

3D PRINTING OF PHARMACEUTICALS: CUSTOMIZED DOSAGE FORMS AND FUTURE PROSPECTS

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Article Received: 21 August 2025 | Article Revised: 11 September 2025 | Article Accepted: 2 October 2025

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DOI: <https://doi.org/10.5281/zenodo.17368517>

How to cite this Article: Sarika Bhabad, Ajay Bhagwat, Swapnil Auti, Nikita Galande, Monika Bhosale (2025) 3D PRINTING OF PHARMACEUTICALS: CUSTOMIZED DOSAGE FORMS AND FUTURE PROSPECTS. World Journal of Pharmaceutical Science and Research, 4(5), 382-395. <https://doi.org/10.5281/zenodo.17368517>



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ABSTRACT

Three-dimensional (3D) printing is a modern manufacturing technology that allows for the creation of objects by building them layer by layer, providing distinct possibilities for use in the pharmaceutical field. 3D printing offers several benefits compared to traditional manufacturing, including the ability to customize medications for individual patient doses, produce items as needed, reduce costs, and create complex and multifunctional dosage forms. Since the approval of the first 3D-printed medication in 2015, there has been a significant increase in interest in using this technology for pharmaceuticals. This is especially true for creating solid oral dosage forms with customized drug release characteristics and personalized devices like implants. Various 3D printing techniques, including inkjet printing, binder jetting, fused filament fabrication, selective laser sintering, stereolithography, and pressure-assisted microsyringe, are being investigated for their ability to produce polypills, manage release mechanisms, and integrate multiple medications into one unit. Although it holds potential for personalized medicine and patient-focused healthcare, there are still obstacles related to scalability, technical issues, and obtaining regulatory approval. Ongoing innovation, improvement of methods, and adjustments to regulations will be necessary for the successful incorporation of 3D printing into standard clinical and commercial pharmaceutical practices.

KEYWORDS: Three-dimensional (3D) printing, stereolithography, microsyringe, polypills, innovation.

1. INTRODUCTION

Over the last ten years, the use of 3D printers has increased significantly among both industries and the general public. Global sales of consumer printers have risen by over 33% in the past three years, amounting to \$4.1 billion in 2014.

The most well-known and unique solid dosage forms have been created using various three-dimensional printing (3DP) technologies. 3D printing, also known as additive manufacturing (AM), is a method of creating three-dimensional solid objects from a digital file. 3D printing is a distinctive and effective technology that was initially introduced by Charles Hull in 1986, and he referred to it as "stereolithography." It utilizes the ".stl file format" to read the data in Computer-Aided Design files.^[1,2] The data instructions are then sent electronically to the 3D printer. These guidelines specify the shape, size, texture, and thickness of the object to be printed. Hull later established his own company, "3D System," where he created a stereolithography-based 3D printer that became commercially available in 1988. Since that time, numerous companies have created 3D printers for commercial use. In 1987, Carl Deckard submitted a patent for the selective laser sintering (SLS) rapid prototyping process in the United States, and it was granted in 1989. In that same year, Scott Crump, one of the co-founders of Stratasys Inc. submitted a patent for a technology that the company still employs. Fused deposition modeling (FDM) was introduced in 1992. Hans Langer established EOS GmbH in Germany, concentrating on the laser sintering (LS) process. The company is recognized globally for its high-quality products and applications in 3D printing and continues to enhance its production capabilities. During the 1990s and early 2000s, many new technologies were introduced.^[3]

SolidScape, ZCorporation, Arcam, Object Geometries, MCP Technologies, EnvisionTec, and ExOne were established in the years 1996, 1997, 1998, 2000, 2002, and 2005, respectively. These companies accelerated the growth of 3D printing in the worldwide market. The term "additive manufacturing" was agreed upon for all the applications. These technologies were large and quite costly for small businesses or individuals. In the past ten years, many new companies have emerged in the market offering small, affordable, and high-quality machines. The first small kit version of a 3D printer was released in 2009 for commercial use, based on the RepRap concept. In June 2012, a different method of 3D printing using DLP technology called "B9Creator" was introduced. In that year, Form 1 was launched, using stereolithography technology. Since then, significant growth has been noted in this area, and it has been shown that 3D printing technology is being used commercially in different industrial sectors. 3D printing grew quickly and brought significant changes to the health care industry. The medical applications of 3D printing include the production of custom prosthetics, body tissues, organ manufacturing, anatomical models, dental implants, and research in pharmaceuticals related to drug dosage forms, delivery methods, and discovery. In December 2015, the FDA approved over 85 medical devices made using 3D printing technology. In 2015, the FDA approved Spritam (levetiracetam), the first 3D printed tablet, which was produced by Aprelia Pharmaceuticals. Aprelia's product, 'Spritam,' is used to treat epilepsy and represents a notable improvement for patients experiencing seizures. This significant development in 3D Pharming could lead to major changes in the future of drug manufacturing.^[3]

