

Special Issue – AI-Driven and Multimodal Innovations in Biomedical Imaging and Sensing

Overview of 3D Printing Technology with Pharmaceutical Applications, Challenges and Future Aspects

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<https://dx.doi.org/10.13005/bpj/3070>

(Received: 29 October 2024; accepted: 27 January 2025)

Since its beginnings in the 1980s, 3D printing has transformed several research areas, including the pharmaceutical sector. The primary objective is to manufacture complex, customized products using a cost-effective, on-demand manufacturing process. In the past decade, 3D printing has gained the interest of several research groups for the development of various drug delivery systems. Advantages of 3D printing technologies over traditional manufacturing procedures include the modification of pharmaceuticals with customized dosages, the capability to produce complex solid dosage forms, on-demand manufacturing, and cost efficiency. Nonetheless, although 3D printing technology has several potential medical and economic advantages, some technological and regulatory obstacles limit its wide application in pharmaceutical products. Thus, further innovation and refinement in 3D printing processes must address existing limitations and provide patient-specific healthcare with customized drugs on demand. This review presents several 3D printing processes useful for pharmaceutical manufacturing, their application in the development of various dosage forms, and the treatment of various disorders, demonstrating the potential of this technology for regular commercial production.

Keywords: Customized dosage, Commercial production, Delivery systems, Economic advantages, Potential applications.

Using a digital design platform, three-dimensional printing (3DP), commonly referred to as additive manufacturing (AM), creates 3D items quickly, effectively, and layer by layer¹. The advent of 3D printing in the pharmaceutical sector has revolutionized drug manufacturing, enabling the conversion of non-digitalized

medicinal products into digital 3D content. Over the past 20 years, there has been a significant advancement in the field of three-dimensional (3D) printing. It has aided in supplying appropriate information for the manufacturing processes of different industries, including pharmaceuticals, medicine, environmental monitoring, aviation,

and autos, as well as in research. Emanuel Sachs and associate researchers at the Massachusetts Institute of Technology in Boston, USA, invented 3D printing technology in the late 1980s (US patent number 5204055) ². In, 2015, the US Food and Drug Administration (FDA) authorized the first 3D-printed drug product, Spritam (levetiracetam), for treating partial-onset seizures, myoclonic seizures, and generalized tonic-clonic seizures, marking a watershed moment in additive manufacturing ³. When compared to traditional manufacturing methods, the use of 3D printing is very cost-effective, with a drug-loading efficiency of up to 1000 mg in a single dose and the opportunity for personalized distribution based on the patient's needs. With the benefits of boosting production efficiency and lowering costs and defect counts by preventing human error, 3D printing technology is expanding quickly across industrial manufacturing sectors. Converting the introductory factors (medicine and excipients) into a "curable essay" or printable material is the primary problem of 3D printing technology. Even the fabrication of things consisting of a single material or a combination of materials is possible with this approach; each substance may be deposited using a different print head or by using additional deposition stages. Customized treatment solutions are provided for individual patients or groups by 3D printing, since it may generate individualized medications to treat specific patient groups. 3D printing can be a successful therapeutic option for the treatment of complicated disorders such as cancer, dentistry, cardiovascular diseases, orthopaedics, diabetes, etc ⁴. Other advantages and some disadvantages are shown in Fig 1. Creating intricate dosage forms with several doses of medications with a narrow therapeutic index to assist long-acting medication therapy may be facilitated by 3D printing. Customized dosage forms in the form of polypills loaded with several doses of one drug or several doses of several drugs are made possible by 3D printing. Additionally, 3D printing enhances the PK performance and solubility of poorly water-soluble medications. The creation of solid pharmaceutical dosage forms has been greatly impacted by 3D printing. These days, 3D printing can be used at every stage of the drug development process, from preclinical research and clinical trials to providing direct patient care.

3 D printing in medicine: technology overview

3-D printing techniques are additive manufacturing methods that include the layer-by-layer material deposition onto a substrate to create the final 3D product, which is created with the use of computer software. All 3D printing methods include two fundamental stages. One relates to product design using computer software, while the other involves deposition of objects using a 3D printer. The design of a 3D object may be performed using numerous software applications like AutoCAD, Fusion 360, 3D Slash, SketchUp, and Solid Works. The following steps involve slicing the developed design using slicer software such as KISSlicer, Cure, OctoPrint, Slic3r, and Simplify3D. This 3D software will transform a 3D design file into 3D printer readable G code. The slicer software established the printing settings for the sliced item, including the number of layers, initial offset height between the print head and platform, infill percentage, printing speed, total printing duration, and layer spacing. The generated G code is then uploaded to the 3D printer, which after receiving a print command, will execute the process to create an object of the specified dimensions and configurations. The product deposition process via a 3D printer differs according to the specific kind of 3D printer used. Different 3D printing technologies are shown in Figure 2 and their diagrammatic representation is shown in Figure 3.

Inkjet printing

For precise and repeatable structure development, inkjet printing also referred to as mask-less or tool-less uses the movement of the inkjet nozzle or substrate. With the use of a powder base, inkjet printing produces exact dosages of active medicinal compounds by spraying ink droplets onto a non-powder substrate, which then solidifies. Many materials can be used, including resins, ceramics, and even edible ink, using Inkjet 3DP. Until the finished product is produced, the technology precisely deposits material droplets in a predetermined pattern using an inkjet print head, LbL ⁵.

