REVIEW ARTICLE

A Comprehensive Review on 3D Printing of Pharmaceuticals

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ABSTRACT

The development of 3D printing technology has caused a paradigm shift in the pharmaceutical industry by making it possible to produce drugs on demand and according to a patient's specific needs. This review paper aims to examine the developments, difficulties, and potential applications of 3D printing in the pharmaceutical industry. We examine the various methods used, the benefits it provide, the regulatory issues, and possible uses of 3D printing in the pharmaceutical sector. Additionally, we talk about how 3D printing will affect drug research, patient care, and the state of healthcare as a whole.

Keywords: 3D printing, Computer-aided design, Personalized treatment.

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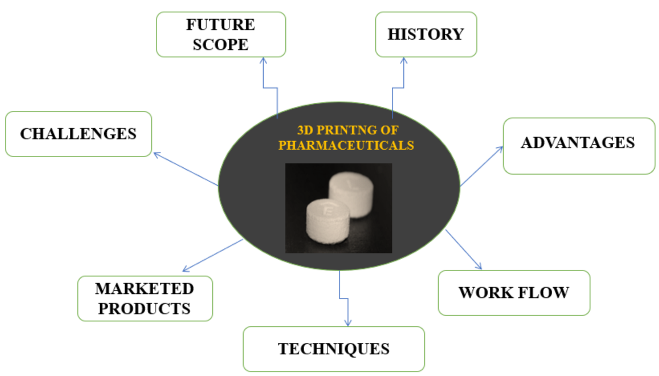

Graphical Abstract

INTRODUCTION

Challenges in the mass production of dosage forms and limitations in the availability of different types of dosage forms have all restricted the traditional pharmaceutical manufacturing process.[1] However, a game-changing technology that can get beyond these restrictions is 3D printing. 3D printing holds enormous potential for personalized medicine, complex medication formulations, and customized dosages by utilizing computer-aided design (CAD) models and exact layer-by-layer deposition of active pharmaceutical ingredients (APIs).

Long-standing mass production techniques have been used in the pharmaceutical manufacturing process, which has limited dosage forms and delayed medication delivery.[1] But a ground-breaking innovation called 3D printing has arisen as a disruptive force that can get through these restrictions.[1] The potential for 3D printing to revolutionize the pharmaceutical business is enormous because it allows for precise layer-by-layer deposition of active pharmaceutical ingredients and the use of computer-aided design models.[2] This novel strategy gives up fresh possibilities for complex pharmacological formulations, personalized dosing, and personalized therapy.[2]

Furthermore, 3D printing technology makes it easier to produce complicated medicine compositions that were previously difficult to make using traditional techniques.[2] Since several pharmaceuticals can be combined into a single dosage form by the layer-by-layer deposition of APIs, complex diseases or disorders that call for a cocktail of treatments can be treated more successfully.[2] Additionally, 3D printing's fine control enables the creation of drug delivery systems with

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unique release profiles, guaranteeing precise dosing and lasting therapeutic benefits.[3]

Beyond patient-specific drugs and intricate formulations, 3D printing considerably impacts the pharmaceutical business.[4] It also has the ability to lower manufacturing costs and streamline production processes.[4] 3D printing gives an opportunity to reduce the amount of expensive tooling and specialized equipment required for each drug version.[5]

Even though 3D printing holds great potential for the pharmaceutical industry, issues must be resolved before it can be widely used.[5] To guarantee the safety and efficacy of 3D-printed drugs, regulatory considerations, quality control, and scalability are crucial factors that need careful consideration. Cooperation between pharmaceutical businesses, regulatory organizations, and technological innovators is crucial to create standards and guidelines that uphold the greatest levels of patient care and product quality.[5]

History

The concept of three-dimensional printing (or 3DP) originated in the early 1970s when Pierre A. L. Giraud described applying powdered material and then solidifying each layer using a high-intensity beam.[5] In this scenario, melting materials like plastic or metal might hypothetically be utilized to prepare the object. Early in the 1980s, Ross Householder described the idea of binding sand with various materials in a patent entitled “A molding process for forming a three-dimensional article in layers”, and Carl Deckard created a technique for solidifying powdered beds with laser beams known as selective laser sintering (SLS). Stereolithography (SLA) was the first technique that Chuck Hull developed and marketed.[5] This technique was based on the UV light-induced photo-polymerization of liquid resin.[6] For fused deposition modeling (FDM), a process that utilized thermoplastic material for object preparation, Scott Crump submitted a patent at the end of the 1980s.[6] Emanuel Sachs, an MIT scientist, developed “Three-dimensional printing techniques” in the 1990s based on combining the chosen powder regions with a binding substance.[7]

Advantages

Personalized medicine

3D printing makes it possible to create specially formulated medicines to meet each patient’s unique needs. Pharmaceutical companies may develop medicines with accurate doses, formulations, and release patterns by using patient-specific data and CAD models. This degree of personalization promotes patient compliance, reduces adverse effects, and increases the effectiveness of the treatment.[8]

Complex medication formulations

Complex drug formulations are frequently difficult to generate using traditional manufacturing techniques. Using 3D printing, numerous APIs can be precisely deposited in a single dosage form; opening the door to the development of novel medicine combinations.[8] This creates opportunities for treating disorders or diseases that demand a combination of pharmaceuticals in a certain dosage form.

