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3D Printing Technology in Pharmaceuticals

Datir Suyash, Gadge Prajakta, Shinde Kiran*

Department of pharmacy: Vidya Niketan Institute of Pharmacy & Research Centre, Bota, Maharashtra, India

ABSTRACT:

Three-dimensional (3D) printing, also known as additive manufacturing, is a transformative technique that utilizes computer-aided design (CAD) software to create three-dimensional objects by sequentially depositing or solidifying material layer by layer on a substrate. This process is particularly notable in the pharmaceutical sector, where it enables the design and production of personalized and complex drug delivery systems. By using CAD, medicinal substances can be digitally modeled and transformed into machine-readable formats. These models are then sliced into layers, each of which is printed in succession to form the final dosage form.

Various 3D printing techniques have been developed to produce novel solid dosage forms, revolutionizing the way pharmaceutical products are manufactured. Some of these techniques include Thermal Inkjet Printing, Inkjet Printing, Fused Deposition Modeling (FDM), Extrusion 3D Printing, ZipDose, Hot Melt Extrusion, Stereolithography (SLA), Selective Laser Sintering (SLS), Laser-Based Writing Systems, Continuous Layer Interface Production (CLIP), and Powder-Based 3D Printing. Each of these methods has its own set of advantages and limitations, and their applications continue to evolve in pharmaceutical manufacturing.

One of the primary benefits of 3D printing in pharmaceuticals is its ability to create customized drug forms, optimizing both the dosage and release profile for individual patients. This technology allows for the rapid production of small batches of drugs with intricate structures or specific drug release patterns, which would be difficult to achieve using traditional manufacturing methods. Additionally, the successful commercialization of 3D printed drugs, such as Spritam in 2015, has demonstrated the potential of this technology. In fact, several 3D-printed drug applications have received investigational new drug (IND) approval from the U.S. Food and Drug Administration (FDA), showcasing the growing sophistication and regulatory acceptance of 3D printing in the pharmaceutical industry.

Despite the promising advancements, there are still challenges that need to be addressed in the commercialization of 3D-printed drugs. Issues such as standardization, quality control, and scalability remain significant hurdles. However, the continued development of 3D printing technologies promises to offer new possibilities for personalized medicine and more efficient pharmaceutical manufacturing in the future. This review aims to summarize the most widely used 3D printing techniques in pharmaceuticals, highlight their unique characteristics, assess their applications, and explore the ongoing challenges and future directions of 3D-printed drug manufacturing.

Key words: Three-dimensional printing technology, structure, printing, pharmaceutical, Drugs, Drug discovery, personalized medicine; research status.

Introduction:

3D printing technology has garnered significant attention from both the medical device and pharmaceutical industries due to its diverse applications within the healthcare sector. It offers the promise of on-demand, personalized drug manufacturing, enabling the creation of customized doses tailored to individual patient needs. The potential of 3D printing lies in its ability to deliver precisely what is needed, in the required quantity, and at the right time. This technology holds the potential to revolutionize pharmaceutical care by providing "tailor-made" medications for each patient, allowing doctors and pharmacists to meet the specific therapeutic needs of individuals.

Initially developed in 1984, 3D printing relies on computer-aided design (CAD) software or 3D scanning to create models for digital production. This technology has made a significant impact on drug delivery, which involves developing formulations that effectively transport pharmacologically active compounds in the body to achieve the desired therapeutic effect safely.

One of the most promising applications of 3D printing in the pharmaceutical industry is personalized medicine. Rather than a "one-size-fits-all" approach, 3D printing allows medications to be customized based on a patient’s specific treatment needs. This customization extends to the creation of multi-active ingredient formulations, which can be printed as single blends or multi-layered tablets with sustained-release properties. This feature significantly reduces the frequency of doses required, improving patient compliance by minimizing the number of individual dosage units taken daily.

The impact of 3D printing in pharmaceuticals is also notable in its ability to provide flexible, time-saving, and highly efficient manufacturing capabilities. By using CAD to design and produce medications, pharmaceutical companies can create highly specific, programmable medicines tailored to individual patient requirements. This technology, often referred to as rapid prototyping or additive manufacturing, involves constructing solid objects layer by layer, based on three-dimensional computer models. The goal is to improve drug delivery by ensuring that the active ingredients are effectively transported within the body to achieve optimal therapeutic outcomes.

In summary, 3D printing in drug delivery represents a revolutionary advancement in manufacturing, where drugs can be produced with precision and tailored to the specific needs of patients. This could mark a new era in personalized medicine, where the creation of drugs and medications is more adaptable, precise, and patient.

