

3D PRINTING OF DRUGS – A BOON OR A BANE?

Abstract

The pharmaceutical sector is developing quickly, and there is a growing demand in the health sectors for the modernization of pharmaceutical drugs and medical devices. The creation of innovative dose forms for targeted therapy is now possible due to modern technologies. 3D printing has evolved into one of the most ground-breaking and powerful instruments for precision fabrication of specifically designed dosage forms, tissue engineering, and disease modeling. However, the industry continues to rely on existing drug delivery methods, mainly modified tablets, and industrial-scale manufacture of novel dosage forms remains limited. The pharmaceutical industry's use of 3D printing technology has broadened the scope of studies on printed materials and equipment. One of the primary benefits of 3D printing technology is the ability to produce customized drugs in small batches with individualized doses, forms, sizes, and release qualities. The manufacturing of medications in this manner may ultimately make the idea of personalized medicines a reality. This chapter introduces 3D printing and its technology, as well as 3D printed dosage forms and the materials used in their production, as well as the benefits and challenges of 3D printing of drugs and their applications.

Keywords: 3-Dimensional printing (3DP) of drugs, 3D manufacturing, 3D printers, personalized medicine, benefits and challenges, Applications.

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I. INTRODUCTION

Three-Dimensional (3D) printing (3DP) is the most advanced technique used in industries such as automobiles, aerospace, biomedical, tissue engineering, and even the pharmaceutical industry (initial phase) [1]. Unlike other production processes, 3DP provides a simple, low-cost manufacturing approach with final goods personalized precisely for patients [2]. The Food and Drug Administration (FDA) encourages the development of innovative manufacturing technologies like 3D printing using risk-based methods [3]. Additive manufacturing is another term for 3D printing. Engineer Charles Hull proposed it in the early 1980s. It is a manufacturing method that involves depositing components layer by layer to build an entity [4].

In the early 1980s, Ross Householder described a concept of sand binding by various materials in a patent titled "A moulding process for forming a three-dimensional article in layers," and Carl Deckard invented selective laser sintering (SLS), a method of solidification of powdery bed by laser beam [5]. In the process of designing a component, the SLS uses a laser beam as an energy source, which is then sliced in the horizontal plane using the necessary software. The powder is placed in a chamber during the manufacturing process. A laser is used to solidify the powder and build up a thin coating of material. Layer after layer is added from bottom to top until the component is complete. The excess powder may be reused, so there is no waste [6]. 3DP is a tool for creating precise, low-cost, simple, structured, and customizable Drug Delivery Systems [DDS]. The 3DP process is a simple tool for producing tablets of various shapes (cube, cylinder, pyramid, sphere, and torus). Different types of 3D printers utilise different inks. Personalized medicine has the potential to revolutionise the healthcare business by personalising treatment to an individual's physiology, drug reactivity, and genetic profile. Many technologies, the most notable of which is three-dimensional (3D) printing, are on their way to ushering in this paradigm shift from traditional "one size fits all" to personalised therapy[7]. More precise treatments are what personalized medicine promises. These are safer and more effective, enhance patient compliance, and are less expensive [8].

Binder jetting, direct energy deposition, material extrusion, material jetting, powder bed fusion, sheet lamination, and vat photopolymerization are the seven types of 3D printers recognised by the American Society for Testing and Materials (ASTM) International. Customized medication, as well as other sorts of customised tablets made by 3D printers, is a possible benefit of 3D printer-based production. A 3D printer's small size might be helpful for production in medical institutions such as hospitals and pharmacies. The structure in 3DP may be produced from a digital 3D file utilizing computer-aided design [CAD], Magnetic resonance imaging, for example, is a type of software. Imaging (MRI) or computer tomography (CT) scans are used to create things or drugs for individual patients [2]. The definition of 3D technology provided by the International Organization for Standardization (ISO) is the fabrication of objects by the deposition of a material using a print head, nozzle, or other printer technology [9].

