**Review paper topics: 3D Printing Technology in Dosage Form Development: A Delineated Review of Public Health**

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**ABSTRACT**

3D printing in pharmaceuticals involves the creation of objects layer by layer using computer-aided design. The process includes modelling, printing, and finishing. Various 3D printing methods and technologies are used, such as inkjet printing, fused deposition modelling, and thermal inkjet printing.

3D printing offers advantages such as personalised medicine, small batch production, and precise dosing of potent drugs. It has applications in prosthesis development, tissue engineering, drug development, and more. The FDA has approved the first 3D-printed pill, which uses Zip Dose technology for rapid disintegration. 3D printing has the potential to revolutionise the pharmaceutical industry by allowing for customised dosage forms and improved drug delivery.

**Keyword: 3D printing**

Three-dimensional (3D) printing, also known as additive manufacturing, is a technology that allows the creation of solid objects by sequentially depositing layers of material. It has emerged as an innovative tool in the field of pharmaceutical sciences, enabling precise manufacturing of dosage forms, tissue engineering, and disease modelling. 3D printing in pharmaceuticals involves creating objects layer by layer using computer-aided design.

**INTRODUCTION**

Three-dimensional (3D) printing is an emerging technology that has applications in various fields, including pharmaceuticals. It involves the creation of 3D objects by depositing successive layers of materials based on computer-aided design models. (1) In the pharmaceutical industry, 3D printing offers advantages such as personalised medicine, precise dosing, and the ability to create complex drug delivery systems. This technology has the potential to revolutionise drug development and manufacturing processes. Three-dimensional (3D) printing, also known as additive manufacturing, is a technology that allows the creation of solid objects by sequentially depositing layers of material. It has emerged as an innovative tool in the field of pharmaceutical sciences, enabling precise manufacturing of dosage forms, tissue engineering, and disease modelling. This technology has the potential to revolutionise pharmaceutical manufacturing and formulation techniques. In this overview, we will explore the applications and advancements of 3D printing in the development of new drug dosage forms. (2,3)

**HISTORY**

1. **The First 3D Printing Technique in Pharmaceutics**

The first 3D printing technique used in pharmaceuticals was achieved by inkjet printing a binder solution onto a powder bed, binding the particles together. This technique was first developed at MIT in the early 1990s.

1. **FDA Approval of Spritam**

The FDA approved Spritam as the first 3D-printed drug. Aprecia Pharmaceuticals released it on the market in the summer of 2016. (4)

1. **Rapid Growth of 3DPrinting**

Since the start of the 21st century, 3D printing machines have rapidly sold out, and their prices have gradually dropped. (5)

1. **Additive** Manufacturing and Stereolithography

Additive manufacturing, also known as 3D printing, gained wider currency in the 2000s. Stereolithography, discovered by Charles Hull in 1988, was the first 3D printing technique using a UV laser to cure photopolymer material layer by layer. (3)

**The major steps involved in a 3D-printed dosage form (16)**

**Modelling**: The first step in 3D printing involves creating a virtual blueprint of the desired object using computer-aided design (CAD) software.

**Printing**: Once the model is created, it is converted into a machine-readable format that describes the external surface of the 3D dosage form. The computer programme then slices this surface into several distinct printable layers and transfers them layer by layer to the 3D printer.

**Finishing**: After the printing process is complete, the support structures are removed or dissolved to obtain the final product. In some instances, post-processing steps such as drying using hot air, microwaves, or infrared sources may be required to remove or dissolve the final product. In some instances, post-processing steps such as drying using hot air, microwaves, or infrared sources may be required to remove residual solvents from the printed dosage form. (16)

**Advantages of 3D Printing in Pharmaceuticals (15)**

1. **Production Flexibility:** 3D printing allows for the production of small batches of customised medications in a single run, reducing the need for mass production and enabling personalised medicine.

