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3D PRINTING IN PHARMACY: BRIDGING INNOVATION AND PRECISION MEDICINE

K.Akash, B.Samuel Shekhar, G.Roopa, I.Vamshi, K. Sai Bhargav, Dr. SNVL Sirisha*, P.Shivani

Malla Reddy College of Pharmacy, Maisammaguda, Secunderabad, India

*Corresponding author E- mail: snvlscops@gmail.com

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ABSTRACT

Three-dimensional printing (3DP), also known as additive manufacturing, has emerged as a transformative technology in pharmaceuticals and healthcare. By enabling precise and personalized drug delivery systems, organ-on-chip development, and rapid prototyping of implants and prosthetics, 3DP is addressing long-standing challenges in conventional manufacturing and drug development [1]. This review explores the principles, key applications, and limitations of 3DP technology in medicine, focusing on its role in personalized therapeutics, biomedical research, and clinical applications. Current challenges, including regulatory hurdles, material limitations, and cost constraints, are discussed, alongside future directions that integrate artificial intelligence (AI) and novel biomaterials

INTRODUCTION:

Three-dimensional printing, first developed in the 1980s by Charles Hull.[12] The name 3d printing itself gives an idea that we can create or print objects of desired shape with desired material. 3d printing is widely used in various fields such as Aerospace industry, Automotive industry, food industry, healthcare and medical industry, Architecture, building, and construction industry etc [12]. In healthcare industry, this 3d printing has being showing a tremendous effect in the pharmacy field during the preparation of formulations. In preparation of formulation, we use various types of excipients and drugs which will have a great diversity in their physicochemical properties. Because of these differences making them into a suitable formulation will be difficult. By using this 3d printing we can overcome the difficulties in the preparation of formulations. Moreover, personalized medication can be achieved.

Before working with 3d printer we need to have basic knowledge on its working and terminologies used frequently.

TERMINOLOGY: 3D printing, also known as additive manufacturing, comes with its own set of unique terms. Here's a handy guide to some of the most commonly used terminology:

1. Additive Manufacturing (AM): The process of creating a 3D object by adding material layer by layer.

2. Fused Deposition Modeling (FDM): A popular 3D printing method where material is extruded layer by layer to build the object.

3. Stereolithography (SLA): A 3D printing technique that uses a laser to cure liquid resin into hardened plastic.

4. Selective Laser Sintering (SLS): A method where a laser sinters powdered material into a solid structure.

5. G-code: A language in which people tell computerized machine tools how to make something.

6. Extruder: The part of the 3D printer that pushes out the filament to form each layer.

7. Filament: The material used for FDM 3D printing, typically made of plastic like PLA or ABS.

8. Build Plate: The surface on which the 3D printed object is built.

9. Nozzle: The part of the extruder that actually releases the filament onto the build plate.

10. Infill: The internal structure of the 3D printed object, which can vary in density.

11. Layer Height: The thickness of each layer of material in a 3D printed object.

12. Raft: A base layer printed to help the object adhere to the build plate.

13. Support Structures: Temporary structures printed to support overhanging parts of the object during printing.

14. Slicing: The process of dividing a 3D model into layers and generating the G-code needed for printing.

TYPES OF 3D PRINTING: Although there are other forms of 3D printing, there are mainly 2 types:

1. Binder jetting: This is the most often utilized. Binder jetting is a 3D printing and rapid prototyping technique that joins powder particles by selectively depositing a liquid binding agent. The layer is created using the binder jetting technology, which sprays a chemical binder onto the distributed powder. [8]

2. Directed energy deposition: The more complicated printing technique known as "directed energy deposition" is frequently used to repair or add material to already-existing components. Directed energy deposition can create high-quality objects and offers a great degree of control over grain structure. [8]

HOW IT WORKS? : 3D printer works with different principles. some of the principles are Stereolithography and Selective Laser Sintering[2]. Now a days, A.I (Artificial Intelligence) and M.L (Machine learning). At first we need to select the desired shape or structure we need to print[12]. Then a suitable material should be selected. Here the materials most commonly used are metals, polymers, ceramics and smart metals, Then the shape or data should be incorporated into the machine and it will produce the structure [12]. For this process of printing there are mainly 4 basic steps

Digital Design: **The Basis of 3D Printing** Digital design is the first step in the 3D printing process, which acts as a blueprint for the final object. This step involves creating or acquiring a detailed and precise 3D model of the desired structure[13]. Usually, this is done using advanced computer-aided design (CAD) software, which allows for the creation of intricate and customizable designs tailored to specific requirements[15]. These designs can be obtained from online repositories, where pre-designed models are downloadable. In the case of more complex applications, such as in pharmacy or engineering, digital design is the core of the process that ensures the final product's functionality, accuracy, and ability to perform specific tasks. The design phase allows for the modification, optimization, and simulation of the object before printing in the physical form, thus minimizing errors and wastage[13]. This step sets the stage for the entire 3D printing workflow, ensuring precision and alignment with desired outcomes.