3D printing is a method that creates three-dimensional drug products by building them up layer by layer from a digital design. 3D printing technology that utilizes computer-aided design offers significant flexibility, reduces time, and provides outstanding manufacturing capabilities for pharmaceutical products by shaping drug materials into the required dosage forms. The process includes creating 3D prototypes through layer-by-layer fabrication using computer-aided design models to produce drug materials in the required dosage form.^[4]

The concept of a 3D printer can be considered similar to that of a regular printer. A 3D printer has an extruder that moves side to side along a horizontal axis. This axis is positioned on top of two additional axes, which enable it to move back and forth in the x-y plane to form the base of the object. These two axes are connected to the sides of the

printer. The only distinction is that the 3D printer has a base that moves up and down on the z-axis to build layers on the object. During the printing of the first layer, the extruder stays at the top and moves only in two dimensions.^[5] The base supporting the substrate will be lowered to allow for the construction of the next layer on top. The process continues according to the computer-aided drafting instructions until the object is constructed layer by layer. This procedure is known as additive manufacturing, rapid prototyping (RP), or solid freeform technology (SFF). 3D printers are utilized to create different porous structures with specific chemical properties, interconnected pores, and unique shapes. These prints are biodegradable and have been shown to be suitable for drug delivery purposes. This technique can produce intricate structures that include living cells and has become widely used in cancer treatment.^[6]

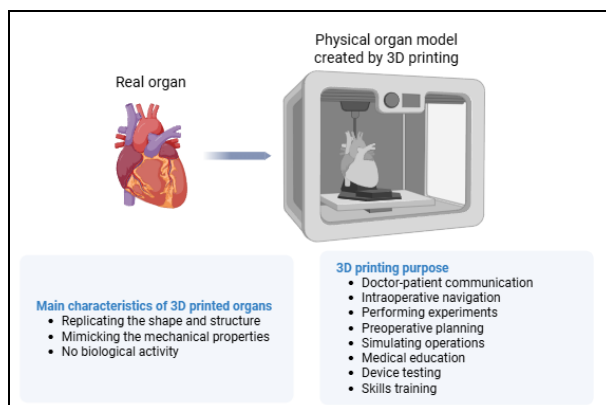


Fig.1: 3D Printing in the Medical Field.

2. HISTORY OF 3D PRINTING

The initial studies on 3D printing began in the late 1970s, during which several patents were filed for methods of computer-aided additive manufacturing using various platforms. In the mid-1980s, Charles (Chuck) Hull, who is considered a pioneer in this field, invented and patented stereolithography (SLA), a key technology in 3D printing. This process used resins that were polymerized with UV light to create the intended object. 3D Systems, established by Hull, later commercialized these SLA printers.

In 1986, Carl Deckard, a student at a university in Texas, created a technology called Selective Laser Sintering that used a laser to bind powder materials together. In 1989, Scott and Lisa Crump at Stratasys received another patent for fused deposition modeling. This process included heating and forcing plastic or metal through a nozzle. In 1989, Emanuel Sachs and his colleagues at MIT created three-dimensional printing methods that used a binding solution applied to a powder bed by adapting an inkjet printer. This method later became known as "binder jetting." In 1989, Hans Langer concentrated on direct metal laser sintering, a process that used lasers to create 3D objects from computer models.^[7]

Several initiatives were implemented to ensure that people could access affordable and non-proprietary printers. The Replicating Rapid Prototyping (Rep Rap) project was established and conducted by Andrew Bowyer at the University of Bath. The project focused on creating 3D printers that can manufacture most of their own parts, leading to significant growth through various collaborations.