HISTORTY:

The first 3D printing technique used in pharmaceuticals involved inkjet printing a binder solution onto a powder bed, which bound the particles together. This process was repeated layer by layer until the desired structure was achieved. This innovation occurred in the early 1990s at the Massachusetts Institute of Technology (MIT), where it was developed and patented by Sachs et al.

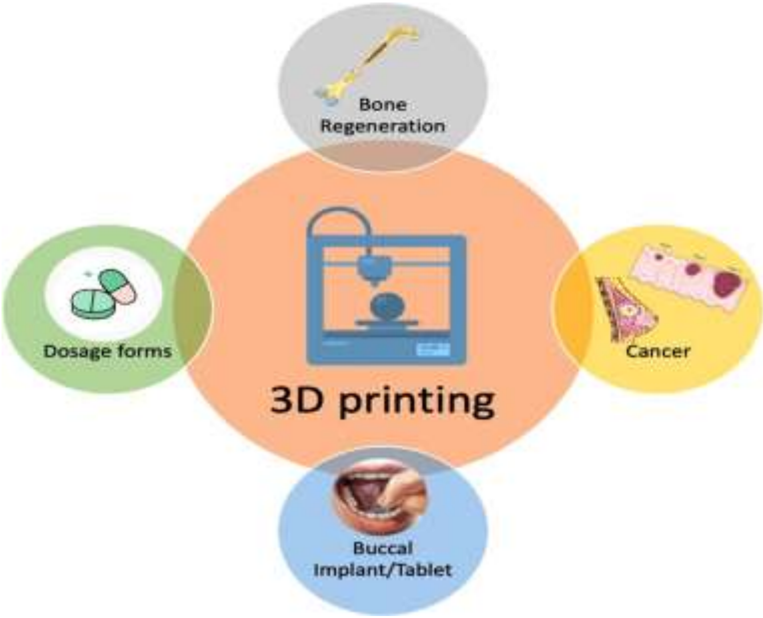
1980s: The concept of 3D printing, also referred to as additive manufacturing, began to emerge. The first commercially available technology, stereolithography (SLA), was developed by Chuck Hull. SLA utilized ultraviolet light to photopolymerize liquid resin, marking an early breakthrough in the field.

1990s: Researchers at MIT developed a rapid prototyping method, which provided the foundation for the use of 3D printing in pharmaceuticals.

1997: MIT created the first experimental 3D-printed pills. While these early prototypes were not commercially viable, they laid the groundwork for subsequent advancements in the field of pharmaceutical manufacturing.

2015: The U.S. Food and Drug Administration (FDA) approved the first 3D-printed drug, Spritam, a medication used to treat epilepsy. Manufactured using ZipDose technology, Spritam dissolves rapidly when taken with a sip of liquid, making it easier for patients to consume.

This timeline highlights the significant milestones in the development of 3D printing in pharmaceuticals, culminating in the approval of the first 3D-printed drug, marking a key advancement in the industry.



ADVANTAGES OF 3D PRINTED DRUG DELIVERY

- High drug loading ability when compared to conventional dosage forms. Accurate and precise dosing of potent drugs which are administered at small doses.
- Reduce cost of production due to lesser material wastage.
- Suitable drug delivery for difficult to formulate active ingredients like poor water-soluble drug.
- Narrow therapeutic window as well as increase compellability.
- In case of multi drug therapy with multiple dosing regimen, treatment can be customized to improve patient adherence
- As immediate and CR layers can be incorporated due to the flexible design and manufacture of this dosage form, it helps in choosing the best therapeutic regime for an individual.

- Avoid batch –to –batch variation seen in bulk manufacturing of conventional dosage forms.
- 3D printers occupy minimal space and are affordable.
- Manufacture of small batches is feasible and the process can be completed in a single run.
  - Easy to used, no skilled person needed.

PRINCIPELS OF 3D-PRINTING:

- ✦ Modelling Virtual blueprints from computer aided designs (CAD).
- ✦ Printing 3d printers read the design and laydown successive layers of materials.
- ✦ Finishing After printing the supports are removed or dissolved to get the final product.

WORKING OF 3D PRINTER

The process of 3D printing involves creating a physical object by adding material layer by layer, starting from a digital design. In pharmaceutical applications, this method is used to develop dosage forms by combining drug excipients in a precise manner. The process begins with the creation of a virtual design, often in the form of a CAD (Computer-Aided Design) file. This file is generated using specialized 3D modeling software or through 3D scanning, which creates a digital replica of an existing object. A 3D scanner can capture the shape and details of a physical object to produce an accurate digital version.

Steps involved in 3D printing:

Design: Create a digital model of the desired pharmaceutical product using computer-aided design (CAD) software.