Drop-on-demand printing

Ink droplets with a diameter of 10–50 μm and a volume of 1–70 pL are generated during DOD printing ⁶. In DOD printing, thermal heads and piezoelectric crystals are employed as printer

heads. The liquid ink in the DOD printing thermal head is locally heated to as high as 300 °C. It creates bubbles that force the ink out so that printing can occur. However, only volatile liquids can be used with this thermal head. Additionally, employing such a high temperature and high vapor pressure might damage medications and pharmaceutical substances. They can be classified into drop-on-deposition and drop-on-solid types.

Binder jet printing

Using an industrial printer to carefully apply a small coating of powdered materials like ceramics, foundry sand, metal, or composite along with a liquid bonding agent, binder jetting is used to create expensive and distinctive parts and machinery⁷. For example, Spritam is produced by Binder jetting.

Selective laser sintering

By heating and fusing powder particles at their surfaces, it uses a laser beam to produce solid things⁸. Carl Deckard created the SLS technology in 1984. It was based on a 100 W neodymium-doped yttrium aluminium garnet (Nd: YAG) laser. Most commercial SLS printers today use carbon dioxide (CO₂) lasers, which offer more power at lower cost and allow a wide range of powdered thermoplastic materials to be used. Compared to other 3DP formats, SLS offers several benefits, including excellent resolution and the ability to dispense and consume pointlets right away without the need for post-processing steps like drying or UV curing.

Stereolithography (SLA)

Stereo (solid) and lithography (photo) are the two words from which the term SLA is derived which suggests the form of writing with light. Despite being the first and oldest, SLA can produce items with smooth surfaces and intricate geometries because of its high printing resolution. SLA is a laser-based 3D printing technique that uses UV-sensitive liquid resins to create models, patterns, and prototypes through photochemical reactions in a layered format. High resolution and speed of printing, along with less localized heating, are benefits of this printing technique that make it appropriate for printing thermolabile medications. Initially employed for Nano and Micro patterns for micro-electro-mechanical systems, stereolithography's high-resolution

capabilities allow for high-quality microneedle patch production. Using this printing method in pharmaceuticals, miscible components like excipients and APIs can be incorporated into the polymeric matrix when crosslinking takes place⁹.

Digital light projection

The DLP technology projects light onto the photopolymerizable material using tiny pixels (rectangular cubes) from an entire cross-sectional layer of objects using a digital projector screen. Upon light projection, the entire cross-sectional region solidifies. The final 3D object has a rough surface finish because it is made up of tiny rectangular cubes known as voxels. When it comes to building 3D objects, the DLP approach is faster than SLA and allows easy modification in the thickness of the polymerized layer. Example- Using a top-down DLP printer (Gizmo® 3D printer), fluticasone-eluting oesophageal-targeted 3D rings (pre-loaded and post-loaded) dosage forms and drug-eluting devices are made¹⁰.

Semi-solid extrusion

A material extrusion technique called semi-solid extrusion (SSE) uses successive layers of paste or gel to form three-dimensional objects. The goal of the first clinical trial utilizing an SSE 3D printer in a hospital was to produce chewable Printlets™ a customized medication for kids suffering from Maple Syrup Urine Disease¹¹. SSE 3D printing operates at room temperature throughout the entire process, highlighting its benefits that can be extended to a wider range of active medications and excipients, including hydrogels and epoxy resins. This technique is commonly utilized in tissue engineering and regenerative medicine to fabricate scaffolds.

Fused deposition modeling

Another term for it is fused filament fabrication. A solid-based rapid prototyping method called fused deposition modeling creates a model by layer-by-layer extrusion of material. It works by heating and extruding a semi-liquid thermoplastic ink, which is then gradually settled with the use of a detachable scaffold to create a three-dimensional object. Several materials, including pastes, polymers, silicones, suspensions, and other semisolids, are used in extrusion printing. This approach has several benefits, including low cost, easy accessibility, and simplicity, but it also

has drawbacks, including inadequate drug loading, poor drug dissolution speed, and heat degradation of components¹².

Pressure-assisted micro syringe (PAM)

PAM is a nozzle-based deposition technique that releases semi-liquid and viscous materials by extrusion using a micro syringe and pressurized air. Using PAM technology, a microstructure as small as 5–10 μm can be produced¹³. Room temperature is required for this 3DP technology to function in a continuous flow.

Types of materials used in 3d printing

Biodegradable polymers

Biodegradable polymers are ecologically conscious or bio-based polymers that show great promise in addressing the problem of plastic waste. In the environment, these polymers spontaneously break down. Good mechanical strength, thermal behaviour, and barrier qualities are just a few of the various characteristics they exhibit. When it comes to technology and the environment, 3D printing with biodegradable polymers has many advantages. Among the many advantages of 3D printing are its adaptability and simplicity, which allow for complex designs and accurate prints¹⁴. Examples include polypropylene, polyhydroxyalkanoates, acrylonitrile butadiene styrene (ABS), polyamide, polycarbonate, polycaprolactone (PCL), polylactic acid (PLA), polyvinyl alcohol (PVA), nylon.