Since its creation, 3D printing technology has been applied in a range of industries. At first, clinical applications in healthcare were used for planning and guiding surgeries as well as for creating implants. Implants containing active

pharmaceutical ingredients were also created, showing strong potential for customization. 3D printing was utilized for educational purposes in clinical settings. 3D printing is now being utilized in the pharmaceutical industry to create different types of dosage forms. In 2015, the FDA approved Spritam (Levetiracetam), the first drug to be produced using 3D printing technology. This prescription medication for epilepsy was developed by Aprelia Pharmaceuticals. This was produced using the binder jet printing method and can dissolve quickly in the mouth due to its highly porous structure.^[8]

3. TYPES OF 3D PRINTING

3.1. Fused Deposition Modeling (FDM)

Fused deposition modeling (FDM) or fused filament fabrication is the most widely used method for 3D printing. Thermoplastic filaments containing drugs are created and then supplied to the printer. In the printer, these filaments are heated to a specific temperature and pushed through the nozzle. The printhead moves across a raster platform, and the extruded filament is deposited onto the printer platform, forming the first layer of the object. Additional layers are added as the platform is lowered each time to create space for the next layer. The filaments decrease in temperature and adhere to the layer below them. This process is carried out multiple times to create the finished 3D object (Fig.2). In most printers, the temperature of the printhead can be adjusted, enabling the use of different polymers and polymer mixtures.^[9]

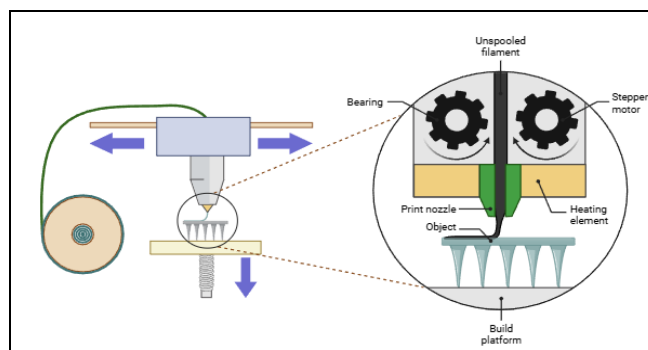


Fig.2: 3D Printing in Pharmacy Fused Deposition Modeling (FDM).

The filaments used for FDM are primarily produced through the hot melt extrusion (HME) process, in which the drug is mixed with the polymer and different excipients. This method employs a screw-driven extrusion system within a barrel. A motor powers the system, applying heat and pressure to melt the mixture, which is then allowed to cool. This combination then solidifies to create the filament that will be used as the input for FDM. The extensive application of FDM in the pharmaceutical industry is due to its affordability, printing precision, assured quality standards, and the integration of HME.^[10]

Research was conducted on direct powder 3D printing (DPP), which is a one-step Fused Deposition Modeling (FDM) process that does not involve Hot Melt Extrusion (HME). The powder mixtures were loaded into a stainless steel extrusion cartridge, heated, and successfully printed to create tablets with a honeycomb pattern.^[11]

Table 1: Characteristics of Fused Deposition Modeling (FDM).

Materials Used	Layer Thickness	Accuracy	Build Speed
PLA, ABS, PETG, Nylon, Polycarbonate, TPU (flexible filament).	Typically 0.1 mm – 0.3 mm.	$\sim \pm 0.1\text{--}0.3$ mm depending on printer quality.	Moderate, depends on part size and layer height.

➤ **Application**

- Creation of customized oral dosage forms that provide a regulated release of medication.
- Development of multilayer tablets that incorporate both immediate and extended release characteristics.
- Creation of intricate shapes such as hollow tablets, rings, or shells for enhanced drug delivery.
- Applicable in pediatric and geriatric medicine where accurate, smaller doses are necessary.

➤ **Advantage**

- Low cost and widely available.
- Can print strong, functional parts.
- Simple process with minimal waste.
- Wide range of thermoplastic materials available.
- Good for rapid prototyping and small-batch production.