Fig 1: 3d printing machine

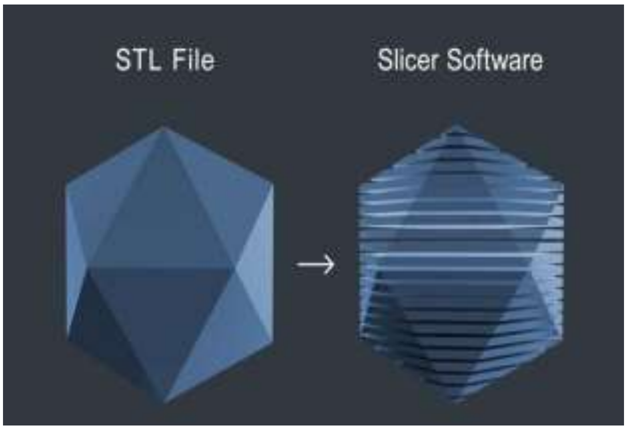


Fig: 2 the process of converting an STL file into sliced model using slicer software

Slicing: **Preparing the Design for 3D Printing**: Slicing is a critical step in the 3D printing process where the digital design, created or acquired during the digital design phase, is converted into a series of thin, horizontal and vertical layers. This is achieved through specialized slicing software, which essentially translates the 3D model into instructions that the 3D printer can understand [2]. The design is divided into small slices, allowing the printer to build the object layer by layer with greater precision and efficiency. The slicing procedure also defines a number of parameters that are highly critical, which include layer height, infill density, and speed of printing, which impacts the quality of the final product, including strength and resolution [9]. Slicing also allows adding support structures to the model as needed, particularly for printing objects with complex geometry or overhangs.This is to ensure that the 3D printer is able to replicate the finer details of the digital model correctly and at the same time optimizes material use while minimizing printing mistakes [9].

Printing: Bringing Your Design to Life: The printed version is what takes the virtual 3D model from its computer design environment into the tangible form by using layers of deposits, and most importantly, utilizes the nozzle, along with its possible alternatives like others deposition devices[13]. Material-wise, this normally occurs through materials made from plastic and metal resins to specific specially bio compatible polymers to produce the entire model, almost similarly shaped to its electronic blueprint model.

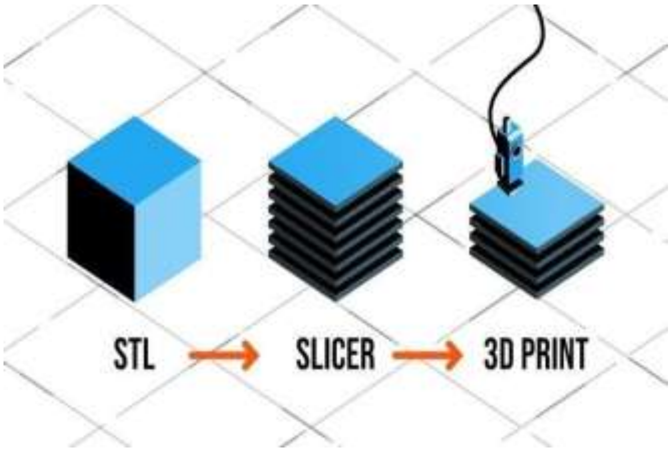


Fig 3: Illustrating the transformation from an STL file to sliced layers and final 3D printed output

[2] The printer follows the instructions from the slicing software to deliver accurate and detailed output. Depending on the type of 3D printer or the material used, the process can include techniques such as melting (in fused deposition modeling), curing with light (in stereolithography), or binding particles (in powder-based methods). This stage proves that hardware and software can easily integrate, providing the ability to produce complex geometries, intricately detailed geometries, and highly customized structures that are almost impossible to be manufactured through other conventional manufacturing techniques. [13]