1. **Space and Cost Efficiency:** 3D printers are compact and affordable, requiring minimal space for operation. This can lead to cost savings in manufacturing and storage.

1. **Improved Drug Delivery:** 3D printing enables the design and manufacture of dosage forms with controlled release properties, allowing for precise dosing and tailored therapeutic regimens.

1. **Customisation and Personalisation:** With 3D printing, medications can be tailored to individual patients based on factors such as genetic variations, age, gender, and environmental factors.

1. **Enhanced Drug Formulation:** 3D printing technology allows for the production of complex dosage forms with high drug filling capacity, making them suitable for drugs with poor water solubility or a narrow therapeutic window.

1. **Reduced Material Wastage:** 3D printing can decrease the cost of production by minimising material waste compared to traditional manufacturing methods.

1. **Potential for Clinical Trials:** 3D printing can be useful in preparing dosage forms for clinical trials, allowing for efficient testing and evaluation of new medications.

**Disadvantages of 3D Printing(6)**

1. **Size Limitations:** Currently, 3D printing technology is limited by size restrictions. Very large objects cannot be built using 3D printers.

1. **Cost:** The cost of purchasing a 3D printer is still high, making it unaffordable for the average household. Different types of 3D printers are required for printing different objects, and printers that can manufacture in colour are more expensive than those that print monochrome objective.
2. **Impact on Manufacturing Jobs:** Like with any new technology, the introduction of 3D printing can lead to a decrease in manufacturing jobs. This can have a significant impact on the economies of third-world countries, particularly those that rely on a large number of low-skilled jobs.

1. **Limited Range of Raw Materials:** Currently, 3D printers can work with approximately 100 different raw materials, which is not comparable to the vast range of raw materials used in traditional manufacturing. More research is needed to develop methods that enable 3D-printed products to be more durable and robust

**Types Of 3D Printing Technology:-**

1. **Selective Laser Sintering:** This process uses a continuous laser beam to scan and align particles in predetermined sizes and shapes. It is commonly used for rapid prototyping and can create 3D models based on computer-aided design or stereolithography files. (7) In 1986, Charles et al. introduced SLA, the pioneering technology in solid-free fabrication. (18) This technology utilises ultraviolet laser sources to selectively photopolymerize liquid photosensitive resins, forming the basis of SLA's printing criteria. (19) (20)

1. **Fused Deposition Modelling:** This type of 3D printing is more common and inexpensive. It uses a print head similar to an inkjet printer to release heated plastic beads, building the object layer by layer. The plastic hardens as it cools, creating a solid object. .(8,9)

1. **Inkjet Printing: I**nkjet printing is used for precise control of droplet size and dose. It requires starting materials with specific characteristics, such as particle size, viscosity, and surface tension. It is commonly used for drug delivery devices and dosage forms. (10,11)

1. **Stereolithography:** Thistechnique4 uses a UV laser to cure photopolymer material, building objects one layer at a time. The laser beam solidifies the liquid photopolymer, and the platform is lowered to form each layer. Support structures are used for objects with overhangs or undercuts. .(12,13)

1. **Hot Melt Extrusion:** Hot melt extrusion is a continuous manufacturing process that involves melting polymers and drugs at high temperatures and applying pressure to blend them. It is commonly used in pharmaceutical research and fabrication for drug delivery systems. (14)
2. **Drop-on powder printing (DOP):** The DOP technique utilises droplets from the print head to bind the powder particles on the platform. (21) The process begins with layers of powder evenly spread on the build platform. The print head then ejects droplets containing binders or active pharmaceutical ingredients onto the powder bed according to a specified pattern. After each layer is printed, the platform is lowered and a new layer of powder is spread. This process continues until the desired dosage forms are completed. Postprocessing involves removing residual solvent and recovering unprocessed powder. There are two main types of drop-on-demand print heads: piezoelectric and thermal. (22) The thermal print head is cheaper but has limitations on solvent choices, while the piezoelectric print head offers more material options. Various parameters, such as nozzle diameter and print head speed, play a crucial role in the preparation process. The thermal print head employs a heating element to vaporise a small quantity of liquid by raising the temperature to 200–300 °C. This causes the formation of bubbles, which in turn expel droplets. (23) Less than 0.5% of the liquid in the print head undergoes this brief period of high temperature, lasting only a few microseconds. (24)

