3D Printing in Pharmaceutical Manufacturing: Advancing Personalized Drug Delivery and Precision Medicine

Golla Venkata Sowmyasree [1]*, S. Misba[2], P. Shinee[2], J. Anjali[2], K. Deena Swarupa[2], K. Mahendra[2]

1.Assistant Professor, Department of pharmaceutics, Annamacharya college of pharmacy, Rajampet, Andhra Pradesh, India.

2.Annamacharya college of pharmacy, Rajampet, Andhra Pradesh, India.

ABSTRACT:

3D printing in healthcare is unquestionably a game changer, with multiple applications in pharmaceuticals, medical equipment, and even regenerative medicine. The technology has improved significantly since its inception, and its applications in drug manufacturing, patient-specific treatments, and medical devices are rapidly expanding. 3D printing allows for precise control over the shape, composition, and dosage of therapies in a wide range of applications, including the creation of sophisticated tissue-engineered structures and bioprinting, tailored medicines, and drug delivery systems, as well as the ability to produce small batches of drugs with custom dosages, forms, weights, and drug release profiles. This method of producing medicines may eventually help to realize the notion of individualized medicine. This results in more effective therapy and significantly fewer side effects, which is especially important in sensitive populations. The key advantages include customization, reduced side effects, innovative manufacturing, faster production, and precision medicine. The first FDA-approved 3D printed drug exemplifies the technology's promise in the pharmaceutical industry. Customized Dosage Forms created with CAD software and 3D printers, Medical, Drug Delivery, and Regenerative Medicine are some of the specific applications.

Keywords: 3D printing, Customized Dosage Forms, Manufacturing, Bioprinting, CAD software**.**

INTRODUCTION:

Charles Hull created 3D printing technique, known as stereolithography, in the early 1980s. Three-dimensional printing technology, also known as additive manufacturing technology, is utilized to create customized 3D-printed pharmaceuticals using computer-aided model design. In recent years, the usage of 3D printing technology in the pharmaceutical industry has gotten more sophisticated. A model is developed with computer-aided design software, then cut and transmitted to the printer. The 3D product is subsequently constructed layer by layer utilizing the layered manufacturing technique. [1,2]. Several new 3D printing technologies have emerged as a consequence of research and development. The American Society for Testing and Materials classified 3D printing technologies into seven categories based on their technical principles [3,4] material extrusion, binder jetting, powder bed fusion, vat photopolymerization, material jetting, directed energy deposition, and sheet lamination. This is because each 3D printing process employs unique materials, deposition techniques, stacking manufacturing mechanisms, and final product characteristics.

Many industries, including automotive, construction, aerospace, and medicine, rely substantially on three-dimensional printing technology. The pharmaceutical business is currently experiencing a surge in 3D printing research. [5,6] In contrast to traditional preparation technologies, 3D printing allows for the design of intricate 3D structures within medications, allowing for quick prototyping and manufacturing, precise control of drug release to meet a variety of clinical needs, a high degree of creativity and flexibility to customize pharmaceuticals, and a significant reduction in preparation development time, resulting in a breakthrough. Advanced drug manufacturing technology is transforming how we generate, produce, and consume pharmaceuticals [7,8,9]. Pharmaceutics. Many pharmaceutical products, including immediate-release tablets, controlled-release tablets, dispersible films, microneedles, implants, and transdermal patches, have been created utilizing three-dimensional printing technology [10].

The use of data sets that specify each component's placement within the manufactured item using three coordinates is prevalent throughout 3D printing systems. Typically, a digital blueprint of the product is developed using computer-aided design (CAD), and the digital information is then used to build the things in an additive, layer-by-layer method. This results in exceptionally

accurate material arrangement control, which is uncommon in other manufacturing processes where uniform component placements across the dosage form are occasionally required to assure adequate dosing. As a result, 3D printing allows for the creation of innovative and uncommon morphologies and material configurations that can be used to control release behaviours or to construct distinct compartments inside a single dosage form.
Because the methods are either free-forming or inside a material bed/bath with only certain parts solidified, the volume and/or outer dimensions of the dosage form can be easily modified, allowing for dose adaptation without the need to change tooling, etc. There are also approaches for managing inner structures using infill. According to a 2017 study, the FDA supports the development of such technologies, as well as other potential benefits of 3D printing dosage forms [11].