3.2. Inkjet 3D Printing

Inkjet printing mainly functions in two modes for creating droplets: Continuous Inkjet Printing (CIJ) and Drop-on-Demand (DOD) Printing. Each mode has its own distinct methods of operation, benefits, and drawbacks, and the selection depends on the particular needs of the application. The diagram shows these two methods clearly. The following is a detailed discussion of both methods.^[12]

3.2.1. Continuous Inkjet Printing (CIJ) Mode

In continuous inkjet mode, liquid material, commonly known as ink, is continuously fed through a nozzle to produce a constant flow of droplets. This procedure includes multiple elements:

- **Pump:** The pump creates pressure that pushes the ink out of the nozzle.
- **Piezoelectric element:** A piezo element generates vibrations to divide the liquid stream into evenly sized droplets.
- **Charge electrode:** Every droplet can acquire an electric charge as it leaves the nozzle.
- **High-voltage deflector:** Charged droplets can be redirected from their initial trajectory, allowing them to reach a specific location on the surface or into a recycling channel.
- **Recycling gutter:** Droplets that are not used or are redirected are gathered and reused in the system.

CIJ offers the benefit of fast operation and the capability to print continuously without breaks, making it ideal for high-volume production settings.^[13] It enables printing at very high frequencies, reaching up to hundreds of kilohertz, which allows for the production of thousands of droplets each second. This is especially helpful in situations where ongoing marking, coding, or coating is needed.^[14]

CIJ has certain limitations. The need for droplet deflection and recycling adds complexity to the system and increases energy consumption. Furthermore, since droplets are produced continuously, it can be more difficult to manage the precise application of materials compared to printing that is done on demand. The dependability and speed of CIJ make it a favorable option for large-scale printing, such as in pharmaceutical coating, packaging, and decorative printing.

3.2.2. Drop-on-Demand (DOD) Mode

The drop-on-demand mode operates in a manner that is quite different from continuous inkjet (CIJ). This system produces droplets only as needed, which is why it is called "on-demand." There is no constant flow of liquid; rather, the printer releases droplets individually based on a digital signal. The method for generating droplets can use either a heater (thermal inkjet) or a piezoelectric component.^[4]

- **Thermal inkjet:** A small resistor heats the ink rapidly, creating a vapor bubble that forces a droplet out of the nozzle.
- **Piezoelectric inkjet:** A piezo element deforms mechanically when voltage is applied, pushing out a droplet of ink.

In both situations, the droplet directly reaches the substrate at the intended spot without requiring recycling gutters or high-voltage deflection.

The main benefit of DOD is its accuracy and effectiveness. Droplets are created only when necessary, resulting in little material waste. This mode enables high-resolution printing, making it suitable for tasks like printing pharmaceuticals, biomaterials, electronics, and 3D tissue scaffolds where accurate placement of small quantities of material is important. An additional significant advantage is the capability to manage various types of inks, such as bio-inks, polymers, or nanoparticle suspensions, since the process is milder than CIJ. This makes DOD well-suited for sensitive uses such as bioprinting cells or creating drug-loaded tablets with specific dosages.^[15]

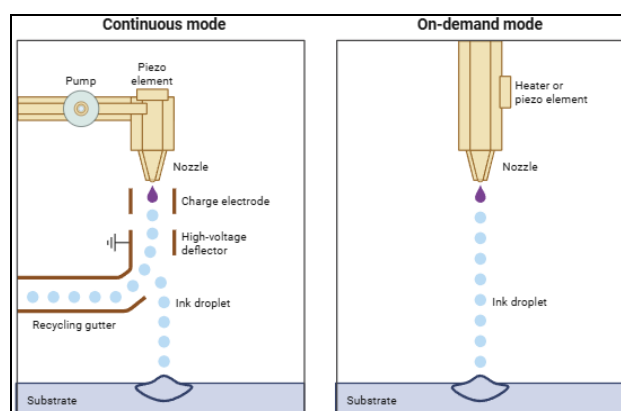


Fig. 3: Inkjet Printing Modes in 3D Printing.

Table 2: Comparative Overview of Continuous Inkjet (CIJ) and Drop-on-Demand (DOD) Mode.