Flexible dosage forms

By using 3D printing, dosage forms may be adapted to the individual requirements of each patient. Creating tablets, capsules, or other medication delivery systems with different sizes, forms, and release mechanisms falls under this category. It permits the creation of convenient dose forms for patients, especially for groups like toddlers or elderly patients who might have trouble swallowing conventional pills.[9]

Greater control over drug particle size, distribution, and formulation

3D printing enables precise control over drug particle size, distribution, and formulation, which can improve drug solubility and bioavailability. This is especially advantageous since 3D printing techniques can enhance the dissolving qualities and boost the therapeutic efficiency of pharmaceuticals with low solubility.[9]

Enhanced drug delivery systems

With the help of 3D printing, advanced drug delivery systems can be created, including microneedles, transdermal patches, inhalers, and implants. These gadgets can be specially made to offer controlled release mechanisms, boost drug stability, target particular body parts, and increase patient comfort and compliance.[9]

Accelerated development and prototyping

The quick prototyping and iterative development of pharmaceutical goods is made possible by 3D printing. It shortens the time and expense of development by allowing researchers and pharmaceutical companies to swiftly develop and test various formulations, dosage forms, and drug delivery methods.[10]

Overall, 3D printing of medicines has many benefits, including individualized medicine, complicated drug compositions, adaptable dosage forms, enhanced drug administration systems, quicker development, and less waste.[10] 3D printing has the potential to revolutionize the pharmaceutical sector and enhance patient care as long as regulatory issues are resolved and technology keeps improving.

Workflow in 3D Printing

The 3D printing technology workflow consists of the following steps:

Design

A virtual design of the 3D product model is developed using computer-aided design software, and the chemist can design the formulation [for example, size and shape, etc.]. The chosen 3D printer receives the digital formulation, after which the design is digitally transferred and saved as a file. The programmer divides the file into several thin layers.[10]

Develop

Print-lets are created by placing the necessary ink cartridge a combination of drugs and excipients into the chosen 3D

Figure 1: Workflow in 3D printing

printer, where it is solidified layer by layer on substate. The best printing settings (such as resolution, printing time, temperature, etc.) are chosen, often depending on the printer type, drug characteristics, and desired results.[11]

Dispense

The final 3D product may require additional dusting, drying, polishing, etc., before the chemist may dispense it.[12]

The workflow involved in 3D printing is presented in Figure 1.

Techniques in 3D Printing

Pharmaceuticals are printed using a variety of processes. The intended medication formulation, printing medium, printing speed, and needed resolution are only a few variables influencing the process choice.[12] Here are several ways that are frequently utilized for printing medications in 3D

Fused deposition modeling

Fused deposition modeling (FDM) is one of the 3D printing processes that the pharmaceutical industry uses the most. A heated nozzle is used to extrude a thermoplastic filament through it. To produce the desired 3D structure, the material is placed layer by layer. FDM is quite easy and economical and enables the use of a range of thermoplastic materials.[13] The procedure involved in the FDM technique is given in the following Figure 2.

Stereolithography

A photosensitive liquid resin is used in the photo polymerization-based process known as stereolithography (SLA). Layer by layer, the resin is selectively cured by a light source, usually an ultraviolet (UV) laser, solidifying it to create the desired 3D shape. SLA can be used to create sophisticated dosage forms and intricate medicinal compositions because of its great resolution and accuracy.[13] The procedure involved in the SLA technique is given in the following Figure 3.

Selective laser sintering

Selective laser sintering (SLS) is a powder bed fusion method that selectively joins powdered materials using a powerful