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Formulation: Develop a suitable formulation for the pharmaceutical product, considering factors such as drug release, stability, and bioavailability.

↓

Material selection: Choose suitable materials for printing, such as polymers, lipids, or ceramics.

↓

Optimization: Optimize the design and formulation for 3D printing.

TECHNIQUES IN 3D PRINTING:

3D printing encompasses a range of manufacturing methods that involve the controlled deposition of material layer by layer. These techniques allow for the creation of complex, freeform geometries directly from digital designs.

1. **Thermal inkjet printing.**
2. **Inkjet printing**
3. **Fused Deposition Modelling**
4. **Extrusion 3D printing**
5. **3D printer**
6. **Hot Melt Extrusion (HME)**
7. **Powder bed 3D printing.**
8. **Stereo-lithographic 3D printing.**

1: Thermal inject printing:

Thermal inkjet printing works by heating the ink fluid using a micro-resistor, which converts the aqueous ink into vapor, causing it to expand and eject ink droplets from a nozzle. This technique is applied in several areas, including:

I. Preparation of drug-loaded biodegradable microspheres

II. Formulation of drug-loaded liposomes

III. Patterning and coating microelectrode arrays, as well as loading drug-eluting stents

IV. Producing biological films while maintaining protein activity

V. Dispensing extemporaneous drug preparations or solutions onto 3D scaffolds.

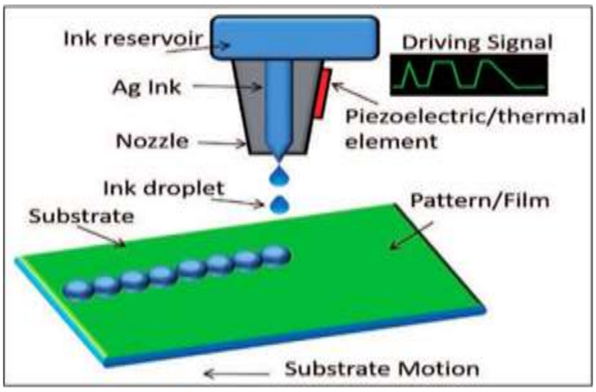


Figure 1. Thermal inkjet printing.

2.Inkjet printing:

Inkjet printing operates similarly to traditional inkjet printers but uses bioinks or drug-loaded formulations for applications in personalized medicine and wound healing. This technology works by propelling droplets of ink onto substrates like paper or plastic to recreate digital images. While commonly used in home and office printers for producing high-quality color prints, inkjet printing also offers several advantages. These include low processing costs, fast processing speeds, minimal waste generation, the ability to directly transfer CAD data in a "direct write" manner, and the capability to process materials over large areas with minimal contamination.

Figure 2.Inkjet printing

3.Fused Deposition Modelling:

Fused Deposition Modeling (FDM) is a widely used technique for producing solid dosage forms such as tablets and capsules. It works by extruding a heated filament, typically made of a polymer, layer by layer to build the desired shape. As the material cools, it solidifies and forms the 3D object.

How FDM Works: In this process, a thermoplastic filament is fed into an extruder, where it is heated to its melting point. The molten filament is then deposited layer by layer in a precise pattern. As each layer cools, it fuses with the previous one, gradually forming the complete object.

Limitations of FDM: Despite its versatility, FDM has some drawbacks:

The availability of suitable polymers for use in drug delivery is limited.

Drug release can be slow and incomplete, as the drug may remain trapped within the polymer matrix.

The compatibility and miscibility of the drug and additives with the polymers are often not thoroughly evaluated, which can affect the performance of the final product.

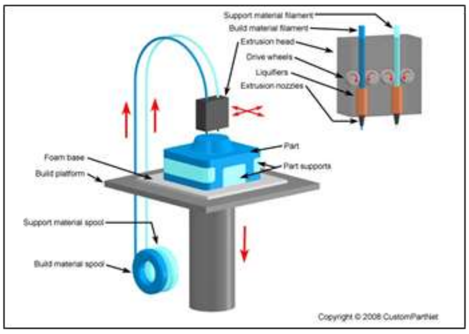
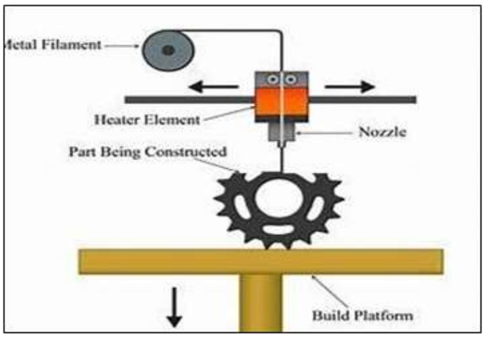