**Types of 3D printing**

**1: Binder Jetting**

Binder jetting is an additive manufacturing process that involves depositing a liquid binding agent onto a powder bed to create solid objects. The process begins with a thin layer of powder being spread across the build platform. Then, a print head moves over the powder bed, selectively depositing the binding agent in the shape of the desired object. This process is repeated layer by layer until the final object is formed. Binder jetting is known for its ability to produce complex geometries and is commonly used in the production of metal parts. (25,26)

**2: Material Jetting**

Material jetting is an additive manufacturing process that involves the deposition of liquid photopolymer materials through a print head nozzle. The materials are then cured using ultraviolet light to solidify the layers. This process allows for high-resolution printing and the ability to create complex geometries. Material jetting is commonly used in industries such as aerospace, automotive, and healthcare for the prototyping and production of small, detailed parts. It offers advantages such as high accuracy, a fine surface finish, and the ability to create complex geometries. It offers advantages such as high accuracy, a fine surface finish, and the ability to print multiple materials simultaneously. (27)

**3: Vat Photopolymerization**

Vat photopolymerization is a 3D printing process that uses a vat of liquid photopolymer resin. The process involves selectively curing the resin using a light source, such as a laser or projector, to create solid layers. The cured layers build upon each other to form the desired 3D object. This process is commonly used in stereolithography (SLA) and digital light processing (DLP) 3D printers. (29,30)

**4: Powder Bed Fusion**

Powder bed fusion is an additive manufacturing process that involves the use of a powdered material, such as metal or plastic, to build three-dimensional objects layer by layer. In this process, a thin layer of powder is spread over a build platform, and a laser or electron beam is used to selectively melt or fuse the powder particles, forming a solid layer. The build platform is then lowered, and a new layer of powder is spread over the previous layer. This process is repeated until the desired object is fully formed. Powder bed fusion is commonly used in industries such as aerospace, automotive, and medical for the production of complex and customised parts. (27,30,31)

**5: Direct Energy Deposition**

Direct Energy Deposition (DED) is a 3D printing technique that involves the use of a focused energy source, such as a laser or electron beam, to melt and fuse material. It is commonly used in additive manufacturing processes to build up complex metal parts layer by layer.

DED offers several advantages, including the ability to work with a wide range of materials, including metals, ceramics, and composites. It also allows for the production of large-scale parts and the ability to repair wire, which is then fed into the molten pool, where it fuses with the existing material. This process is repeated layer by layer until the desired part is complete.

DED is commonly used in industries such as aerospace, automotive, and medical, where the production of complex, high-performance parts is required. It offers a cost-effective and efficient method for manufacturing components with intricate geometries and tailored properties.

Overall, direct energy deposition is a versatile and powerful additive manufacturing technique that enables the production of complex metal parts with high precision and efficiency. (30,32,33,34)

**6: Sheet Lamination**

Sheet lamination is a process used in additive manufacturing to create objects by layering sheets of material on top of each other. It involves bonding or fusing the sheets to form a solid object. This method is commonly used with materials such as paper, plastic, or metal sheets. Sheet lamination can be an efficient and cost-effective way to produce prototypes or small-scale production parts. However, it may not be suitable for complex geometries or high-strength applications. (27,30,31,35)

**7: Material Extrusion**

Material extrusion, also known as fused deposition modelling (FDM), is a 3D printing process that involves the deposition of molten material layer by layer to create a three-dimensional object. In this process, a thermoplastic filament is fed into an extrusion nozzle, which heats and melts the material. The molten material is then extruded through the nozzle and deposited onto a build platform, where it solidifies to form the desired shape. Material extrusion is widely used in various industries for rapid prototyping, the manufacturing of functional parts, and even the production of food and medical devices. (27,30,33,36)