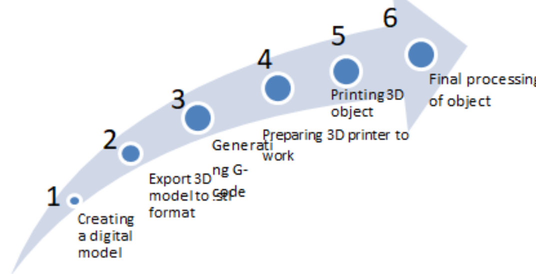

Figure 2: Process of FDM

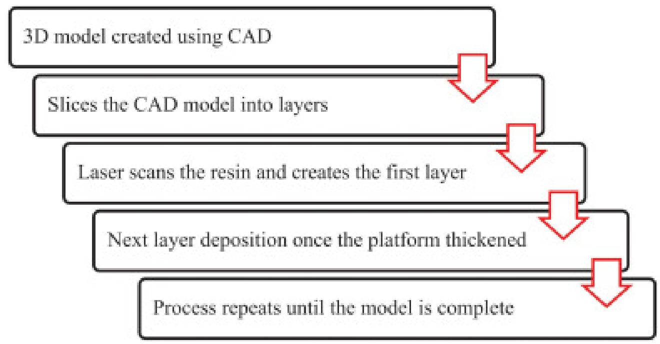

Figure 3: Process of SLA

laser. SLS can be used in conjunction with substances like biocompatible polymers or excipients made of sugar in the context of pharmaceuticals.[13] The final 3D structure is produced *via* layer-by-layer selective laser fusion of the powder particles. The procedure involved in the SLS technique is given in the following Figure 4.

Direct ink writing

It is a procedure in which a viscous ink or paste containing the pharmacological ingredients is extruded through a nozzle.[13] The material is carefully deposited onto a substrate or a layer that has already been printed to create the desired 3D object. Direct ink writing (DIW) can produce complicated structures with high resolution and allows for fine control of material deposition.[14]

Inkjet printing

It uses droplet-based deposition of liquid compositions, including medicinal components. The inkjet printer produces the 3D object by dispensing tiny droplets of the formulation onto a substrate or prior layers.[14] Inkjet printing allows for material versatility and produces high-quality prints.

Table 1: Marketed dosage forms prepared by 3D printing[17]

Dosage form	*Printing technologies*	*API*	*Manufacturer*	*Trade name*
Tablets	FDM Laser-assisted system	Lisinopril, Amlodipine Paracetamol	Allen Dale Biosciences JB Pharmaceuticals	Teladale 3D Moviz-3D
Capsules	FDM	Ascorbic acid	Steris health care (INDIA)	Tenixma 3D Glow
Microneedle	Stereolithography digital light processing	Insulin Diclofenac	Unaxo India Pharma	Dicloran 3D tablet
Controlled release Implant	FDM	Nitrofurantoin		

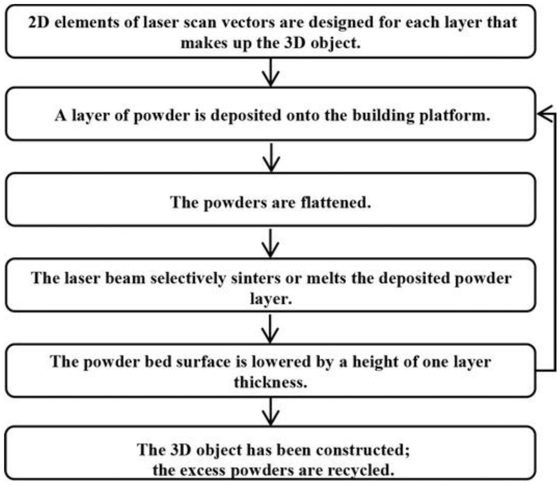

Figure 4: Process of SLS

Powder bed printing

Using a liquid binder, powdered components are deposited and joined layer by layer using this technique. Drug-loaded tablets or multiarticulate dosage forms are frequently made using this method in the pharmaceutical industry. Active pharmaceutical ingredients (APIs) may be combined with excipients or binders in the powder bed, and these components may then be selectively bonded to one another to create solid structures.[15]

Continuous liquid interface production

This process employs light and oxygen to manufacture objects out of liquid resin.[15] A photo-polymerization reaction occurs when a certain pattern of light is shone upon the liquid resin. Continuous printing is made possible by the use of oxygen, which is needed in some locations to prevent the curing process. High-resolution items with a clean surface finish can be produced using continuous liquid interface production (CLIP) at faster printing speeds (Table 1).[16]

These are only a few instances of the methods utilized in 3D printing medications.[16] The subject of 3D printing is constantly developing, and new methods and innovations are being created to expand its potential and range of uses in the pharmaceutical sector.[16]

Challenges

Considerations for regulation

The regulatory environment for 3D printing in pharmaceuticals is continually evolving. For 3D-printed medicines, there are questions about the validation requirements, quality control standards, and approval procedure. Regulatory organizations must develop precise norms and standards to guarantee the security, effectiveness, and caliber of medications produced by 3D printing.[17]

Material selection and compatibility

Finding materials that are appropriate for 3D printing medications might be difficult.[18] The substances must deliver the medicine successfully, be stable, and be biocompatible. It takes a lot of research and development to make sure the printing materials are compatible with the printing technology and the medicine formulation.[18]