Feature	Continuous Inkjet (CIJ)	Drop-on-Demand (DOD)
Droplet generation	A steady flow divided into individual drops.	"Only when necessary."
Speed	Extremely high (thousands of droplets per second).	"Moderate"
Material usage	Not as efficient (requires recycling).	Very effective.
Precision	"Moderate"	Accurate placement of droplets.
Complexity	High (requires charging, redirection, recycling)	Relatively simple
Applications	Industrial-scale printing, coding, labeling	3D bioprinting, pharmaceuticals, electronics

3.3. Stereolithography (SLA)

Stereolithography (SLA) is an early 3D printing technology utilized in the pharmaceutical industry, recognized for its accuracy and capability to create intricate designs. SLA operates based on photopolymerization, a process in which a liquid resin, typically a photosensitive polymer, is cured selectively layer by layer with a focused ultraviolet (UV) laser.

The process starts with a build platform positioned just below the surface of the resin tank.^[16] The UV laser follows a specific pattern on the surface of the liquid resin, causing it to harden into the intended shape. After a layer has hardened, the platform shifts slightly downward (or the resin surface rises, depending on the system), enabling a fresh layer of liquid resin to cover the layer beneath it. This method of building is carried out one layer at a time until the entire three-dimensional object is created.^[17] SLA is especially beneficial in pharmaceutical applications because it can create highly detailed dosage forms, implants, and drug delivery devices with accurate shapes that are challenging to produce using traditional methods. Additionally, SLA enables the creation of customized medications with specific dosages, porous designs for regulated drug release, and intricate internal pathways, which improve the effectiveness of the drugs and patient adherence to treatment. While SLA has benefits, it is important to carefully assess the biocompatibility of the resin, the presence of any leftover monomers, and the necessary post-processing procedures, such as washing and UV curing, to guarantee that the final product is safe and effective for pharmaceutical applications.^[18,19]

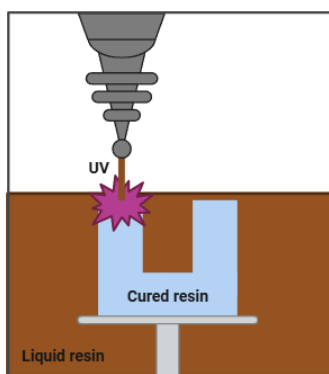


Fig. 4: Stereolithography (SLA).

➤ **Application**

- **Personalized Medicine:** The creation of personalized medication forms designed to meet the specific requirements of each patient.
- **Complex Drug Delivery Systems:** Development of tablets and implants featuring complex shapes and internal pathways for regulated or prolonged drug delivery.
- **Rapid Prototyping:** Creation of initial models for new drug formulations and medical equipment.
- **Implants and Medical Devices:** Production of biocompatible implants, scaffolds, and other medical devices with accurate measurements.
- **Porous Structures:** Creating porous structures to improve dissolution rates or facilitate targeted drug delivery.
- **Research and Development:** Supports the testing and improvement of new dosage forms prior to mass production.
- **On-Demand Manufacturing:** Facilitates the production of medicines on a small scale or tailored to individual requirements as necessary.
- **Complex Oral Dosage Forms:** The production of multi-layered or combination tablets that are difficult to create using traditional techniques.

➤ **Advantage**

- High Precision and Accuracy.
- Customization of Dosage Forms.
- Ability to Produce Complex Structures.
- Rapid Prototyping and On-Demand Production.
- Smooth Surface Finish.
- Material Efficiency.

3.4. Selective Laser Sintering (SLS)

Selective laser sintering uses laser energy to heat and bond powder particles, which then solidify to create a three-dimensional object. The key parts of the selective laser sintering (SLS) system include the spreading platform, powder bed, and laser system. The spreading system initially distributes the powder evenly across the platform, and a roller blade is then used to smooth the surface.^[10] The laser system follows a predetermined scanning pattern in a two-dimensional plane, which is based on the characteristics of the final product. The material is heated to a temperature lower than its melting point to achieve fusion through melting with a laser, and the height of the bed is adjusted to focus the laser on the newly created surface. The loose powder on the platform offers assistance during the process. The powder bed is lowered by the thickness of one layer each time, and then the subsequent layer is added and fused. This process is repeated to create the final 3D-printed object, which, after cooling inside the printer, is collected from the loose powder either by hand or with a sieve. (Fig.5) This method is beneficial because it is a quick, one-step production process that does not require any solvents. It also creates objects with high resolution because of the precision of the laser.^[11]

