [63]

The temperature, pressure, and weight of the various 3D printing methods vary, which can have an impact on the stability of chemical compounds.

Utilized pharmaceutical products: The final product's stability is also impacted by the solubility, stability, and biocompatibility of pharmaceuticals.

Storage conditions: The product's stability will be impacted by factors like light, humidity, and temperature. In order to make sure the product satisfies specific standards, security measures are also crucial. Press to see how various designs and procedures affect the outcome.

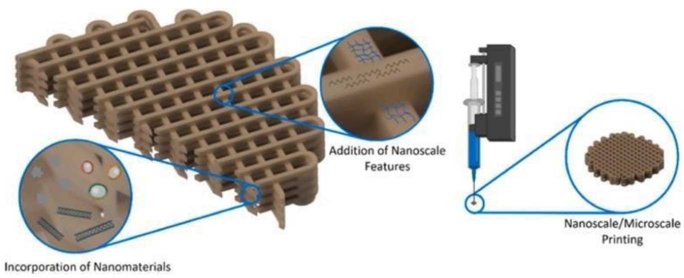


Figure 5 3D Printing Technology

These Printlets have good stability, high integration and isolation, no chemicals or changes in the product's crystal structure. Tablets containing paracetamol are released, and physical characteristics such melting point, stability, and rate of disintegration are assessed. TheXRPD, FTIR, DSC, and SEM data demonstrated that the acetaminophen form remained unaffected by the printing process, as well as by the acetaminophen and specific components (PVP K25 and CCS). The results indicated that the tablets exhibited good stability. They don't communicate with one another. - Estradiol recrystallization. Because crystallization diminishes stability, this observation points to the explosive's stability. Additionally, DSC analysis verified that the pieces were stable in the face of heat stress. [64]

- **Artificial intelligence, machine learning and smartphone-based 3D printing**
- Artificial intelligence (AI), digitization, and 3D printing have all come together to become significant in modern medicine. When combined, these technologies can make it easier to produce personalized medicine by enabling the 3D printing of medicinal materials that are specifically customized for each patient. This is made possible by the various geometric patterns that can be created using 3D printing to produce enormous amounts of paper with precise sizes, shapes, and display information. Artificial intelligence, digitization, and 3D printing together have the power to transform customized medicine by creating novel medications and therapies that will enhance the prognosis and quality of life for individuals with long-term illnesses is a branch ofartificial intelligence made consists of algorithms designed to find patterns in vast amounts of intricate data. It is well known that machine learning can offer insight in manyfields where conventional approaches fall short. The 2020 study served as the basis for an increase in ML product authorization by the US FDA. In contrast to conventional techniques, which invariably need X-ray crystallography, Google DeepMind's AlphaFold,for instance, can predict the 3D structure of proteins based just on their amino acid sequences, saving medical practitioners a great deal of time and effort. [65]
- **Case Study Artificial Intelligence and 3D Printing:**

An artificial neural network (ANN) was investigated by Mazur et al. in order to identify geometries appropriate for the intended dosage and release data. To anticipate the compatibility of layer shapes, an artificial neural network was created using different dosage and area/volume (SA/V) comparisons with in vitro data. The outcomes demonstrate that while the AI is not precise for geometry, it can anticipate the SA/V ratio. Outcomes Dissolution curves for every tablet's active component (API). This approach is meant for issues with gradual oscillation curves and a lot of time. The method may be used to produce 3D printed tablets with patient-specific medication release for personalized treatment. Orbitalfloor burst fracture restoration using a patient-specific implant (PSI). They successfullydisplayed 3D printed PSI cards using augmented reality technology. The liquid resin is polymerized by the light to create a robust structure. Because the technology makes it possible to produce drugs quickly and individually, it has the potential to completely transform the pharmaceutical sector. Because of its mobility, it is perfect for situations where resources are few, like in developing nations or during crises. Furthermore, more patients can use this technique due to its affordable cost. Smartphones can greatly benefit from the use of patient models. Preoperative planning, surgical training, and patient education can all be revolutionized by the system, which even novice users can use to construct these kinds of models. [66]

- **Smartphone-based application example:**

Liu and associates created a deep learning model using yolov3 and a WeChat application to quickly identify ADA and Thione (GSH area discovery) using an image processing technique. This study demonstrates how biomedical analysis might be impacted by integrating cellphones with ratiometric fluorescence detection and machine learning. In the end, accessibility results in improved healthcare. [67]