Cooling and Solidification: Stabilizing the 3D Structure: Cooling and solidification are critical steps in the actual 3D printing process because they are what guarantee the ultimate stability and strength of the final product[14]. In the printing process, the material is always in a liquid or semi-liquid form . This is obtained either through heating previously solid materials, such as in FDM, or through dissolution in a solvent that allows them to dissolve, such as in some resin-based or bio-printing techniques. Once the material is deposited layer by layer to form the 3D structure, cooling or curing is necessary to change the material from its liquid state to a solid state[14]. This process is crucial in forming a strong, stable, and durable structure. For thermoplastic materials, cooling happens naturally as the material solidifies at room temperature. For resin-based or photopolymer materials, solidification is achieved through exposure to ultraviolet (UV) light or other curing agents. Proper cooling and solidification prevent any deformation, warping, or shrinkage from the structure; besides, the strength of the structure is properly provided. This step helps produce a highly precise and reliable 3D model as per specifications with the desired function[15].

ADVANTAGES OF 3D PRINTING IN PHARMCEUTICS

1. Personalized medicine for vulnerable populations: Earlier it had raised the issues of safety and health in medications for special populations, especially the elderly and children,[8] . Children are in the growth and development stages with specific reactivity and sensitivity to medications; the elderly have limited absorption and metabolic capacity, and the presence of a myriad of diseases combined with polypharmacy is rather common[4]. While the dosages of drugs nowadays are standardized, special drugs for special populations are hardly available, and children's medications are given to them in tablets that have been broken down, which is both inaccurate and sometimes damages the special structure of the preparation and even causes adverse reactions.

This is very flexible because the three-dimensional printing technology can be used to print targeted medicines by adjusting the parameters of the model, for example, size, shape, or fill rate[8]. For pediatric patients, 3D printing technology can produce low-dose personalized medicines that are suitable for children, and improve the appearance and taste of medicines, thus increasing the compliance of the pediatric patient; for elderly patients, 3D printing technology can prepare loose and porous preparations to help them swallow medicines; for patients who take multiple drugs at one time, different drugs can be partitioned and combined into a single tablet to avoid errors or missed drugs, which can increase the safety and effectiveness of medication; in addition, special-shaped preparations can be printed or special symbols can be printed on the surface of the preparation to provide convenience for the patients with visual impairment[8]. The technical benefits of 3D printing technology supporting personalized drug delivery support people for achieving personalized medicine, and several 3D printed drug companies aim toward the vision of personalized medicine, like the UK-based firm FabRx in preparing drugs with personalized use of children with maple diabetes and which has installed its SSE printers inside the pharmacy of Spanish hospital during undergoing clinical trials for the subject.[4]

2. Accurate Dosage Delivery: Being the most widely prepared solid oral dosage form, tablets occupy 70% of the entire dosage form manufactured . Though conventional production techniques make it easier to manufacture tablets at a cheaper price, the old traditional production processes were less innovative in developing preparation formulation. Preparation development time is lengthy and they could not easily produce individualized preparations as needed[8]. Compared to traditional tablets, controlled-release preparations may allow for better control of the drug release profile so that there are fewer side effects and increased efficacy of the drug. On the other hand, the traditional processes pose a bigger challenge in developing and manufacturing controlled-release preparations in relation to their current processes[4]. Three-dimensional printing technology is highly flexible, and therefore, it is properly well-suited for the development and manufacture of complex preparations through the combination of different drugs, the design of complex models, and the adjustment of printing parameters. For example, a controlled release preparation for the circadian rhythm of rheumatoid arthritis by 3D printing, Triastek's T19 product which was approved by the FDA on January 2021[8]. Administration is at bedtime and the blood concentration peaks in the morning when patients experience the worst symptoms of pain, joint stiffness, and dysfunction, with stable blood concentration levels throughout the day for the most effective therapeutic results, thus affording more drug options to the patients.