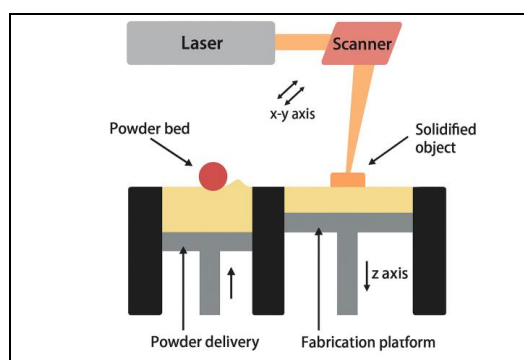


Fig. 5: Schematic of selective laser sintering.

➤ **Application**

- **Personalized Medicine:** Dosage forms tailored to individual patients, including variations in size, dose, and shape.
- **Controlled Drug Release:** Tablets that have altered or extended drug release characteristics.
- **Pediatric & Geriatric Formulations:** Small, easy-to-swallow tablets or dissolvable films.
- **Implantable Drug Delivery Devices:** Implants that can break down naturally for targeted and extended delivery of medication.
- **Microneedles & Transdermal Systems:** Microneedle arrays designed for accurate and painless administration of medication.
- **Tissue Engineering Scaffolds:** Frameworks for cell development, bone repair, or healing of wounds.

- **Medical Devices:** Personalized prosthetic limbs, biological sensors, and portable medical devices.
- **On-Demand Manufacturing:** Rapid manufacturing of medications in hospitals or pharmacies [20,21].

➤ **Advantage**

- Solvent-free process.
- High drug loading capacity.
- Complex geometries.
- Tailored drug release.
- On-demand production.
- No need for support structures.

Table 3: Comparison of 3D Printing techniques.

Technique	Accuracy	Scalability	Material Compatibility
Fused Deposition Modeling (FDM)	Moderate (± 0.1 – 0.3 mm); layer lines visible	High scalability; widely used and cost-effective for large-scale prototyping	Limited; mainly thermoplastic polymers (PLA, ABS, PVA, PETG, etc.)
Inkjet 3D Printing	High (± 0.05 – 0.1 mm); smooth surface finish	Moderate scalability; suitable for small-to-medium production runs	Broad; photopolymers, ceramics, biomaterials, some metals (with binder jetting)
Stereolithography (SLA)	Very high (± 0.025 – 0.1 mm); excellent surface detail	Moderate scalability; limited by resin curing speed and build volume	Limited; primarily liquid photopolymer resins
Selective Laser Sintering (SLS)	High (± 0.05 – 0.15 mm); good mechanical strength	High scalability; supports batch production without support structures	Wide; thermoplastic powders (nylon, polyamide, composites, some metals in variants)

Table 4: 3D printing techniques Material used.

3D Printing Technique	Materials Used
Fused Deposition Modeling (FDM)	- Pharmaceutical-grade polymers: PVA (Polyvinyl alcohol), PLA (Polylactic acid), HPMC (Hydroxypropyl methylcellulose) - APIs (Active Pharmaceutical Ingredients) - Excipients such as plasticizers and stabilizers
Inkjet 3D Printing	- Liquid formulations of APIs - Printable excipients (binders, stabilizers, solvents) - Polymers like HPMC, PEG (Polyethylene glycol)
Stereolithography (SLA)	- Photopolymerizable resins with pharmaceutical-grade polymers - APIs incorporated into resin formulations - Biocompatible excipients for curing
Selective Laser Sintering (SLS)	- Powdered pharmaceutical polymers (e.g., PVA, HPMC, PLA) - APIs in powder form - Excipients enhancing flow and sintering properties (e.g., lactose, mannitol)

4. 3D PRINTED SOLID DOSAGE FORMS (SODFS)

4.1. 3D printed approved solid dosage forms (SODFs)

Spritam®, produced by Aprelia Pharmaceuticals, is the only solid oral dosage form that is currently available for sale and made using 3D printing technology. The FDA granted approval in August 2015, and the product was subsequently launched in the United States. In March 2016, it was released in four strengths (250 mg, 500 mg, 750 mg, and 1000 mg) and is used as an additional treatment for myoclonic and tonic-clonic seizures in different types of epilepsy.^[22]