Natural fillers as reinforcing material

It is highly advised to use polymers as 3D printing matrices since they provide high resistance to chemicals, low cost, and simple processability. However, one of their primary production process constraints is their low functionality and low mechanical and tensile qualities, which refer to the end product's modulus, strength, and impact resistance. Using reinforcing materials is one of the most promising approaches among the various solutions proposed to address these problems. These substances can absorb moisture, have poorer thermal stability, degrade more quickly, be less compatible with polymeric matrices, and have batch-to-batch fluctuations in chemical composition. All these limitations have an impact on filler quality¹⁵. Examples include chitosan, cellulose, and keratin.

Metals

The novel process of “metal 3D printing” uses wires or molten metal powders to build

objects in layers, allowing for localized geometry modification according to internal tensions. Numerous studies have examined the use of 3D printing for metal materials, each with a distinct purpose and set of restrictions. Malekjafarian¹⁶ attempted an experimental investigation into the buckling capacity of metal materials 3D printed by laser, but encountered difficulties since there was no set buckling criterion. A metal-plated 3D-printed electrode was created for the electrochemical detection of carbohydrates¹⁷. Titanium, zinc, stainless steel, and chromium-cobalt alloys are a few of the metals used in 3D printing¹⁸.

Applications of 3D printing in cardiovascular diseases

Cardiovascular diseases (CVD) are the foremost cause of death and a significant contributor to global disability, affecting 523 million individuals and resulting in about 18.6 million deaths per year¹⁹. The clinical diagnosis and therapy of CVD mostly depend on less invasive imaging techniques, including computed tomography (CT), magnetic resonance imaging (MRI), and echocardiography. Although commonly used in routine practice, translating 2D images of cardiovascular anatomy and pathology into 3D representations poses significant challenges, particularly when visualizing complex cardiovascular structures and conditions, such as congenital heart disease, which typically includes multiple cardiac components exhibiting a range of abnormalities. 3D printing has overcome these limitations by delivering realistic models, hence presenting significant benefits over existing image visualization. Various 3D printing technologies used to treat cardiovascular diseases are Antiplatelet tubular grafts²⁰, Artificial blood vessels²¹, Cardiovascular stents²², and Nanocomposites²³.

Cancer

Cancer is said to be the cause of many reported fatalities worldwide as well as treatment-related suffering. The remarkable capabilities of Additive Manufacturing technology provide better options for treating malignant tumors. This technology's models aid in understanding a patient's behaviour related to their illness. Three-dimensional printing has a significant impact on research that uses cancer models for diagnosis and treatment. In research on drug screening, cancer metastasis, and prognosis, 3D-printed tailored

tumor models including physical, bio-printed, and tumor-on-chip models display better correlation. Various 3D printing technologies used in cancer are cardiovascular implants²⁴, Scaffolds²⁵, Fe-CaSiO₃ Bio-scaffolds²⁶, nanoparticle-loaded hydrogel-based scaffold²⁷.

Dentistry

Due to its rapid fabrication, excellent accuracy, and personalized customization, whole dentures and implant teeth are more readily accessible. Furthermore, the use of 3D printing in dentistry might facilitate the delivery of cost-effective and customized treatments to patients, while simplifying the complex procedures associated with the fabrication of dental equipment. Before the widespread use of 3D printing technology, restoration was often manufactured via milling. Currently, 3D-printed restorations have several benefits. Certain investigations indicate that the edge and internal gap measurements of 3D printed restorations are significantly lower than those of milled restorations. Dental crowns are often produced using conventional plaster models, however, crowns manufactured using 3D printing technology have gained popularity as well. Recent research indicates that the fit of crowns produced by 3D printing is lower than that created from plaster models, suggesting that 3D printing technologies are innovative but under-researched. Various 3D printing technologies in dentistry are chlorhexidine-coated mouthguard²⁸, monolithic zirconia crown²⁹, occlusal device³⁰, dental implants³¹, dental crown³².

Diabetes

Diabetes is a metabolic condition defined by increased blood sugar/glucose levels. Prediabetes is a metabolic disease characterized by increased blood sugar levels above the usual range. High blood glucose primarily impacts big blood vessels, resulting in macrovascular difficulties, if untreated, it subsequently affects small blood vessels, leading to microvascular challenges³³. Increased blood sugar levels can reduce an individual's immune response, making diabetes patients more prone to infections compared to healthy individuals. In recent years, 3D printing and 3D bioprinting have gained attention as leading technologies in the diagnosis and treatment of diabetes by creating analytical devices for sensing and detecting high blood glucose levels

and other oral medications³⁴. Various 3D printing technologies in diabetes treatment are microneedle biosensing device, electrochemiluminescence biosensor³⁵, self-nano emulsified based 3 D printed tablets³⁶, printed glipizide tablets³⁷, microneedle patches³⁸, orthopaedic insoles³⁹, bio printed scaffolds⁴⁰.

Orthopaedics

The aging of the world's population raises the danger of orthopaedic conditions such as fractures and metabolic disorders, which impair function and cause discomfort in many older people. As an advanced digital manufacturing technique, 3D printing has completely changed the biomedical area. Orthopaedic implants customized to the patient's surgical needs are designed and manufactured by clinic physicians using CT/MRI patient imaging data. It can be applied to orthopedic surgery, mainly for prosthetics, tissue engineering scaffolds, tailored equipment, and surgical planning. Using 3D printing for surgical preparation shortens operating times by helping a surgeon diagnose more accurately, mimic surgery, and comprehend the anatomy of a surgical site. The high cost of production, the length of time required for data processing and printing, and the lack of strength resulting from layer-by-layer manufacturing are the drawbacks of 3D printing in orthopedics⁴¹. Various 3D printing technologies in orthopedics are titanium implants⁴², spinal implant⁴³, pelvic implant⁴⁴, antimicrobial hydrogel⁴⁵, finger splint⁴⁶.