3. Fast Combination of Production: In the mass production of drugs, general pharmaceutical companies, in order to respond to the international demand for traditional drugs, usually have a very high production capacity, and their production equipment is usually large, with a relatively single type of equipment, without the necessary production flexibility to quickly complete the cleaning and change the variety of drugs produced[8]. Three-dimensional printing technology can also integrate rapid manufacturing, compact equipment, fewer steps in production, automated and digital production processes, and ease in changing the variety of drugs to be produced. For instance, SSE technology provides for direct exchange of disposable syringes with varying drug varieties according to the demand of multiproduct production equipment [4] Moreover, 3D printing technology is best suited for small-scale drug production, which requires customization and frequent design modifications, due to its lower small-batch production costs and integrated manufacturing process, which can play an important role in conditions of limited time and resources[3]. This carries very important implications for drug development, where Merck is using 3D printing technology to accelerate clinical trials and predicts that, based on data, in clinical phases I–III, preparation development time will be decreased by 60% and the API needed to prepare the medication will be reduced by 50%.

APPLICATIONS IN PHARMACEUTICS: 3D printing has revolutionized many industries, from manufacturing and aerospace to healthcare and education, by allowing the creation of complex, customized structures with high precision and efficiency. However, its application in the pharmaceutical industry holds unique significance due to its potential to transform the way medications are developed, manufactured, and delivered.

ZIP DOSE OF SPRITAM: The first compound made using 3d printing in pharmacy was **Spritam** (levetiracetam). It was approved by the U.S. Food and Drug Administration (FDA) in 2015, marking a significant milestone in pharmaceutical manufacturing. Spritam is an anti-epileptic drug developed by **Aprecia** Pharmaceuticals. This is a product developed using proprietary 3D printing technology known as **ZipDose**, which can create highly porous tablets that rapidly dissolve in a small amount of liquid. Such tablets are very useful for patients with dysphagia, or difficulty swallowing.[3] This process of 3D printing allowed the control of composition, structure, and dose of the tablet for highly patient-friendly and customizable drug delivery. It had the potential to display the creation of personalized medicines via 3D printing, revolutionizing the traditional ways of drug formulation. Technical description of the design and creation of Spritam, which is a levetiracetam, using the 3D printing technology and the design principles, manufacturing process, and scientific innovations behind them. [3]

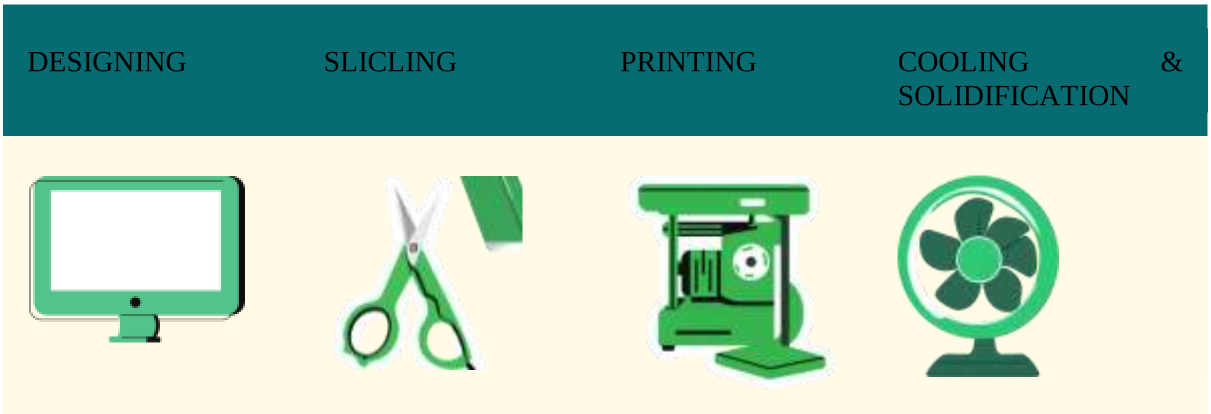
Fig 4: The first FDA approved 3D printed drug.

Technical Workflow in 3D Printing Spritam

***CoreTechnology: Zip Dose:** ZipDose Technology developed by Aprecia Pharmaceuticals, is an advanced application of powder bed inkjet 3D printing. Below are the technical key principles and processes involved:
Input materials and preparations:

1. Active Pharmaceutical Ingredient (API):
- The API, levetiracetam, is processed into a fine powder to ensure uniform distribution within the printed layers. [4] Levetiracetam is used because of its pharmacological properties, solubility, and stability.[3]

2. Excipient Composition: Excipients (inactive substances like binders and disintegrants) are selected for their ability to enhance tablet porosity, structural integrity, and rapid dissolution. Typical excipients include:
- Microcrystalline cellulose: Gives mechanical strength. [3] Cross-linked PVP: Assists in quick uptake of water.