Spritam® offers a notable benefit compared to standard levetiracetam tablets or oral solutions due to its rapid disintegration. It dissolves almost immediately, in approximately 5 seconds, with just a small volume of liquid (up to 15 ml). In contrast, conventional tablets take about 60 seconds to dissolve, and Spritam® reaches its peak plasma concentration in roughly 9 minutes. This is especially useful for children and older adults who might struggle to swallow large tablets, as liquid forms can present difficulties in measuring the correct dosage.^[23]

Spritam® is made using a patented printing technology called ZipDose®, which is based on inkjet DoP (Drop-on-Powder) methods. This method produces tablets with a high level of porosity, allowing water to enter quickly and facilitating rapid disintegration. It also enables taste masking, which enhances the acceptability of the product when taken orally. However, there are limitations such as high friability and low mechanical strength, which means that the tablet needs to be handled carefully during packaging.^[24]

Although Spritam® is an innovative 3D-printed solid dosage form, it does not fully take advantage of the capabilities of 3D printing, such as producing complex formulations, tailored dosing, or personalized tablet shapes. The tablet maintains a standard circular flat cylinder shape that is common for fast-dissolving tablets.^[19]

4.2. 3D printed solid dosage forms (SODFs)

Recent research has investigated the application of 3D printing to create new solid oral dosage forms (SODFs) with customized drug release characteristics. "Khaled and others." A PAM extrusion-based system was utilized to create multi-drug tablets that include glipizide, nifedipine, and captopril. This method achieved a sustained and controlled release using hydroxypropyl methylcellulose (HPMC) matrices and a semi-permeable membrane.^[19] The tablet size of 12 mm created difficulties with swallowing because of the large amount of excipients included.^[25]

"Pietrzak and colleagues." Used Fused Filament Fabrication (FFF) with hot-melt extruded filaments containing drugs to create theophylline tablets with different strengths and release characteristics. The research showed accurate control of dosage ($R^2 = 0.9995$) and indicated the possibility of patient-focused, on-demand printing in pharmacies or hospitals, especially for patients who are taking multiple medications, as well as pediatric, geriatric, or organ-impaired individuals.^[19]

Sun and Soh created SODFs by utilizing 3D-printed molds made from polydimethylsiloxane and biodegradable polyanhydride polymers, resulting in a controlled release of drugs in pulses.^[28] Adjusting the design and choosing different polymers enabled regulation of the release rates. FDM-printed theophylline tablets with structures resembling radiators had a larger surface area, which led to quicker dissolution. In summary, 3D printing allows for the creation of multi-drug, patient-specific solid oral dosage forms (SODFs) with controlled and customizable release characteristics. This method provides benefits over traditional manufacturing in terms of precise dosing, personalized treatment, and adaptable design.

5. REGULATORY PERSPECTIVE

The use of 3D printing technology in the pharmaceutical industry, which is subject to strict regulations, poses both technical and regulatory difficulties. The strict quality and risk management requirements set by regulatory authorities lead pharmaceutical manufacturers to be cautious about adopting new technologies unless there is a considerable amount of validation data available. This careful method is further influenced by the industry's dependence on

established manufacturing processes and the absence of a strong regulatory framework that specifically addresses the unique features of 3D printing. The current regulations were created with traditional manufacturing methods in focus, emphasizing the validation of the manufacturing process instead of the individual parts of the production line. This method guarantees that as long as the final product meets the necessary standards, there is less focus on the particular technologies used in its production. The introduction of 3D printing technology presents a challenge to this approach, necessitating a regulatory review that focuses on individual components because of the unique features of the technology. The current documentation and experience of relevant regulatory bodies regarding new manufacturing technologies like 3D printing lack sufficient detail, resulting in a lack of clear regulatory guidance. The absence of specific guidance may lead to a delay in adopting the technology, as manufacturers wait for clearer regulatory requirements and are concerned about the possibility of non-compliance.^[29]