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| --- | --- | --- |
| 3D printing technology is used. | Formulation | API |
| Semi-solid extrusion (SSE) | ·         Bi-layered tablets (polypill)·         Multiactive tablets (polypill) | ·         Guaifenesin ·         Nifedipine, Glipizide, and Captopril |
| Stereolithography (SLA) | ·         Hydrogels·         Facial mask | ·         Ibuprofen·         Salicylic acid |
| Selective layer sintering (SLS) | ·         Tablets·         Drug delivery device | ·         Paracetamol·         Progesterone |
| Fused deposition modelling (FDM) | ·         Caplets·         Tablets·         Oral films | ·         Caffeine·         Hydrochlorothiazide·         Aripiprazole |
| Binder jet printing | ·         Tabular devices    ·         Cubic tabular devices   ·         Tablets   ·         Orodispersible tablets | ·         Methylene blue and alizarin yellow (dyes)   ·         Pseudoephedrine ·         Chlorpheniramine maleate and fluorescein   ·         Levetiracetam |
| Inkjet 3D printing | ·         Implant | ·         Levofloxacin |
| 3D printing machine | ·         Multidrug implant | ·         Rifampicin and isoniazid |
| Inkjet 3D printing | ·         Nanosuspension | ·         Folic acid |
| Thermal inkjet (TIJ) printing | ·         Solution | ·         Salbutamol sulphate |

**Table: 1 pharmaceutical product formulated through the use of 3DP technology. (28)**

**Mechanical properties:-**

**The mechanical** properties of dosage forms are taken into account as a quality control measure to ensure that the prepared tablet is reproducible and suitable for subsequent postprocessing. 3D printing technology, such as Dop, FDM, and SSE, involves the stacking of different polymers or powders on top of one another, resulting in rough surfaces and relatively weak mechanical properties. (37)The performance of the products is affected by factors such as the viscosity and surface tension of the adhesives, the fineness and thickness of the nozzle, as well as postprinting processes, drying time, and drying temperature. (38)These properties are highly relevant to 3D printing technologies. When it comes to DOP, Spritam, produced using this technology, the high porosity of the formulation gives it a competitive edge over other fast-dissolving tablets; however, its poor mechanical resistance (<40N) remains an issue.

**Preparation of special and customised geometric shapes**

Traditional preparation technologies can produce a wide range of colours of medicinal products, but the ability to produce unique tablet shapes is still limited. 3D printing technology offers greater scalability and spatial positioning accuracy and can be used to create a series of unique geometric shapes (39).

**Preparation of personalised and innovative oral delivery devices**

Traditional manufacturing technology has its advantages in terms of mass production and cost, but it falls short when it comes to adjusting the microstructure and spatial distribution. Therefore, further improvement is necessary. In contrast, the traditional method of preparing dosage forms primarily relies on the selection of excipients and coating methods to regulate drug distribution and release. This approach limits the design of dosage forms with personalised structures. However, the emergence of printing methods has revolutionised the digitization of dosage forms, allowing for flexible design and improved models. This advancement enables the production of preparations with personalised structures and customised release mechanisms, opening up new opportunities for drug delivery systems. As a result, an increasing number of studies are now focusing on researching drug delivery systems with personalised and innovative structures to achieve better clinical treatment effects through structural adjustment and control. (40) (41)

1. **Honeycomb structure**

Kyobula et al. (42) utilised fenofibrate as a model drug and beeswax as a drug carrier to create 3D-printed tablets with honeycomb structures using DOP technology. By adjusting the cell size of the honeycomb structure, the surface area and drug release curve could be modified without altering the formulation. The comparison of experimental and predicted drug factors revealed the importance of considering other parameters, such as honeycomb geometry and material wettability, in the design process of dosage forms to effectively control drug release behaviour. This research highlights the significant potential of DOP technology for printing tablets with personalised structures, thereby enhancing the possibilities for designing drug delivery systems.