However, as of today, 3D printing processes are similarly limited in terms of production quantity. Comparably long manufacturing times appear to be one of the key barriers, rendering the current strategy economically inefficient. However, when customization is desired and small batches are required, these approaches may provide standardized and cost-effective alternatives to traditional compounding procedures. These areas are expected to grow as more information about pharmacogenomics, screening devices, and algorithms becomes available accessible to aid prescribers [12–13]. However, personalized dose forms present additional challenges, such as in terms of regulatory methods to approval and batch release. To illustrate its commitment to addressing these concerns, the FDA published a discussion paper on 3D printing medical equipment at the point of treatment in 2021 [14]. Even if the final items are manufactured in a different fashion, 3D printing techniques may be effective for rapid prototyping of dosage forms as well as generating finished products. For example, they can be utilized to offer dosage forms for early phase clinical investigations that require a high degree of dosing or release profile flexibility.

Since the early 2000s, technology has been employed to directly print medical devices with highly intricate 3D structures and to produce devices customized to fit a patient's specific anatomy, initially for custom prosthetics and dental implants. Furthermore, this approach could reduce the risk of failure in the later stages of developing new drugs by providing a more dependable platform for drug screening. Recently, the application of 3D printing methods in pharmaceutical manufacturing has garnered significant attention due to its numerous advantages over traditional techniques. These benefits include the ability to create complex solid dosage forms with high precision and accuracy, the potential for on-demand production, cost-effectiveness, and the customization and personalization of medications with individually tailored doses. For example, 3D printing technology has been employed to develop various drug delivery systems, such as oral controlled release systems, microchips, implants, pills, instant release (IR) tablets, and multiphase release dosage forms. The rapid advancement of 3D printing technologies also facilitates the design of personalized drug delivery systems, as tailored dosage forms are favoured to minimize unnecessary side effects, modify the dosing schedule, and achieve individualized release profiles.

ADVANTAGES OF 3D PRINTED DRUG DELIVERY [15,16,17]

- Compared to traditional dosage forms, there is a high capacity for drug loading.
- Potent drugs, which are given in small doses, can be dosed with accuracy and precision.
- Production costs are reduced due to minimized material waste.
- Effective drug delivery is possible for challenging active ingredients, such as those with poor water solubility.
- There are a narrow therapeutic window and increased complexity.
- Genetic variances, ethnic differences, age, gender, and environment can all be used to customize a patient's medication.
- Treatment can be tailored to enhance patient adherence in cases of multidrug therapy with several dosage regimens.
- This dosage form's versatile design and manufacturing allow for the incorporation of immediate and CR layers, which aids in the selection of the most appropriate treatment plan for a certain patient.
- Steer clear of batch-to-batch fluctuation, which occurs when conventional dosage forms are manufactured in bulk.
- 3D printers are reasonably priced and take up little room. It is possible to manufacture small quantities and finish the procedure in a single run.

DISADVANTAGES: [15,16,17]

- There are currently no clear regulations for health authorities.
- The equipment and supplies are very expensive.
- Some medications have poor print quality.
- Making a lot of tablets takes too long.
- It's challenging to maintain safe and clean machines.
- Some medications expire more quickly.
- There aren't many 3D-printed medications.
- Files may be altered or stolen.

- Factories and pharmacies are not prepared for it.

APPLICATIONS:

Applications of 3d printing in the pharmaceuticals:

Due to its numerous uses, 3D printing has become a revolutionary tool in the medical field. Personalized care has been transformed by the ability to use patient data to construct models, tools, and implants. Prosthetics can be used to replace limbs, orthopaedic implants can be used to repair bones, and bioprinting can be used to generate organs, tissues, or an organ on a tissue chip. It is as precise and adaptable as people are it makes it possible for pharmaceutical manufacturers to create a wide variety of tablet combination and controlled release systems.

1.Bioprinting of tissues and organs:

3D bioprinting is used to solve critical medical issues such as organ and tissue failure caused by accidents, birth defects. Bioprinting lowers the risk of rejection and the requirement for immunosuppressive medications by employing the patient's own cells. Its advantages include precise cell placement, digitally controlled production, and the ability to create functional tissues [18]. Its use to prosthetic ears, cartilage, bones, heart valves, and even liver tissue demonstrates the technique's immense potential in regenerative medicine.