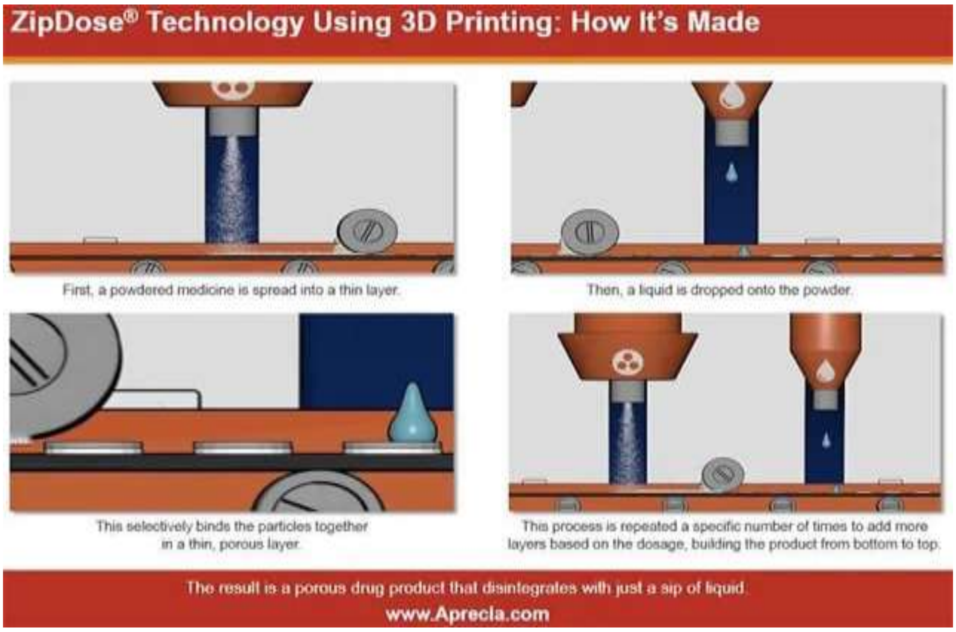


Fig 5: ZipDose® technology process, illustrating how 3D printing is used to create rapidly dissolving pharmaceuticals

Fig 6: A 3D printer used for fabricating pharmaceutical products, enabling precision drug manufacturing

Manitol: Improves taste and dissolving properties [3]

3. Binder Solution: A liquid binder, usually aqueous or alcoholic, is developed to selectively "glue" the powdered layers as it prints.[3]

B. The Printing Process:

1. Powder Bed Layering: A uniform layer of powdered material (API + excipients) is applied using a powder dispensing system (such as a roller or blade) on a flat surface. [3]

- Thickness of the layer is generally in the range of 100–200 µm for accurate precision.[3]

2. Selective Binder Deposition: A piezoelectric print head in inkjet sprays drops of the binder solution to chosen areas on a powder bed and hold particles together in a manner which forms a required tablet shape.[3] Digital control is followed in terms of spray pattern control. It considers the CAD files of pre-conceived designs made for tablet geometries.[3]

3. Step-by-Step Construction: The process continues through repetition stepwise, thereby enabling three-dimensional fabrication of the tablets.[3] It enables accurate control of the tablet's porosity, structure, and geometry.[3]

4. Drying and Post-Processing: After printing, the tablets are dried in a controlled environment to remove residual moisture from the binder. Tablets are evaluated for quality, hardness, and dissolution properties.[3]

C. Structural and Functional Design

1. Porosity Engineering: The porous microstructure is attained by controlled powder deposition and binder application. - High porosity (~60–90%) ensures that the tablet disintegrates almost instantly upon contact with water or saliva. [3]

2. Geometry and Uniformity: The 3D printer allows for precise shaping of the tablets, ensuring consistent weight, size, and API distribution. In contrast to compression, 3D printing eliminates the density gradient effect; hence, uniformity of release is ensured. [3]

3. Control of Dissolution Profile: By optimizing porosity and binder concentration, the drug release rate can be optimized. Spritam dissolves within <10 seconds, meeting rapid onset criteria for the management of epilepsy.[3]

D. Scientific Advancements of Spritam

1. Powder Bed Fusion in Pharmaceuticals:

- PBF 3D printing enables precise dose control and tailored release profiles, which is a major step forward from the traditional compression-based manufacturing.[3]

2. Patient-Centric Design: Direct engineering of high-porosity tablets with rapid disintegration directly addresses patient adherence challenges, especially in populations with swallowing difficulties (pediatrics and geriatrics). [3]