1. **Caplet structure**

Sadia et al. (43) conducted a study where they used FDM 3D printing technology to create caplets with perforated channels to enhance drug release. The width of the perforations ranged from 0.2 to 1.0 mm, while the length varied. The results showed that when the channel width exceeded 0.6 mm, the drug release met the rapid release standard set by the USP. Additionally, the shorter multichannel (8.6 mm) was found to be more effective in accelerating drug release compared to the longer channel (18.2 mm), possibly due to faster fragmentation and reduced flow resistance upon dissolution. This design concept could be applied to stents or implants to facilitate drug release from tablets.

1. **Sandwich structure**

In a study conducted by Huang et al. (44) in 2007, a sandwich-type gentamicin implant was developed and fabricated using DOP. The dissolution behaviour analysis showed that the cumulative release amount of the sandwich structure implants on day 5 was below 45%, whereas the common framework structure implants had a burst release amount of 70% on the same day. These findings confirmed that the sandwich structure effectively reduced the surface area of drug release, leading to significant inhibition of burst release and prolonging the effective release time of the drug. Ultimately, this design achieved the desired outcome of long-term, sustained release of the implant.

1. **Lattice internal structure**

Li et al. (45) investigated the potential of SSE 3D printing as a novel manufacturing method for creating gastro floating tablets. They developed a tablet with a unique low-density lattice structure to prolong its residence time in the stomach. The dissolution profiles showed that the tablets, even without foaming agents, could float for more than 8 hours, enhancing the drug release effect and extending gastric retention time. Additionally, Chai et al. (46), Wen et al. (47), Li et al. (48), and Giri et al. (49) also utilised different 3D printing technologies to design and print gastro floating tablets with internal hollows or low densities. These studies highlight the adaptability of 3D printing technology in producing long-lasting gastro floating tablets and demonstrate its potential for printing controlled-release targeted formulations, laying the groundwork for industrial-scale production of these dosage forms.

**Application of 3D Printing (17)**

**Prosthesis development:** 3D printing is being used to create customised prosthetic limbs and other assistive devices, allowing for a better fit and improved functionality for individuals with limb loss or limb differences.

**Tissue engineering:** 3D printing is used to create scaffolds that can support the growth of cells and tissues, enabling the development of complex and functional tissue structures for transplantation or research purposes.

**Skin for Burn Victims:** 3D printing technology has been used to create artificial skin grafts for burn victims, providing a more precise and customised solution for wound healing.

**Drug Development:** 3D printing is being explored as a method for personalised medicine, allowing for the creation of customised drug formulations with specific dosages and release profiles.

**Social change**: 3D printing has the potential to democratise access to medical devices and supplies, particularly in resource-limited settings, by enabling local production and customisation of healthcare products.

**3D Model Libraries:** 3D printing is used to create anatomical models for surgical planning and training, allowing surgeons to practice complex procedures and improve patient outcomes.

**Future perspectives:-**

In some cases, the technology of 3D printing and traditional preparation technologies complement each other. After many years of practice, traditional preparation technologies have advanced to a level that gives them special advantages in the context of industrialization. At the same time, 3D printing is an emerging technology that can be used to achieve precise shaping of a variety of materials as well as solve many issues in conventional preparation technologies. At the same time, 3D printing is an emerging technology that can be used to achieve precise shaping of a variety of materials as well as solve many issues in conventional preparation technologies.

**Conclusion:-**

3D printing has created a valuable and soon-to-be-useful tool for the pharmaceutical industry, with a primary focus on personalised medicine. 3D printing is emerging as a new opportunity for innovative drug delivery with built-in scalability that is well-suited for personalised medication. 3D printing will revolutionise the pharmaceutical manufacturing process and formulation techniques.

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