Figure 3. Fused Deposition Modelling

4.Extrusion 3D printing:

Extrusion is one of the most commonly used 3D printing techniques, where material is pushed through robotically controlled nozzles. Unlike binder jetting, which requires a powder bed, extrusion methods are versatile and can print on various substrates. A wide range of materials can be used in extrusion, including molten polymers, pastes, colloidal suspensions, silicones, and other semi-solid materials. One well-known extrusion-based method is Fused Filament Fabrication (FFF), which is commonly employed in the fabrication of tablets, such as those containing Guaifenesin, an expectorant.

In the extrusion process, semi-solids, such as gels or pastes, are deposited in a layer-by-layer fashion on a movable stage. This technique uses a syringe-like tool head to precisely place the material. The semi-solid is typically a mixture of polymer and solvent, blended to achieve the right consistency for 3D printing.



4.Extrusion 3D printing:

5 .3D printer:

3D printer is a valuable tool which is used to create customized medication with tailored release profiles & the medication is changed as per the patient comfort.

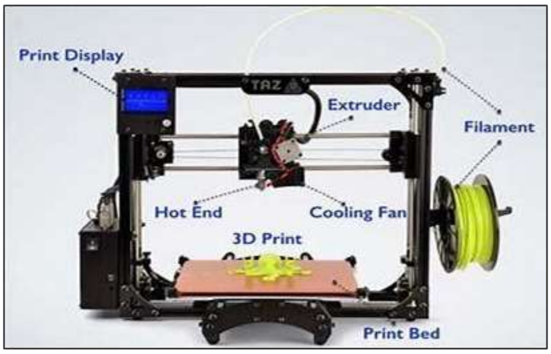


Figure 5 .3D printer

6.Hot Melt Extrusion (HME):

Hot melt extrusion (HME) is a process where a polymer and drug are heated to a high temperature, and pressure is applied continuously to blend the components. This is a continuous manufacturing method that involves several stages, including feeding, heating, mixing, and shaping. In recent years, HME has demonstrated its ability to enhance the solubility and bioavailability (BA) of poorly soluble drugs, making it an effective technique for improving drug delivery.

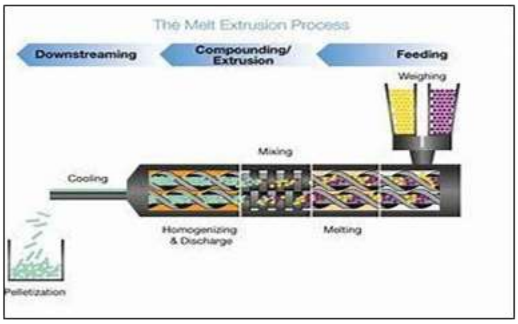


Figure 6.Hot Melt Extrusion (HME):

7.Powder bed 3D printing:

In Powder Bed Fusion (PBF), layers of powdered material (such as sugar or starch) are selectively bonded to form a 3D object. This technique is commonly used for rapid prototyping and the creation of customized dosage forms.

Process Overview:

PBF builds 3D structures layer by layer using fine powder as the base material.

1. An energy source, usually a laser or electron beam, is employed to selectively fuse the powder particles.

2. As the energy source moves across the powder bed, it melts or sinters the particles, gradually forming solid, detailed shapes.

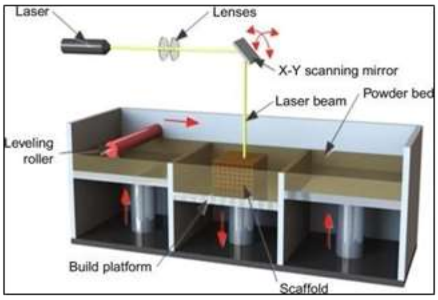


Figure 7.Powder bed 3D printing

8. Stereo-lithographic 3D printing:

Stereolithography (SLA) utilizes liquid photopolymer resin to create 3D structures. A laser selectively cures the resin layer by layer, enabling the production of complex and detailed objects. SLA is particularly useful for creating drug delivery devices and personalized medicine.

How SLA Works:

SLA relies on photo-polymerization to build 3D models. The process begins with a UV-sensitive resin that holds the liquid material. A laser, controlled by mirrors (galvanometers), solidifies the resin layer by layer. This process is similar to Fused Deposition Modeling (FDM) but instead of extruding filament, SLA uses a laser to cure the resin to form the object.