2.Creation of unique dosage forms:

The pharmaceutical business uses 3D printing to develop other dosage forms, including nanosuspensions, antibiotic micropatterns, and microcapsules. Using inkjet and powder technology, 3D printing makes it possible to create incredibly intricate drug delivery systems with particular features[19]. These developments provide new opportunities for the creation of novel, intricate pharmacological corporeality while also bolstering the therapeutic efficacy and stability of medications [20].

3.Personalized drug dosing:

3D printing enables personalized medications that consider the age, race, and genetic profile of the intended user [21]. In order to help patients adhere to their treatment plans, it makes it easier to create multi-dose tablet formulations containing multiple active components [21]. Furthermore, it promotes the creation of stable formulations and unconventional drug release methods that accurately and successfully provide the intended therapeutic effects

4.Complex drug release profile:

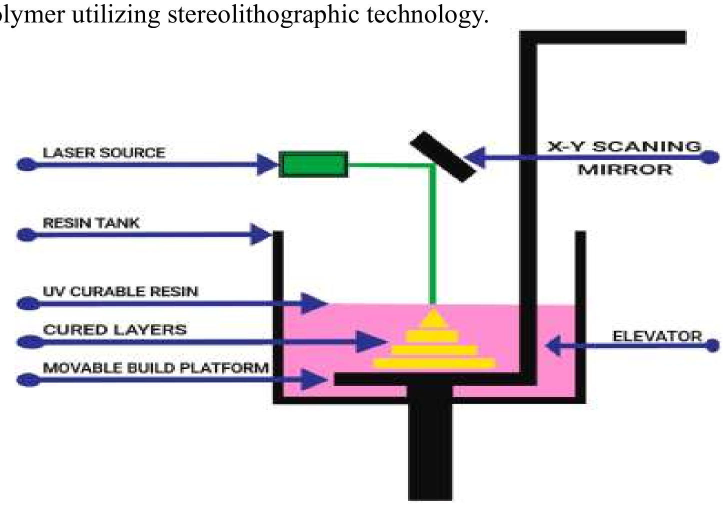
Designing dosage forms with intricate mechanisms to control the medication's release is made easier using 3D printing. This makes it possible to create structures with several porosity and geometrical degrees of freedom, which enable controlled and planned drug release [22]. Examples of these include printed antibiotics for particular purposes and prostheses that release various medications on a regular basis. Compared to what has historically been employed, these improvements enhance the accuracy and effectiveness of drug delivery systems.

3D printing technologies employed within pharmaceutical manufacturing:[23]

1. Stereolithography (SL) Technology:

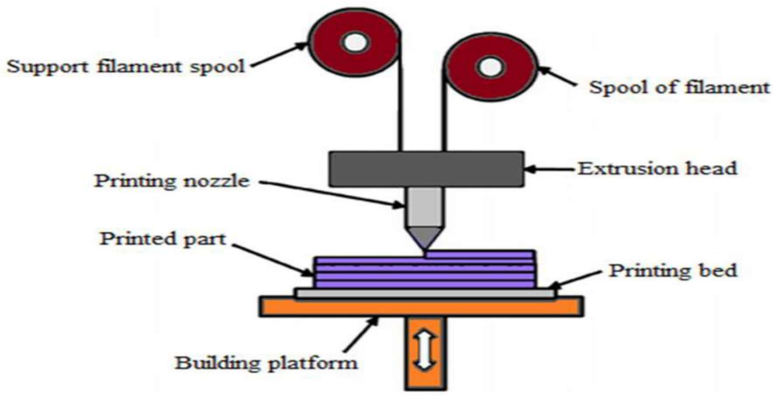
The 3D printing revolution started in the late 20th century, with stereolithography being the first commercially available 3D printing method. SL machines, the pioneers of 3D printers, were employed to produce 3D models, prototypes, components, and designs. Although extensive research on 3D printing took place in the 1970s, it was not until 1984 that Charles Hull patented this groundbreaking technique. To understand the principle of stereolithography, one must grasp the SL process. This process initiates with the creation of a CAD file, which is then converted into an STL file format. The STL file encompasses the geometric details necessary for a 3D printer to fabricate an object. There are four main components involved in this process: a laser source, a perforated build platform, a UV-curable photopolymer liquid, and a computer system to manage the process. Once the STL file is processed, the perforated platform is submerged into the liquid polymer tank to control the 3D printer. As the platform descends, the liquid polymer flows through the holes, and it solidifies quickly upon exposure to a UV laser. Beginning at the base and progressing downwards, the platform constructs the object layer by layer, with each new layer bonding to the previous one.