It has many benefits over conventional pharmaceutical product manufacturing methods, such as high production rates due to its quick operating systems, the ability to achieve high drug loading with the desired precision and accuracy for only powerful drugs that are applied in small doses, a reduction in material waste that can lower production costs,

and adaptability to more classes of pharmaceutical active ingredients with poor solubility [10].

II. FIRST 3D PRINTED DRUG - GUESS WHAT?

Spritam is the first 3D-printed drug authorised by the FDA in 2015; it was developed by Aperica Pharmaceuticals in New Jersey, USA, using powder bed ink jet printing and contains the epileptic treatment levetiracetam [11]. People with dysphagia can utilise Spritam more easily (a condition that makes it difficult to swallow pills is common in patients who have epilepsy). It literally melts in your mouth, so you won't have to worry about choking on large, airway-restricting pills [12].



Figure 1: First 3D Printed Drug

III. PERSONALIZED MEDICINE

The pharmaceutical sector had little interest in cutting-edge 3DP before the introduction of the first medicine that makes use of ZipDose technology, a form of 3DP platform [13]. Zip Dose[®] Technology is a drug-formulation platform that enables the production of fast-disintegrating variants of highly prescribed drugs. It is the first and only platform that makes drugs using 3D printing. While traditional techniques like direct compression of tablets, capsules, and film casting are economical for mass manufacturing; cutting-edge 3DP technology provides flexibility and the ability to produce free-form geometries. This contrasts with current technology, which is time-consuming, labour-intensive, and dosage-inflexible [14]. Personalized dosage medication forms with controlled release profiles may be created using the innovative method of fused filament 3DP. Personalized dosage medication forms with controlled release profiles may be created using the innovative method of fused filament 3D printing.

Personalized medicine combines patients' pharmacogenetic profiles and pharmacokinetic traits, either individually or in a subgroup, with clinical tools and treatments that account for genetic variation in order to develop therapies that are appropriate for their conditions while reducing adverse drug reactions and providing more effective treatments Fig 2. The pharmaceutical industry was encouraged and subsequently shaped to

customize medicines for individuals based on their genetic profiles [15]. For patients who are taking many drugs, 3DP offers this adaptability, which is very advantageous.