3D printing of drug delivery systems

The most common method of drug administration is oral, using solid dose forms. Oral tablets provide dosage accuracy, chemical and microbiological stability, controlled release characteristics, and convenience of administration. Oral tablets are conveniently portable for the patient, facilitating on-demand administration. despite these benefits, traditional tablet manufacturing techniques involve a time-consuming and laborious process. 3D printing technology facilitates the production of custom-designed oral tablets characterized by significant architectural, structural, and compositional complexity, potentially leading to an important change in tablet manufacturing from a uniform approach to personalized medicine. Various drug-loaded oral tablets prepared by 3D printing

technology are Amitriptyline Hydrochloride ⁴⁷, Indomethacin ⁴⁸, Ondansetron ⁴⁹, Clindamycin palmitate hydrochloride ⁵⁰, Carvedilol and haloperidol⁵¹.

The first 3D-printed capsular devices were produced in 2015 by Melocchi. Hydroxypropyl cellulose-containing filaments were produced using hot-melt extrusion and then 3D printed. The produced samples were swellable, erodible capsules designed for oral pulsatile drug release⁵². Fused deposition modelling and inkjet printing were used to manufacture capsules from various polymer compositions. The capsules included three components: two hollow sections with a closed

cylindrical end and a rounded open end; the central section functioned as a junction and a partition. The hollow sections differed in geometry and wall thickness. The samples included model APIs, and the findings indicated that the device successfully released the model APIs in pulses within 2 hours. Acetaminophen and furosemide⁵³, Metoprolol and nadalolol ⁵⁴, Isoniazid and acetaminophen⁵⁵, Norfloxacin⁵⁶ are a few examples of drug-loaded capsules prepared by using 3D printing technology.

3D printing technologies have significant potential to produce advanced drug implants and customized macro-porosity implants with personalized drug release characteristics. Presently,

Table 1. Clinical trials

S. No.	Trial ID	Sponsor	Purpose/Aim	Ref.
1.	NCT05273060	Mayo Clinic	To collect data on safety and contrast 3D printing with conventional planning for nasal repair.	85
2.	NCT05741892	Insel Gruppe AG, University Hospital Bern	The study's objective is to evaluate the efficacy of fracture reduction in cases of comminuted femur- and tibia-shaft fractures when surgical guides are created and 3D printed at the point of treatment.	86
3.	NCT05845099	Ain Shams University	This research is a controlled clinical experiment that randomly assigns individuals to one of two groups—conventionally made CRD or 3D-printed CAD/CAM CRD—and compares patient satisfaction and oral microbiota growth in each group.	87
4.	NCT06035211	University Hospital, Bordeaux	This clinical trial evaluates the impact of presenting and manipulating a three-dimensional model of a patient's tumored kidney before nephron-sparing surgery.	88