Once the final layer has been completed, the printed object is submerged in another resin to assist in separating it from the liquid polymer. The sculpture is then cured in a UV oven at a specified temperature, solidifying all layers and providing the desired finish. At this stage, the layers of resin bond more effectively with one another. As a result, these stages contribute to the creation of the final product. Thus, stereolithography (SL) is a 3D printing method that fabricates three-dimensional objects from liquid photopolymer utilizing stereolithographic technology.



2. Fused Deposition Modelling (FDM) Technology:

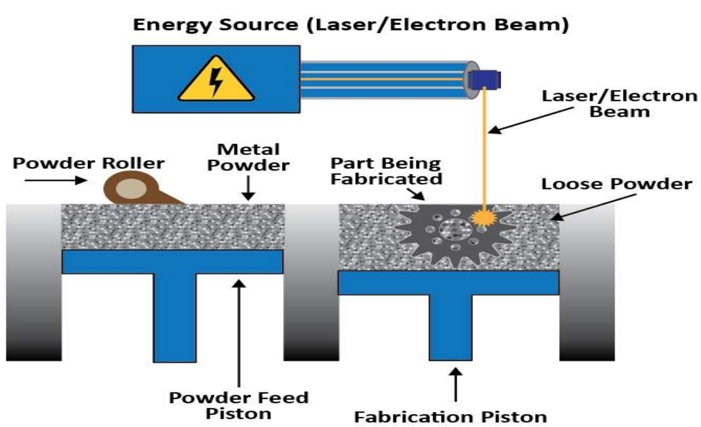
Thermoplastic filament is heated until it melts and then extruded in layers to create three-dimensional shapes. This method was invented by Scott Crump in the early 1990s and was brought to the market in the US by Stratasys INC. FDM 3D printers feature an extruder that supplies the filament, heats it to its melting temperature, and then extrudes it through a nozzle to construct the object layer by layer. Additionally, the extruder is equipped with a support base that facilitates vertical movement. The extruder possesses mobility in three dimensions (x, y, and z). The technique known as "fused deposition modelling" involves the extruder fusing adjacent layers together during deposition, while the 3D printer is responsible for shaping the final product. Depending on the desired finish, the completed object may also undergo a resin dip, similar to the Stereolithography (SL) process.



3. Powder Bed Fusion (PBF) Technology:

A technique employs a fine layer of powder to create a component. An energy source, like a laser or an electron beam, is used to fuse the powder according to the shape of the component. By selectively melting the powder layer by layer, the laser can generate three-dimensional forms. The Powder Bed Fusion (PBF) process results in a distinct output by layering ground material over the previously formed layer rather than creating a continuous one, though each layer remains connected to its adjacent layers. After being placed into a hopper, a brush or roller is used to uniformly distribute the ground powder across the powder bed. The ideal thickness of each powder layer is influenced by the specific materials and process parameters.

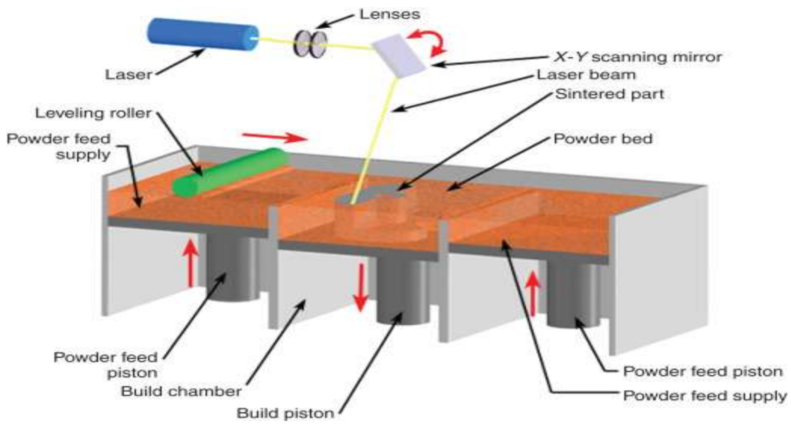
Techniques included in the Powder Bed Fusion category consist of Direct Metal Laser Melting (DMLM), Electron Beam Melting (EBM), Selective Laser Melting (SLM), Selective Laser Sintering (SLS), and Direct Metal Laser Sintering (DMLS). In the mid-1980s, a rapid prototyping method called Selective Laser Sintering (SLS) was developed by Drs. Carl Deckard and Joe Beaman at the University of Texas in Austin. This technique enables the consolidation and layering of powdered materials to create complex shapes. The solidification process is facilitated by either CO2 or nitrogen lasers, based on the required fusion properties and surface finish. This method can accommodate various powders, including metals, glass, ceramics, and thermoplastics. When metal powders are used, the process is referred to as Direct Metal Laser Sintering (DMLS). The initial chamber of an SLS printer delivers power to the second chamber, where production actually occurs. After being heated to a temperature below its melting point, the powder is distributed in layers using a levelling roller. Once the production phase is finished, additional finishing procedures are necessary.