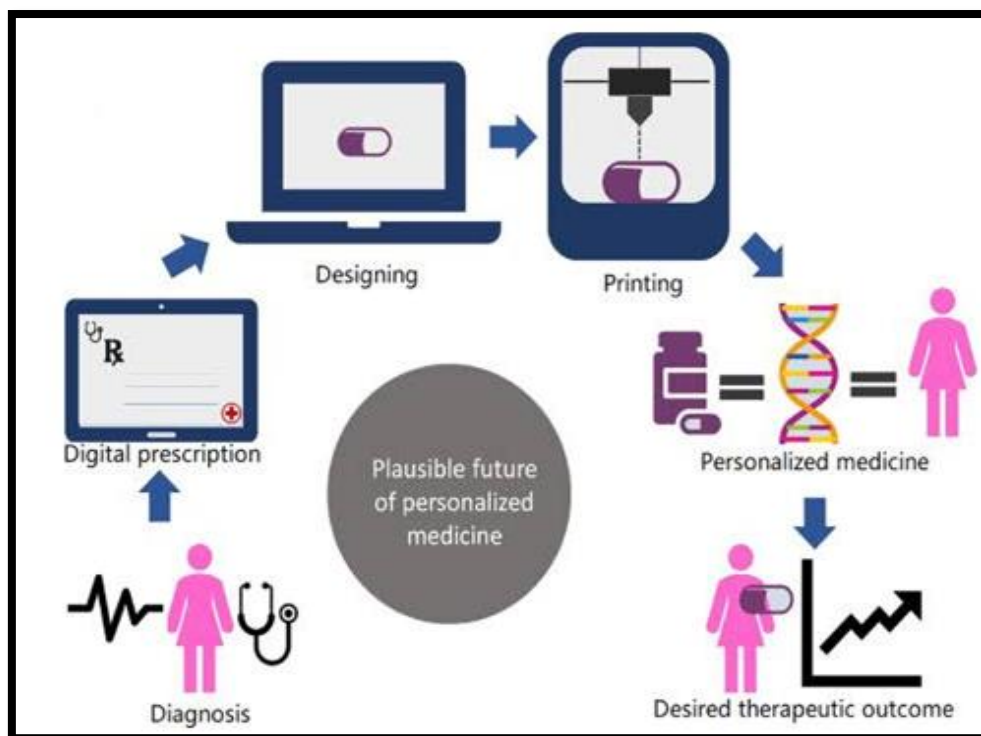


Figure 2: Personalized Medicine

IV. 3D PRINTER MATERIALS

Polymers used in 3DP for medical purposes:

- 1. Acrylonitrile butadiene styrene:** One of the materials that has been utilized the most since 3DP first became popular. This material is ideal for 3DP since it is lightweight, moderately flexible, and extremely durable. Compared to another common 3D filament, Poly Lactic Acid, it extrudes with less force [9]. The fact that acrylonitrile butadiene styrene needs a higher temperature (250 °C) is a disadvantage.
- 2. Poly lactic acid:** Another common substance used in 3DP is biodegradable poly lactic acid, which is generated from corn [9]. It is a thermoplastic that degrades naturally and is made from renewable materials. Therefore, compared to other plastic materials, poly lactic acid polymers are more environmentally friendly. The biocompatibility of poly lactic acid with the human body is another outstanding quality. Poly lactic acid has a tougher structural makeup than Acrylonitrile Butadiene Styrene Temperature is between 60 – 65 ° C [16].
- 3. Collagen:** Collagen, which is found in the extracellular matrix, is another natural polymer utilised to boost cell cultures (ECM). Collagen has lately been employed as a biomaterial in 3D bio printing and tissue engineering. When collagen is hydrolyzed, gelatin is produced, which when coupled with alginate, generates a bio composite ink for 3D

printing scaffolding material [17]. It was possible to 3D bio print cross-linked cell-laden constructions with 80% cell viability using a hydro gel made of alginate dialdehyde, gelatin, and platelet-rich plasma. Another linear polysaccharide that has been shown to produce very stiff structures is agarose. The agarose was changed (by TEMPO-mediated oxidation) and mixed with trace quantities of negative agarose to create a bio composite ink for 3D printing by micro-extrusion [18]. 3DP in suspension media provides a platform for patterning mechanically weak bio inks into complex, highly defined patterns. A cell-containing formulation called bio inks can be used in 3D bio printing.

Poly(lactic acid), poly(vinylidene fluoride), hypromellose, 2-hydroxy propyl ether, and polycaprolactone are some of the other components utilised in the medication 3DP. Enteric-based coating polymeric materials like hypromellose acetate succinate, hypromellose-1-polyacrylic acid, and hypromellose-2-methyl propenoic acid have demonstrated their 3D printing capabilities for gastro applications [19].

V. 3D – PRINTED TECHNOLOGY

- 1. Fused deposition modelling (FDM):** The most common 3DP method is fused deposition modelling (FDM), often known as fused filament manufacturing following the development of thermoplastic drug-loaded polymeric filaments, which are fed into the printer where they are melted at a specified temperature and extruded via the nozzle [20]. The majority of the filaments used in FDM are made using the hot melt extrusion (HME) method, in which the medicine and other excipients are integrated into the polymer. This method employs a motor-driven screw-based extrusion mechanism in a barrel to melt the mixture under pressure and heat before allowing it to cool. The liquid is then allowed to solidify, producing the filament that will be utilized as the FDM feed [21] [22]. Due to its affordability, printing precision, assured quality criteria, and inclusion of HME, FDM is widely used in the pharmaceutical industry [23].