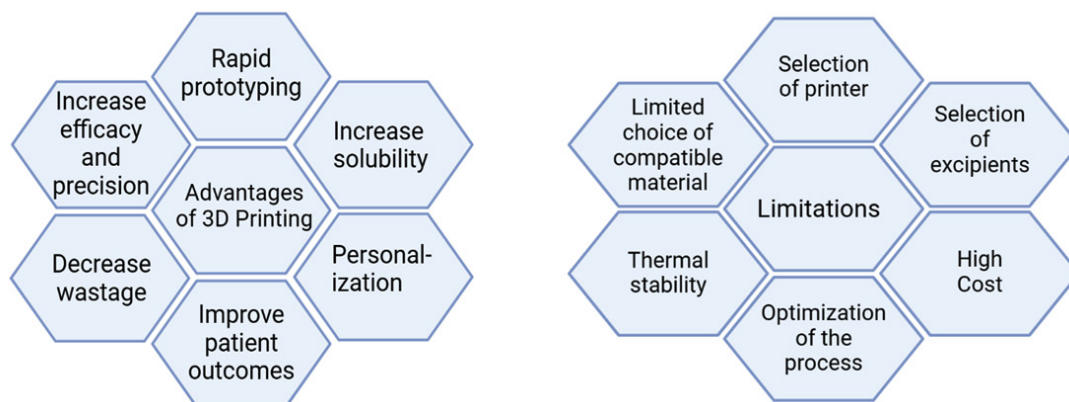
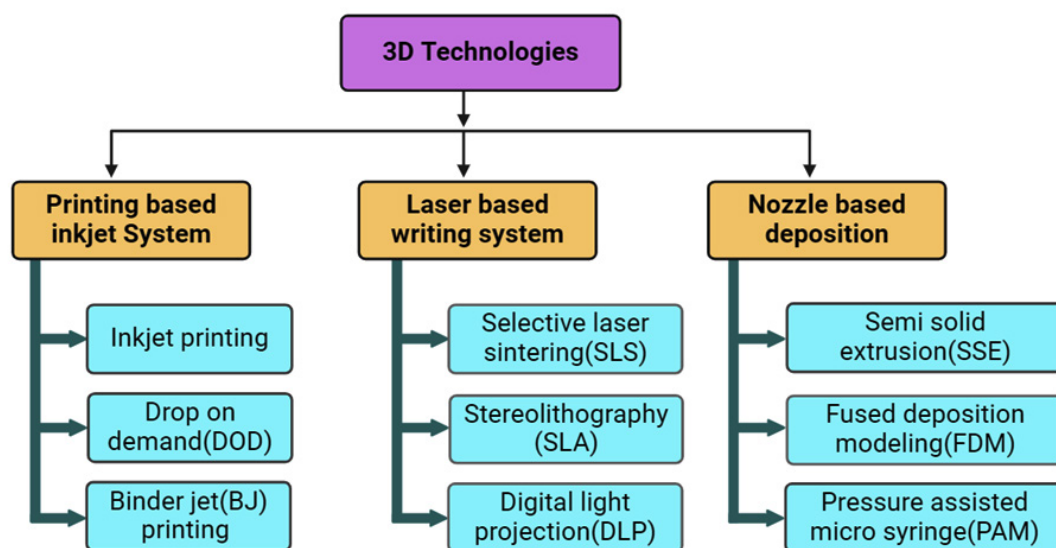
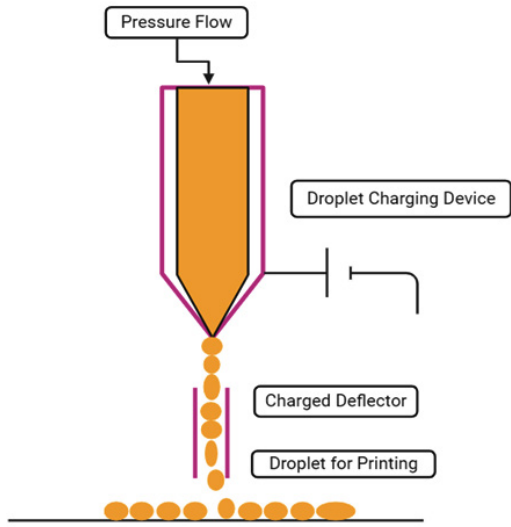


Fig. 1. Advantages and disadvantages of 3D printing technology

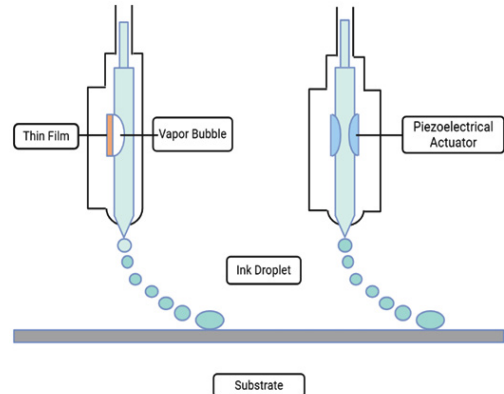
Table 2. Patented 3D printed pharmaceutical products, devices, and organs

S. No	Patent no.	Inventor	Title	Status	Ref.
Pharmaceutical Products					
1.	WO2020145898A1	Seng Han LIM, Wei Jiang GOH	Three-dimensional printing of personalized pills	Active	89
3.	CN109125912B	Lei Yifeng	3D printing microneedle patch for intelligent blood sugar regulation	Active	90
4.	ES2966388T3	Morten	Procedure for 3D printing, use of a 3D printing suspension and a 3D printer	Active	91
5.	US11305480B2	Charles W. Hull	Methods and apparatus for 3D printed hydrogel materials	Active	92
3D printed devices					
6.	CN108724712B	G.Weii	3D printing of porous implants	Active	93
7.	CN108724713B	G.Weii	3D printing of mesh implants for bone delivery	Active	94
8.	JP7045386B2	Wallace Anthony	3D printing of optical devices	Active	95
9.	US10543638B2	DionysiosDouroumis	3D printed stent	Active	96
3D printed organs					
10.	EP2970896B1	Benjamin R	Engineered liver tissues, arrays thereof, and methods of making the same	Active	97
11.	AU2017359330B2	Kapil BHARTI	3D vascularized human ocular tissue for cell therapy and drug discovery	Active	98
12.	EP3215603B1	Kelsey Nicole Retting	Engineered three-dimensional skin tissues, arrays thereof, and methods of making the same	Active	99

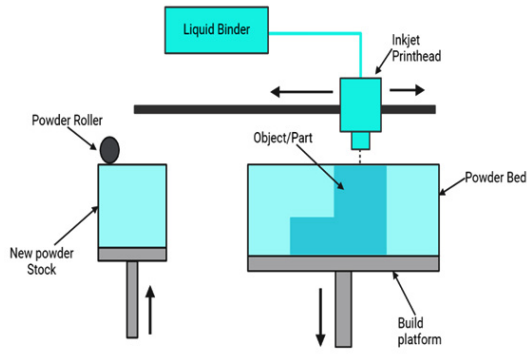
**Fig. 2.** Various 3D printing technologies used in drug designing