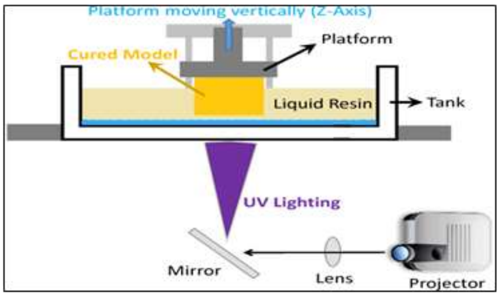


Figure 8. Stereo-lithographic 3D printing

APPLICATIONS OF 3D -PRINTING IN PHARMACEUTICALS:

Medical Applications:

3D printing has been utilized in medicine since the early 2000s, initially for creating dental implants and custom prosthetics. Since then, the scope of its applications in healthcare has expanded significantly. Recent reviews highlight the use of 3D printing to produce various medical devices and components, including bones, ears, exoskeletons, windpipes, jawbones, eyeglasses, cell cultures, stem cells, blood vessels, vascular networks, tissues, and even organs. Additionally, 3D printing is being used to develop novel dosage forms and drug delivery devices.

Healthcare Applications:

In healthcare, 3D printing plays a crucial role in creating prototypes for new products in the medical and dental fields. In dentistry, it is used to design patterns for casting metal dental crowns and to manufacture tools for dental aligners. The technology also aids in the direct manufacturing of knee and hip implants, along with other standard medical items. Moreover, it allows for the creation of patient-specific devices, such as personalized prosthetics, hearing aids, and orthotic insoles.

Pharmaceutical Applications:

The use of 3D printing in the pharmaceutical industry is growing rapidly and is expected to revolutionize healthcare. The technology is already being applied in pharmaceutical research and the production of medications. Advantages of 3D printing in pharmaceuticals include precise control over droplet size and dosage, high reproducibility, and the ability to create complex drug release profiles for various dosage forms.

Automotive Applications:

In the automotive industry, particularly among racing teams like those in Formula 1, 3D printing is used for prototyping and manufacturing specialized components. Companies in this sector are also exploring the potential of 3D printing to meet aftermarket demands by producing spare parts as needed, rather than maintaining large inventories.

Limitations and Challenges of 3d Printing Dosage Forms:

1. The range of materials, colors, and surface finishes available for 3D printing is currently limited compared to traditional tablet compression methods.

2. Surface imperfections in the final product may arise due to the stacking of plastic beads or large powder particles. These imperfections are more likely with powder-based and extrusion-based techniques, as the drying time required for these methods can lead to uneven surfaces. The rate and method of drying can also influence the occurrence of such imperfections.

3. As 3D printing technology is still evolving, it faces several challenges, including the optimization of processes, improving device performance for diverse applications, selecting suitable excipients, and refining post-treatment methods.

4. To ensure the quality of 3D-printed products, it is crucial to optimize several key parameters, such as printing speed, layer interval time, and the distance between nozzles and powder layers.

5. Some manufacturing processes may not be suitable for thermolabile drugs, particularly when printing at high temperatures, as they can degrade sensitive compounds.

6. When selecting raw materials, factors such as printability, physicochemical properties, thermal conductivity, print fluid characteristics, and viscoelasticity must be carefully considered. Additionally, the safety of the raw materials for human use is critical.

7. To enhance the performance of 3D-printed products and broaden their application in innovative drug delivery systems, continuous improvements in the technology and material selection are necessary.

FUTURE PROSPECTS:

Design and develop innovative drug delivery systems.

Optimize the release profiles of active pharmaceutical ingredients.

Create new excipients while preventing incompatibilities between multiple drugs.

Focus on advancing drug dosage forms and supporting their effective delivery.

Minimize the degradation of biological molecules and contribute to research aimed at developing cures.

Explore the potential of 3D printing to unlock new opportunities in pharmaceutical research and biotechnology applications.

CONCLUSION:

3D printing technology has the potential to revolutionize product development, manufacturing, and distribution within the pharmaceutical industry.

This advanced manufacturing method enables the precise formulation of different dosage forms with an accurate API-to-excipient ratio, offering a novel approach compared to traditional pharmaceutical manufacturing.

As a transformative tool in the pharmaceutical sector, 3D printing enables the creation of personalized medicine tailored to the specific needs of patients, offering new possibilities in customized drug delivery.

The FDA's first approval of a drug produced using 3D printing sparked rapid advancements in research on oral, oro-mucosal, and topical dosage forms, highlighting the formulation flexibility that is challenging to achieve with conventional manufacturing methods.

With its inherent flexibility, 3D printing is emerging as a promising solution for advanced drug delivery systems, paving the way for more personalized and customized treatments in the pharmaceutical field.

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