A one-step FDM approach called direct powder 3D printing (DPP), which does not need HME, was studied. Here, the powder mixtures were loaded into an extrusion cartridge made of stainless steel, heated, and successfully printed to create tablets with a honeycomb pattern [24]. In order to create the new double-chamber dosage form known as the dual tablet using a dual-nozzle FDM printer, two filaments, each having a different drug concentration, had to be produced using HME (hot melt extrusion). The FDM approach made it possible to create tailored pills with reduced adverse effects from under- or overdosage, increased ease of distribution, and enhanced patient adherence to medication [11].

- 2. Selective Laser Sintering (SLS):** In selective laser sintering, powder particles are heated and fused with laser radiation before being solidified to create 3D objects. The spreading platform, powder bed, and laser system make up the selective laser sintering (SLS) system's primary parts. [20]. It belongs to the class of 3DP developing technologies. To create the desired 3D structures just requires one step in which a laser selectively sinters particles into layers. This method involves creating accurate patterns on the surface of powders by stacking powder materials while employing focused lasers.[25]

- 3. Stereolithography technique (SLA):** A method of 3D printing is stereo lithography. Charles Hull discovered the SLA technique in 1988 as the first technique of the 3D system. The product uses a laser beam to transform it from a liquid state into a solid state. Wang and colleagues created tablets of paracetamol (Acetaminophen) and 4-aminosalicylic acid (4ASA) via SLA 3D printing [26]. It is completely based on the principle of photo polymerization [19]. In SLA, UV light is permitted to travel perpendicular to the surface of the liquefied resin. Once a particular deposit is solidified upon exposure, another layer of liquid resin is placed. This procedure continues until a completed product is produced. An excess of resin is pumped off once a certain product is finished. To get rid of excess resin, the finished product is cleaned [27][28]

VI. STEPS INVOLVED IN A 3D PRINTED DOSAGE FORM

1. A pharmaceutical product uses computer-aided design to create a three-dimensional design.
2. The design is converted into a machine-readable format that specifies the exterior of the three-dimensional dosage form.
3. The computer program then splits this surface into a number of unique printable layers and sends each layer individually to the printer. [29]

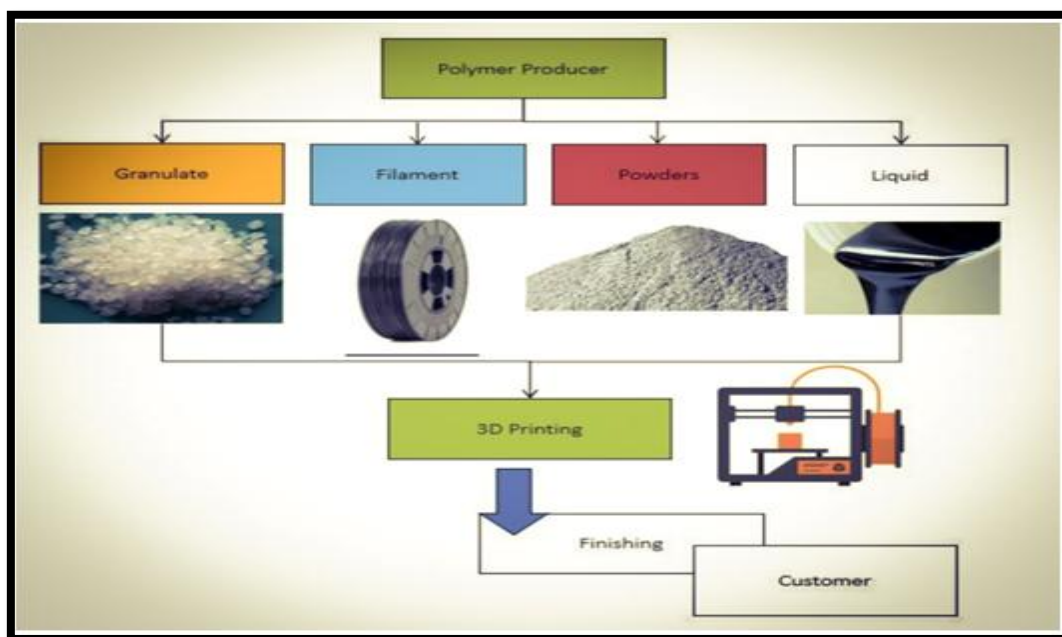


Figure 3: Manufacturing of Drug using 3D Printing.