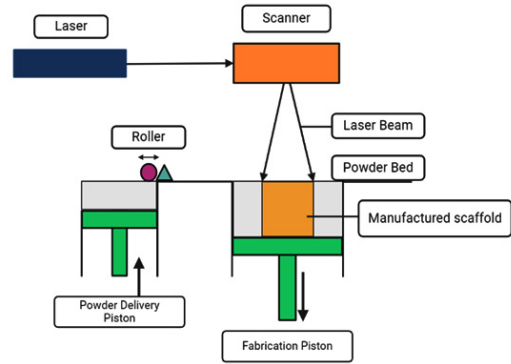
(a)



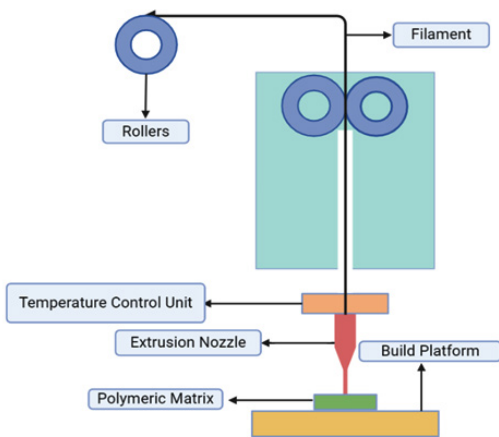
(b)



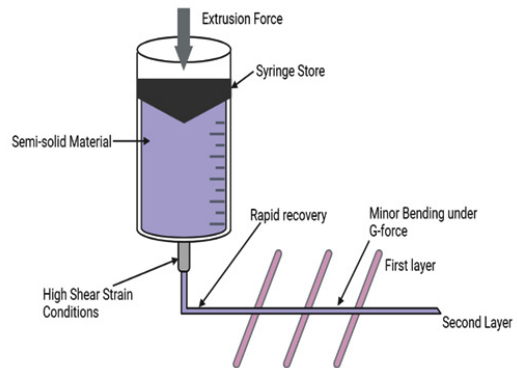
(c)



(d)



(e)



(f)

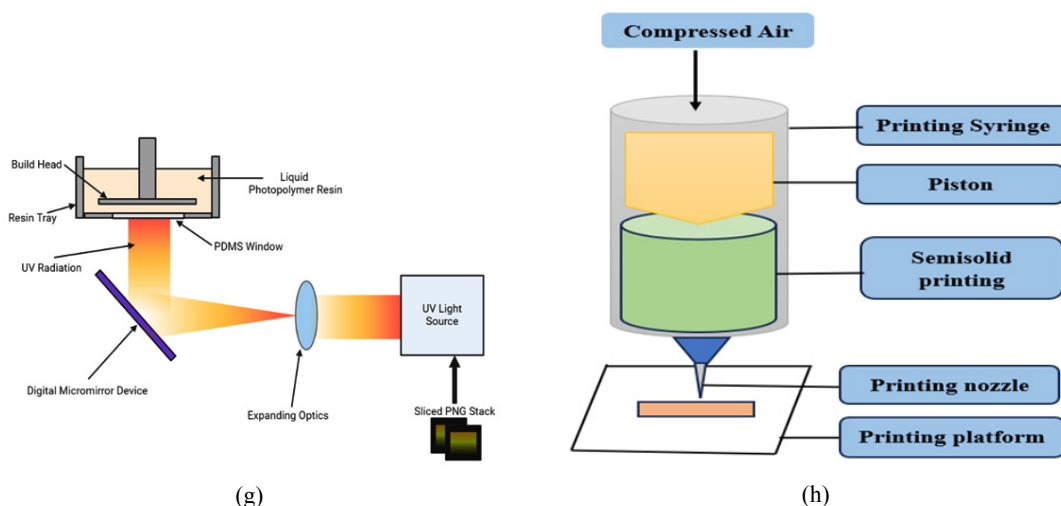


Fig. 3. (a) Inkjet printing; (b) Drop on-demand printing; (c) Binder jet printing (d) Stereolithography; (e) Digital light projection; (f) Semi-solid extrusion; (g) Fused deposition modeling; (h) Pressure assisted micro syringe

commercially marketed implants often lack the personalization of treatment and consideration of several factors, including anatomical variances, age, gender, and disease conditions. A study group found that 3D-printed implants may exhibit complex drug release patterns compared to traditionally manufactured drug implants. The manufacturing of 3D printing technology has enabled the production of smaller, less invasive, and more site-specific implants in contrast to traditional methods⁵⁷. Various 3D printed implants are Doxycycline⁵⁸, Ciprofloxacin⁵⁹, Diclofenac sodium⁶⁰, Lidocaine⁶¹.

Microneedle technology is a method of active transdermal administration of drugs designed to replace conventional syringe injections. The microneedle array is used to transverse the stratum corneum and administer the drug with minimum invasive action. These arrays consist of micro-sized needles with heights varying from 25 to 2000 μm . A significant benefit of 3D printing is its ability to incorporate drug substances with complex solubility profiles into microneedles optimized for patient requirements. The manufactured microneedles provide precise dosing while maintaining mechanical strength compared to conventional microneedles. Additionally, microneedles with small tips at the nanoscale allow effective skin penetration and can facilitate targeted cell delivery. Many researchers carried

out studies on 3D printed microneedles, Insulin⁶², Diclofenac⁶³, 5-fluorouracil, curcumin and cisplatin⁶⁴, Fluorescein⁶⁵.