3. Large-Dose Accommodation: Spritam proves that up to 1,000 mg of API can be incorporated into one tablet using a 3D printer without it becoming a large or easy-to-swallow tablet.[3]

4. Scalability: Aprecia produced 3D printers capable of printing millions of tablets every year, addressing potential scaling bottlenecks for additive manufacturing in commercial use.[3]

2. 3D-PRINTED POLYPILLS FOR CHRONIC DISEASES: Background: Polypills are single tablets that combine multiple medications, simplifying complex drug regimens for patients with chronic conditions like cardiovascular diseases. 3D printing technology has enabled the creation of such polypills with precise dosages and tailored release profiles.[10] **Key Developments:** University College London (UCL) Research (2019): Study: Researchers from UCL's School of Pharmacy created a new stereolithographic (SLA) 3D printing process to create multi-layered polypills with up to six different drugs. Drugs used: Paracetamol, caffeine, naproxen, chloramphenicol, prednisolone, and aspirin. Results: The results showed the ability to create complex, multi-drug tablets that could have individual release profiles for each drug. This is potentially an application in personalized medicine. FabRx and UCL Collaboration (2021): Innovation: FabRx, a UCL spin-out company, developed the M3DIMAKER™ pharmaceutical 3D printer that can produce personalized medicines on-demand. Recognition: In 2020, FabRx won the Manufacturing Technology and Equipment category at the CPhI Pharma Awards for this work. **Significance:** These developments show that 3D printing can transform the pharmaceutical manufacturing process by producing customized polypills. This method can enhance patient compliance, minimize medication errors, and allow for tailored release profiles to individual therapeutic needs. [10]

3. 3D-Printed Antibiotic-Releasing Bone Scaffolds for Osteomyelitis: Background: Osteomyelitis is a serious infection of the bone, and its treatment typically involves surgical intervention and long-term antibiotic therapy. The application of 3D-printed bone scaffolds releasing antibiotics provides an exciting potential to offer structural support and direct drug delivery at the site of infection[11]. Key Developments: Wu et al. (2015) Research Study: Wu et al. designed 3D-printed porous scaffolds using β-tricalcium phosphate (β-TCP) in combination with the antibiotic vancomycin. Results: The scaffolds showed controlled release of the antibiotic and enhanced bone regeneration in animal models, which suggested their use in the treatment of osteomyelitis. Publication: The article was published in Biomaterials in 2015. Advancements in Composite Scaffolds (2019): Study: Composite scaffolds of polycaprolactone (PCL) and hydroxyapatite (HA) loaded with gentamicin were designed by researchers. Findings: Those scaffolds made possible the gradual release of drugs and supported proliferating bone cells, which pointed to their great potential in a treatment of an osteomyelitis. Source: The published article was by Materials Science and Engineering: C in 2019. Importance : 3D-printed releasing antibiotic bone scaffolds are also a breakthrough regarding the treatment process of osteomyelitis: they provide combined mechanical support for bones to heal plus localized delivery, which can greatly reduce systemic secondary effects and be more effective.[11] These examples show how 3D printing can change the face of modern medicine and offer personalized, efficient, and targeted therapeutic solutions.

CONCLUSION: The review of relevant literature will be about the 3D-printing technologies that have come to be well-known within the pharmaceutical Industry, as well as reveal some characteristics about each technology, adequate dosage forms suitable for each technology, and assessment concerning the trend in development. Also, such review will tackle which companies or organizations give lead in the development of 3D-printed drugs, drugs maintained breakthroughs in innovation throughout history, commercialization directions, and that carried through to those governmental or commercial innovators[8]. It is novel because it is a new technology, and until now, no registration and filing path for 3D-printed preparations has been the same; still, intellectual property rights and the policy of no other way toward IP, undergraduates do not know a few marks in reports prescribed for this while more of the drug law and similar drug-following indications are unheard-of. Ideologically, it is believed that all intentions are thereby realized at a certain turn in development, industry characteristics, and on the whole, in trend[8].That review provides the current development of 3D-printed drugs, industry features of interest to various investors throughout the world, and a broader trajectory concerning generic drug development trends among 3D-printed drugs. Hopefully, it will be insightful for those interested in related research[8]. With the continuous endeavor, we believe in the promising 3D-printed drug's future; it certainly is the force that drives intelligent and personalized drug preparation in healthcare.

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