VII. DOSAGE FORMS

- 1. Oral tablets:** Multidisciplinary techniques provide a wide range of dosage forms, each with its own set of consequences that are influenced by the tools and procedures used. To generate suitable dosage forms, active pharmaceutical ingredients (APIs) are mixed with materials such as polymer filament, hydro gels, or smart material polymers. In the pharmaceutical sector, these materials are used as drug carriers. They are sensitive to

transforming into new shapes when exposed to specific environmental conditions such as temperature, light, or humidity [30].

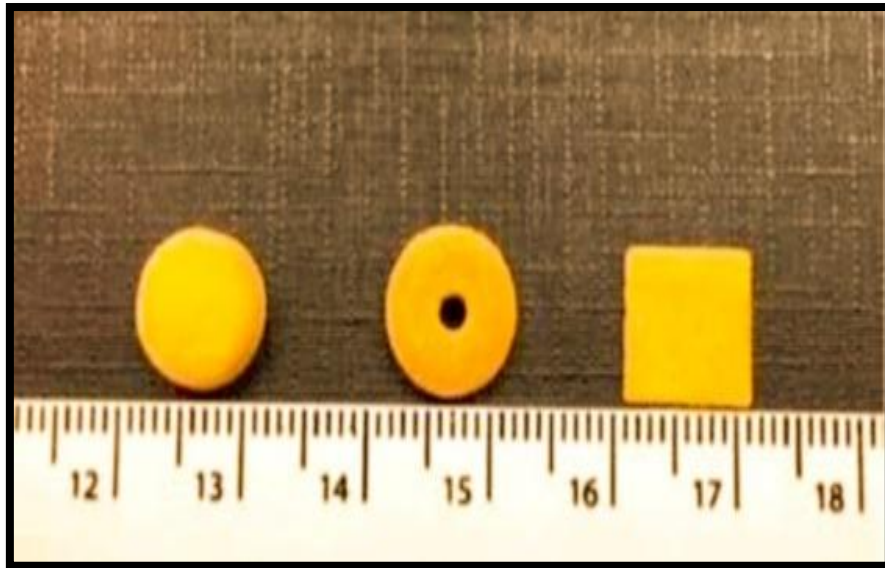


Figure 4: 3DP Oral Dosage Form

Hot melt extrusion is used to produce two filaments with different medicine concentrations for oral dose forms. The breakthrough twin chamber dosage form known as the "Duo pill" was created using dual nozzle FDM printers. The use of computer-aided design in 3DP technology allows for the production of medicine formulations with the desired release rate and pattern. Regarding the patient's willingness or capacity to swallow the tablet, specific forms and sizes are preferable in 3DP. The adoption of conventional techniques might pave the way for the creation of tablets that are easier to use. The main benefits of 3D pharmaceuticals include their low cost; the absence of organic solvents; and the ability to combine the medications and polymers using hot melt extrusion, making multi-drug devices and being able to alter drug release profiles via changing shape and density.