Present methodologies did not consider the specific anatomy of each patient, along with their medical problems, age, and gender specificity, which limits the effective therapy, since each patient is unique and requires different dosages of drugs and hormones. Moreover, factors such as variability in drug absorption associated with the menstrual cycle, menopause, and pregnancy varied across individuals. Therefore, patient-specific methods are essential for delivering customized shapes, sizes, and drug releases to enhance effectiveness and increase compliance. The 3D-printed delivery system may provide customized geometry, ensure a secure fit, enhance effectiveness, improve patient adherence, and prevent post-surgical complications⁶⁶. Estrogen/progesterone⁶⁷, Paclitaxel and cidofovir⁶⁸, Chloramphenicol and metronidazole⁶⁹ are studies performed for the preparation of 3D-printed vaginal drug delivery systems.

Challenges

Void formation

One of the main drawbacks of 3D printing is the formation of voids between layers of material. Because additive manufacturing can produce extraordinarily high levels of additional porosity, the interfacial adhesion between printed layers can

be reduced, lowering mechanical performance. One of the key faults that lead to poorer and anisotropic mechanical properties in methods that use filaments of materials like FDM is the production of voids, which is more common in these processes. By reducing the height of each layer in the powder-bed printing of alumina/glass composite, the high porosity of additive manufacturing can be significantly decreased⁷⁰. The decreased height can lessen the creation of interlayer voids by increasing laser penetration through the top layer and facilitating the diffusion of ceramic powders between layers.

3D printer-related challenges

Geometric restrictions

Geometric flexibility can be achieved with 3D printing, but there are drawbacks as well. Certain geometrical possibilities restrict the printing method⁷¹.

Dependency on direction

One characteristic of layered manufacturing processes is thought to be directional dependency. The strength and load-bearing capacity of the material are significantly impacted by the printing direction⁷². For most 3D-printed shapes, a linear filament deposit is necessary. Since filament has a direction, directional dependency is a problem.

Quality of 3D printer

The size and drug concentration of the intended printed drug items must be considered when selecting a 3D printer for printing pharmaceuticals. The tolerance ranges of various printer machines can affect how accurately a pharmacological product is printed.

Contamination

Contamination concerns arise when drug formulation components are reused in 3D printing operations because of the possibility of meeting ink that has been used previously. Printer components can also be a source of contamination. For instance, FDM printers come equipped with brass nozzles that contain lead; these nozzles need to be updated to stainless steel nozzles for use in medical applications⁷³.

Raw materials

Physicochemical stability and printability of APIs and excipients, along with the kind of 3D printer to be utilized, are the determining factors in their selection. Rheological characteristics and

mechanical resilience are the primary variables that can affect how printable the raw materials are. One important component of print viability has been identified as mechanical resilience. The type of material will determine the standards for that material. Common requirements for solid materials are filament diameter and diametric tolerances for filaments, particle size, distribution, and pertinent rheological performance for powders. Viscosity and viscoelasticity are significant properties of fluid materials; similarly, composition, glass transition temperature, chemical structure, purity, water content, and molecular weight, are significant properties of polymers or monomer mixtures⁷⁴.

Mechanical properties

The fundamental principle of 3D printing is the stacking of various polymers or powders, which leads to a rough surface and inadequate mechanical strength of the objects⁷⁵. The mechanical characteristics of dosage forms, which are impacted by variables including adhesive viscosity, surface tension, and nozzle fineness, are critical for quality control because they impact tablet performance, repeatability, and postprocessing appropriateness. It is possible to enhance the mechanical behaviour of products by the optimization of the printing apparatus, including computer control programs, adhesive nozzle refinement, and printing process parameter adjustments.

Cost

The high expense of creating computer models and printing them, together with the need for materials, 3D printing knowledge, segmentation software, and medical-grade printers, prevents 3D printing from being widely used.

Anisotropic microstructure

Anisotropic behaviour is a problem for additive manufacturing because layer-by-layer printing produces different microstructures within each layer than the borders between layers. When new layers are added to metals and alloys that are 3D printed using heat fusion (SLS or SLM), the borders of the earlier layers are reheated. This causes the microstructure to change and causes anisotropic behaviour because of thermal gradients⁷⁶.

Challenges relating to liability and regulations

Liability issues

Different companies are involved in 3D-printed object development, but accountability

and liability issues arise regarding responsibility in case of failure. To determine who is accountable for an accident, a precise legal framework needs to be established.

Absence of norms and guidelines

Because there are no set rules governing the use of 3D printing in construction, it is difficult to follow all construction norms and guidelines. There are attempts to amend these rules to incorporate 3D printing. To incorporate 3D printing into the construction guidelines, a few Chinese enterprises are collaborating with the National Construction Standards agency⁷⁷.

Differential in both conception and implementation / Divergent from design to execution

The primary tool for designing an item that can be 3D printed is computer-aided design (CAD) software. Boundaries and solid geometry combine to form the CAD system. However, translating CAD data to a 3D-printed component frequently leads to errors and flaws, especially in curved surfaces⁷⁸. Cutting the part into enough layers, creating supporting materials, planning, and determining the part's ideal orientation are all essential to minimizing divergence from concept to execution.