As technology progresses, there is an increasing demand for regulations that align with these advancements. This involves setting standards for the qualification of 3D printing equipment, validating processes, and implementing quality control measures tailored to its use in pharmaceutical manufacturing. Regulatory agencies are starting to create guidelines that take into account the unique aspects of 3D printing in order to tackle these issues. The FDA has provided guidance on technical aspects related to additive-manufactured medical devices, which could lead to more comprehensive guidelines for 3D printing in the production of pharmaceuticals. The future of 3D printing in the pharmaceutical industry will rely on its capacity to manage regulatory requirements, prioritizing patient safety while promoting technological advancements. Collaboration among regulatory agencies, manufacturers, and technology experts will be essential for creating a regulatory framework that promotes the safe and effective use of 3D printing in pharmaceutical research, development, and manufacturing.

Support from regulatory bodies for new technologies is essential for promoting innovation in the pharmaceutical industry. Regulatory support for technologies such as 3D printing promotes their development and helps ensure that their entry into the market is in line with public health priorities. Regulators can reduce potential risks related to new technologies by offering clear guidelines and frameworks. This approach helps ensure patient safety while encouraging scientific progress. Regulatory approval is important for ensuring the reliability and effectiveness of the pharmaceutical manufacturing process. Additionally, actively engaging with technology developers can speed up the process of turning research into treatment options that meet unfulfilled medical needs. The relationship between regulation and technological advancement is essential for the development of personalized medicine and improving healthcare delivery. In the area of 3D printed pharmaceuticals, it is expected that there may be physical quality defects. Z-layer separation, bending, layer shifting, and similar issues pose challenges for quality control. The existing quality control measures and current technology may not be adequate to prevent these defects. This highlights the essential role of regulatory bodies in establishing regulations that take into account the limitations of the technology, its performance, and the safety and effectiveness of pharmaceutical products. Regulatory oversight is important for the pharmaceutical industry to effectively utilize innovative technologies like 3D printing and improve healthcare results.^[30]

6. Limitation And Challenges

Although 3D printing technology is becoming more popular in the production of medical devices, its use in creating pharmaceutical drug products remains restricted because of technical, material, and regulatory issues. A key technological constraint is production yield.^[31] Traditional tableting can manufacture more than 15,000 tablets per

minute, while 3D printing may take anywhere from 2 minutes to 2 hours for each tablet, depending on the technique used. Nonetheless, 3D printing allows for localized and small-scale production in pharmacies or hospitals, making medications more accessible to patients.^[29]

Common challenges consist of differences in layer thickness, a restricted range of material choices, and leftover unreacted starting materials.^[32] Different techniques face unique challenges: laser-based systems require safer and more adaptable materials for precise drug release; DoD and PAM methods need enhancements in drying and post-processing to avoid API degradation; and Fused Filament Fabrication (FFF/FDM) operates at high temperatures that could impact drug stability or lead to polymorphism.^[33,34,35,36] Studies indicate that changing excipients can address these thermal challenges, as shown with heat-sensitive drugs such as ramipril and 4-aminosalicylic acid. Powder-based methods have issues related to mechanical strength; however, some products, such as Spritam®, take advantage of porosity to allow for quick disintegration.

Excipients are important in determining the final product's structure, physical characteristics, how it dissolves, and its acceptance by patients. Excipients are usually thought to be inactive, but they need to be assessed carefully to prevent negative interactions with active medications.^[32]

CONCLUSION

In the pharmaceutical sector, 3D printing has become a game-changing technology that presents previously unheard-of possibilities for on-demand manufacturing, sophisticated dose designs, and individualized therapy. It is very useful for pediatric, geriatric, and multi-drug therapy because it provides exact control over dosage, form, and release patterns, unlike traditional drug manufacture. An important turning point that showed the clinical potential of this strategy was the approval of Spritam®. Nevertheless, obstacles like limited scalability, limited material options, protracted production periods, and ambiguous regulatory paths continue to hinder wider implementation. It will be necessary to continuously innovate printing methods, create safe and adaptable excipients, and establish precise regulatory standards to guarantee patient safety and quality in order to overcome these obstacles. Pharmaceutical manufacturing could be revolutionized by 3D printing, opening the door to genuinely individualized and patient-centered healthcare, provided scientists, manufacturers, and regulatory bodies continue their research and work together.

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