Powder Bed Fusion (PBF)

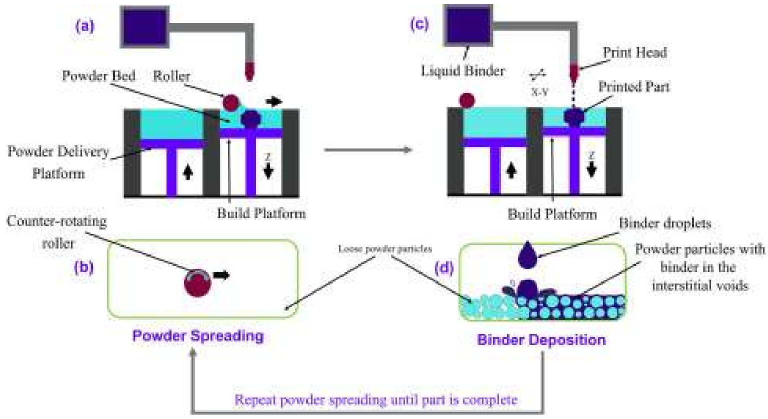
4. Selective Laser Sintering (SLS) Technology:

This rapid prototyping method was created in the mid-1980s by Drs. Carl Deckard and Joe Beaman at the University of Texas in Austin. This technique enables the consolidation and layering of powdered substances to create complex shapes. Depending on the required fusion properties and surface finish, either CO2 or nitrogen lasers can assist in the solidification process. A diverse array of powders, such as metals, glass, ceramics, and thermoplastics, can be utilized in this technique. When metal powders are employed, the process is referred to as Direct Metal Laser Sintering (DMLS). The second chamber of an SLS printer, where actual production occurs, receives power from the first chamber. The powder is heated to a temperature just below its melting point and is then evenly spread by a levelling roller to create layers. After the manufacturing process is finished, additional finishing steps are required.



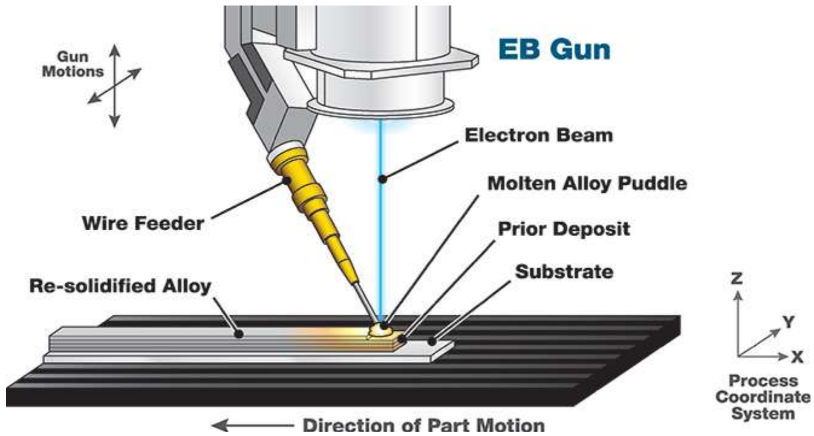
5. Binder jetting (BJ) Technology:

A technique was developed by the Massachusetts Institute of Technology (MIT) that utilizes modified inkjet technology. This approach joins materials together using inkjet technology instead of conventional methods that rely on lasers. To create three-dimensional objects, it constructs layers through 2D printing technology. The process starts with the creation of a 3D model, which is then inputted into the printer's software, similar to other 3D printing techniques. To ensure a steady supply during printing, the required powder is delivered by a dispenser. After applying a layer of powder with different thicknesses, the printhead applies the binder according to the design specifications. Before moving on to the next layer, the binder solvent is dried using electric or fluorescent lights. The powder bed is then lowered, and a fresh layer of powder is added. Once the printing cycle is finished, the binder is placed in an oven; the necessary temperature and time vary based on the binder's composition. Metal and ceramic parts typically undergo processes such as sintering, infiltration, heat treatment, or hot isostatic pressing before they can be used. In contrast, most metals and polymers do not require any post-processing and can be utilized immediately after leaving the printing system.