Interoperability

Data interoperability guarantees that using the same information to express the intended model, all disciplines will collaborate effectively. Because 3D printing relies on digital processes for all operations, compatibility between apps used for structural analysis, architectural design, and printing must be ensured⁷⁹.

Regulatory landscape

Since there are now no regulations governing 3D printing in healthcare, quality control must be established⁸⁰. Focusing on the design, production, and use of 3D-printed medical devices, the FDA published its final advice in 2017 outlining technical factors for regulatory control. The pharmaceutical sector faces issues in identifying critical parameters, assessing the efficacy of 3D-printed medications, investigating their release in vitro and in vivo, and managing formulation quality as printing technology develops. The development of regulatory policies has the potential to greatly speed up the transition of printing technology in pharmaceutical formulations from

theoretical investigation to workable solutions.

Switching to a personalized medication

Some 3D printing techniques alter the drug's physical state, which affects its characteristics. Thus, to anticipate drug content, 3D printing pharmaceuticals must be assayed. Certain polymer filaments can have their diameter changed by heating, which could result in uneven tablet printing or even malfunctioning printers. Lubricant and proper nozzle sizing are two ways to address inconsistent tablet printing outcomes⁸¹. When certain polymers require higher temperatures, drug degradation may become an issue.

Environmental challenges

According to the study, which contrasts additive manufacturing with conventional manufacturing techniques, highly specialized raw materials are required for additive manufacturing technology to function. There are extra environmental implications since the material preparation process needs to take extra steps because of a particular requirement. Firstly, the environmental impact of additive manufacturing techniques appears to be influenced by electrical energy. Because of variations in material characteristics and the requirement for certain raw materials, the recovery of waste materials generated by AM technology is still unknown⁸².

Future aspects

Customized medicine

The use of 3D printing makes it possible to create personalized medicine dosages for each patient. Treating complex disorders such as cancer, cardiovascular diseases, and paediatric care requires personalization, which involves delivering tailored doses depending on age, genetics, and medical history. 3D-printed pharmaceuticals are probably going to be a main choice for customized treatments in the future⁸³.

Advancement in Biocompatible Substances

A broader spectrum of biocompatible materials, including biodegradable polymers and smart materials for implants and medication delivery systems, will be developed in the future of 3D printing in medicine. Healthcare applications will be further enhanced using these advanced substances to create scaffolds for tissue engineering and regenerative medicine.

On-Demand Pharmaceutical Manufacturing

The capacity to print medications on demand eliminates the need for large supply chains by enabling local, decentralized manufacture at pharmacies or hospitals. When supply systems are disrupted during health emergencies like pandemics, such as in rural or isolated areas, this can be quite helpful.

Integration with Nanotechnology

The combination of nanotechnology with 3D printing to create targeted medication delivery systems has the potential to completely transform medical therapy. These will provide more accuracy and control over the delivery of drugs, particularly in cancer treatments where it is essential to target cells²³.

Sustainable and Economical Manufacturing

Compared to traditional manufacturing, 3D printing uses less energy and produces less waste materials, which means that technology will provide more environmentally friendly ways to produce drugs. The method will be a desirable alternative for the development of rare and orphan drugs due to its cost-effectiveness, particularly in small-batch production.

Innovations in Regulatory and Quality Control

It is predicted that authorities such as the FDA will modify and enhance their protocols for approving 3D printed pharmaceuticals as technology advances. This will speed up the transfer from research to clinical applications by guaranteeing that printed pharmaceuticals fulfil safety and efficacy standards⁸⁴.

Various clinical trials conducted on 3D printing technology are given in Table 1 and, Table2 enlisting various patents of 3D printed pharmaceutical products, devices, and organs.

CONCLUSION

Numerous 3D printing systems have been developed and classified into subgroups according to their operational principles. 3D technology facilitates the production of complex and sophisticated dosage forms, providing more control over their shape and microstructure. Moreover, 3D printing represents an innovative and highly promising techniques for on-demand manufacturing and the personalization of dosage forms, potentially enhancing patient compliance

and drug efficacy, minimizing side effects, addressing stability concerns of drugs with limited shelf life, and ultimately facilitating patient-specific healthcare through customized medicinal products. However, despite several possible medical and economic benefits, certain technical challenges limit the widespread use of 3D printing technology in product commercialization, particularly the limited selection of biocompatible materials available for 3D printers.

This review discusses potential applications of 3D printing technology, outlining the various techniques that have been developed, with the challenges associated with these methods and their implementation in drug delivery systems. 3D printing will transform conventional manufacturing by improving health applications, including drug delivery.

ACKNOWLEDGMENT

The authors expressed their gratitude to Mr. Jitender Joshi, President, Prof. (Dr.) Dharam Buddhi, Vice Chancellor of Uttaranchal University Dehradun, and Prof. (Dr.) Vikash Jakhmola, Director, Uttaranchal Institute of Pharmaceutical Sciences, for their encouragement and guidance in publishing this review work.

Funding Sources

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest

The author(s) do not have any conflict of interest.

Data Availability Statement

This statement does not apply to this article.

Ethics Statement

This research did not involve human participants, animal subjects, or any material that requires ethical approval.

Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required.

Clinical Trial Registration

This research does not involve any clinical trials

Authors contribution

Data collection and manuscript: VS, MB, and SD;
Reviewed and corrected: MC, PK, VJ and AN.

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