- **Quality Control of 3D Printed Medicines**

The ability of 3D printing to improve medications has been the primary driver of the industry's progress for many years. For pharmaceutical goods to be safe and effective, qualitycontrol, or QC, is crucial. The existing pharmaceutical production control system is made for large-scale manufacturing, not the desirable small-scale 3D printed personal paper. Due tothis distinction, standard quality control procedures are frequently laborious and disruptive, making them unsuitable for the quick development that 3D printing enables. Although there are still regulatory obstacles, the MHRA has released guidelines endorsing the use of 3D printing for point-of-care (PoC) production. Tools for non-destructive testing and analytical technology (PAT) are crucial for enabling pharmaceutical 3D printing. [68] It is vital to comprehend the particular items that are currently being assessed in order to make changes tothe final product analysis. Quality through testing (QbT) has historically served as the foundation for pharmaceutical management. QbT entails the individual inspection of completed goods, including tests for compatibility, friability, consistency, and ingredient consistency. Many of these labor-intensive and harmful studies use techniques including gas chromatography (GC), liquid chromatography-mass spectrometry (LC-MS), high- performance liquid chromatography (HPLC), and UV/visible spectroscopy. Differential scanning calorimetry, or DSC, is a destructive method of situation analysis; X-ray powder diffraction, or XRPD, is a non-destructive method. Control over the pharmaceutical manufacturing process is made possible by critical processes (CPP) and analytical tools (CQA). PAT offers more and better information and can be installed offline, online, offline,or online. Spectroscopic techniques like UV/visible, NMR, Raman, and near-infrared spectroscopy are examples of PATs that are frequently utilized. Authorities at the federal level have acknowledged that 3D printing is a business and that quality control needs to be reassessed. However, the distribution model for individual printed materials (3D tablets) determines the best quality control technology and performance. A few variables that keep the best 3D printer for personal medicine competitive are price, variety, stability of paper content, safety, and quality. It is possible to produce oral materials, but depending on where they are produced (medical or commercial), they must adhere to regulatory restrictions. Quality control of the final product is also important. Collaboration between manufacturers, scientists, and suppliers is necessary to develop the best technologies for personalized medicine and put them into clinical practice. [69]

The FDA's Emerging Technologies Team in the US has put a variety of initiatives into practice to support innovation and technology in the fields of product design and production. Despite being a manufacturing capacity, 3D printing has its own set of advantages and disadvantages, including manufacturing inaccuracy, process parameters, and riskmanagement techniques (RMS). Regulations governing pharmacists are more stringent than those governing medical equipment, processes, teaching resources, or training. Regulatoryand safety concerns arise from the absence of clinical studies and post-marketing data in comparison to traditional models, despite the fact that 3D printing expedites the evaluation of material compatibility and drug delivery techniques. Pharmacy management will experience significant changes in the future that will impact local products and hospital strategies. It maynot be necessary to prepare different products (branded and generic). In addition, the difference between chemical composition and finished product is important for the regulationof 3D printed products. Despite its potential, 3D printing still faces regulatory and safety issues. Devices are typically approved by the FDA on an emergency basis or through the regular 510(k) process; This may waive clinical trials if the device is “equivalent to regulatory product work.” High-risk Class III devices, such as bioprinted tissue implants, require higher standards for laboratory testing and premarket approval (PMA). No 3D printed medical devices have yet been approved by the PMA. In October 2014, the FDA held a public workshop to understand the challenges of additive manufacturing (AMD) and develop standards. Following this workshop, the FDA issued decision guidance for AMD in May 2016. This guide focuses on the design, manufacturing and evaluation of devices, including material management, design, printing and post-print analysis, and physical evaluation of the final device. and safety regarding cleanliness, sterility and biocompatibility. However, many questions remain unanswered, such as:

- Can CAD files be considered commercial products?
- How does the FDA treat manufacturers like hospitals? Will the FDA ensure that the quality and GMP compliance of the product is uncertain? [70]

Conclusion

3D printing has great potential in pharmaceutical manufacturing, design and management due to its simplicity and innovative capabilities in creating new medical products. This device is especially designed for personalization of drugs, allowing the drug release model to be controlled and different release profiles to be measured. This capability facilitates the modification and redevelopment of medical products, distinguishing them from generic competitors and providing additional benefits to patients, ultimately reducing product costs. Focusing on the limitations of the research, the use of 3D printing technology in oral prescription production is investigated. The selected studies demonstrate the successful application of current developments in the production of oral pharmaceutical products, which sheds light on an important problem in the pharmaceutical industry, especially regarding the competition of harmful substances in water. Research shows that the solubility and bioavailability of these poorly soluble drugs can be increased by using appropriate 3Dprinting and quality inks. Secure all equipment. In addition, the production of suitable printing material is important because it must meet the physical and chemical requirementsfor successful 3D medicine. However, the more important the complete success is, the moreit is carefully created with 3D paper.

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