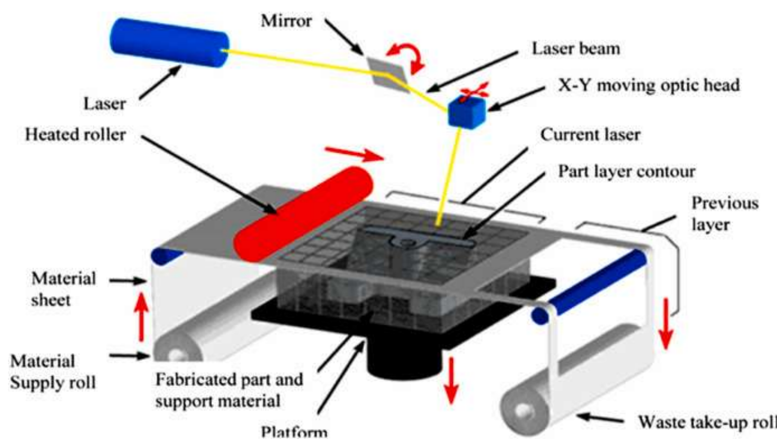
6. Direct Energy Deposition (DED) Technology:

Unlike other 3D printing methods, this technique primarily focuses on repair and maintenance rather than creating new components. By melting the material during the deposition process, Directed Energy Deposition (DED) techniques facilitate the creation of novel materials. The DED setup includes a deposition head that integrates two powder feed nozzles along with an energy source. During this process, either metal powder or a thin wire can be introduced. The component to be fabricated is positioned on a platform, and sometimes inert gas tubing is utilized as well. The deposition head operates on a four or five-axis machine, supplying both the powder and the laser beam. Utilizing a concentrated heat source like a laser or an electron beam, the DED method allows the material to solidify and accumulate layer by layer, effectively repairing and fabricating new material objects atop existing components.



7. Laminated Object Manufacturing (LOM) Technology:

Helisys Inc. (previously known as Cubic Technologies) based in California launched this technology in 1991. This rapid prototyping method produces models by adhering layers of materials such as paper, plastic, or metal with epoxy. A laser cutter then shapes the model appropriately. Initially, a sheet is attached to a substrate using a heated roller. The following layers are then precisely cut with either a laser or mechanical cutter. These layers are bonded to each other either by forming first and then bonding, or vice versa. Once a layer is finished, the platform lowers to prepare for the next layer until the prototype is entirely built. Furthermore, lamination is integrated with CNC machining and ultrasonic metal seam welding in a variant of LOM referred to as Ultrasonic Additive Manufacturing (UAM).



Conclusion and Future Perspectives:

3D printing technology has demonstrated immense potential to revolutionize pharmaceutical manufacturing and drug delivery by enabling precise customization, complex dosage form design, and patient-specific therapy. Compared to conventional manufacturing techniques, additive manufacturing offers superior flexibility, reduced material waste, improved dose accuracy, and the ability to fabricate sophisticated drug release systems. Applications such as personalized dosing, controlled and multi-phase drug release, bioprinting of tissues, and on-demand drug production highlight the versatility of this technology.

Despite these advantages, challenges remain, including limited large-scale production capacity, high equipment costs, regulatory uncertainties, and the need for standardized quality control measures. Addressing these challenges will require collaboration among regulatory authorities, pharmaceutical industries, and academic researchers to establish clear guidelines and scalable manufacturing strategies.

Future advancements in pharmacogenomics, artificial intelligence, and material science are expected to further enhance the capabilities of 3D printing in healthcare. With continued innovation and regulatory support, 3D printing is poised to play a pivotal role in precision medicine, personalized drug delivery, and next-generation pharmaceutical manufacturing.

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