Printing resolution and accuracy

For the creation of exact dosages and intricate medication compositions, excellent printing resolution and accuracy are essential. Maintaining uniformity in printed things can be difficult, particularly when working with micro- or nano-scale components. For consistent and dependable outcomes, 3D printing technology must improve in resolution and accuracy.[18]

Scalability and Production Efficiency

It might be difficult to scale up 3D printing techniques for large-scale production. In comparison to conventional pharmaceutical manufacturing techniques, current 3D printing technologies are comparatively slow.[18] The economic viability of 3D-printed medications depends on increasing the speed and throughput of 3D printing while preserving quality.[19]

Protection of intellectual property

With the simplicity of digital manufacturing and design, intellectual property protection has become a big challenge. Strong defenses must be put in place to safeguard proprietary formulas, stop unauthorized duplication or modification of pharmaceutical goods, and protect design files.[20]

Cost considerations

Although 3D printing technology has become more affordable over time, the cost can still be a major obstacle to its general acceptance in the pharmaceutical production industry. Materials, tools, and processes in the post-processing process can be expensive. It's critical to figure out how to increase the cost-effectiveness of 3D printing techniques without sacrificing quality.[21]

Quality control and consistency

3D-printed medicines must maintain uniform quality throughout batches to ensure patient safety and regulatory compliance. To guarantee consistent product quality, it is crucial to create standardized quality control processes, ensure precise and trustworthy measurements, and implement process validation procedures.

The development of new technologies, regulatory organizations, research institutes, and pharmaceutical corporations must work together to address these issues. Further research and development work will be necessary to overcome these obstacles and fully utilize 3D printing in medicines. Regulatory developments will also aid these efforts.[21]

Future Scope of 3D Printing

The potential application of 3D printing in the pharmaceutical industry is intriguing and looks promising. The following are some fields where 3D printing is anticipated to make a major impact:

Customized dosage forms

3D printing enables the development of dosage forms suited to each patient's requirements. Medication dosages can be tailored to the individual patient to enhance therapeutic results and boost compliance. Such modifications can be made to drug concentration, release rate, and dosage form geometry.[21]

Complex medication formulations

3D printing makes it possible to create complex medication formulations, which are challenging to do with conventional production techniques. Incorporating several medications, controlled release mechanisms, and combination therapy into a single dose form are examples of this. Such formulations can improve the effectiveness of treatment and streamline pharmaceutical regimes.[21]

Patient-specific medication delivery systems

3D printing enables the creation of medication delivery systems for individual patients that are adapted to their unique anatomical and physiological characteristics. This includes creating implants, transdermal patches, and inhalation devices specifically for each patient in order to better distribute drugs and achieve therapeutic goals.[22]

Drug development and rapid prototyping

3D printing makes it possible to produce drug prototypes quickly, accelerating development times and cutting costs. With the use of this technology, pharmaceutical firms may more quickly iterate and test drug formulations, expediting the creation of brand-new drugs and improving the entire drug discovery process.[22]

On-demand manufacture and the drug supply chain

3D printing presents the possibility of decentralized and on-demand pharmaceutical manufacture, eliminating the need for massive production and intricate supply systems. Generating pharmaceuticals as needed helps reduce medication shortages and improve drug accessibility, particularly in rural places or during emergencies.[22]

Combination drug products

3D printing allows the combining many medications or therapeutic agents into a single dosage form, which facilitates the creation of combination drug products.[22] In particular, treating complex disorders can improve treatment outcomes through synergistic effects, enhanced drug compatibility, and easier administration.[22]

Advanced drug delivery systems

Using 3D printing, advanced drug delivery systems can be produced, such as microneedle arrays, microfluidic devices, and custom drug-eluting implants.[22] These devices allow precise drug release control, target certain tissues or cells, and improve therapeutic effectiveness.

Pharmacogenomics and personalized treatment

The combination of pharmacogenomic information and 3D printing can lead to personalized treatment. Medication formulations can be customized to a patient's genetic profile, improving treatment success and reducing side effects. This is accomplished by adding genetic information into the design and formulation process.

Regenerative medicine and tissue engineering

By enabling the creation of intricate scaffolds, bioactive implants, and patient-specific tissue constructions, 3D printing plays a significant role in regenerative medicine and tissue engineering. This innovation has the potential to eliminate the need for organ donors by producing useful tissues and organs for transplantation.[23]

The future scope of 3D printing of pharmaceuticals is projected to broaden as research and development in this area continue, resulting in creative approaches to drug manufacture, personalized treatment, and enhanced patient care.[23]

CONCLUSION

3D printing has emerged as a game-changing technology in the pharmaceutical industry, providing unheard-of prospects for personalized treatment, intricate medication formulations, and on-demand production. The pharmaceutical sector is entering a new era, even though there are still challenges. This is because of the ongoing improvements in 3D printing technology, regulatory structures, and material science. The future of pharmaceutical production and patient care will surely be influenced by use of this technology.

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