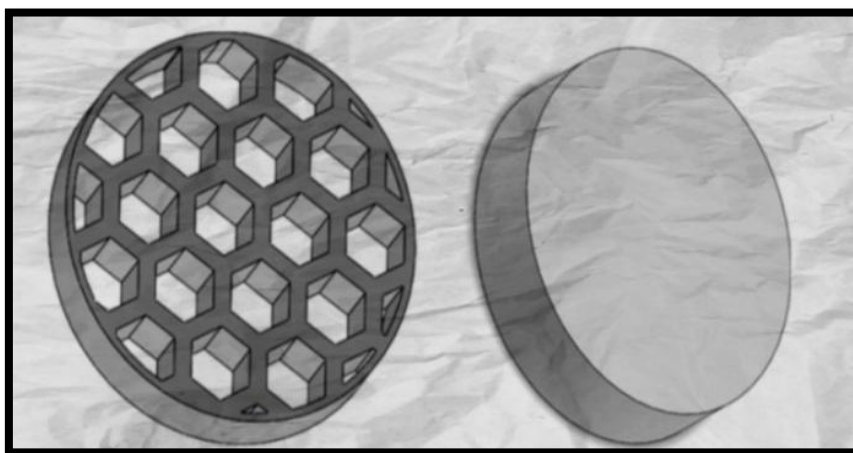


Fig 5: tablet shapes and textures used for 3DP Lattice honey comb tablet (left) and cylindrical tablet on (right)

VIII. POLYPILL

The World Health Organization (WHO) suggested combining many medications into a fixed-dose item, which is referred to as a polypill. It is possible to create an oral dose form with numerous layers using 3DP in Fig 6. These include TB, type 2 diabetes, hypertension, cardiovascular disease, and HIV-1 infection. Polycap™, a type of multi-drug pill, is an illustration [31].

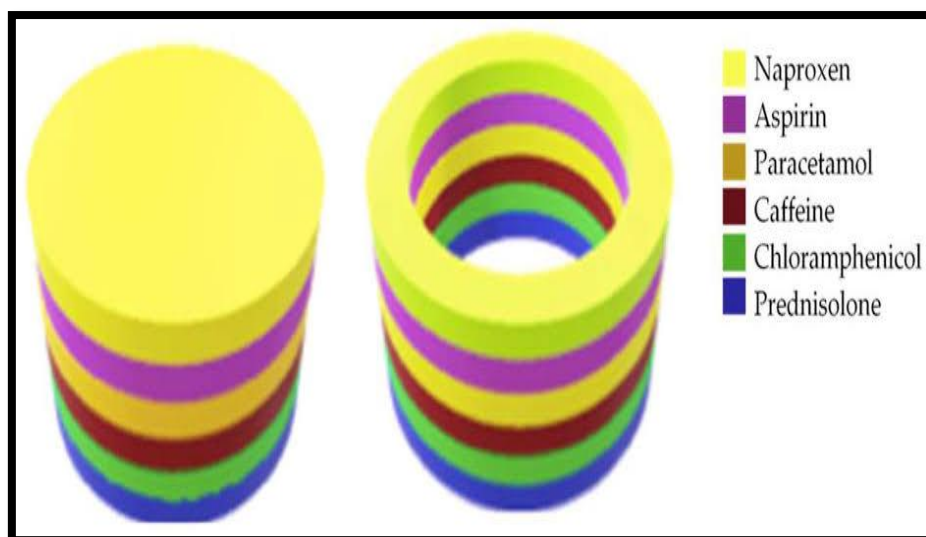


Figure 6: Polypill

IX. BUCCAL WAFERS

In particular, patients with challenges, such as small children or the elderly, as well as patients who are afraid of needles, benefit from buccal and orodispersible dose forms. It has been used to create polycaprolactone (PCL) and poly vinyl pyrrolidone-based antibiotic 3D film patches because of its high-resolution printing capabilities. The innovative dosage form is taken orally, but it does not require water or swallowing. Tablets, wafers, and films are frequently used as buccal dosage forms. However, wafers and films are favoured over tablets for prolonged transmucosal administration. FDM 3DP can speed up the production of buccal films, and the films have the property of unidirectional release. The FDA has approved a brand-new medication (libervant) for the treatment of cluster seizures that contains a diazepam buccal film [32].

X. TRANSDERMAL MICRO NEEDLES

In contrast to syringes, biodegradable 3DP polymer micro needles have been created for transdermal medication administration that is painless and sanitary. These micro needles were made using PLA. Different sizes, lengths, and densities might be produced using 3DP [33]. Using this method, medicine may be delivered via the skin without feeling any pain. Without activating the pain nerve, this permeates the skin and releases the medication in the dermis [31].

Table 1: An Example of 3D Printed Dosage Form Developed by Different Technology

Sl. No	Dosage Form	Drug	Excipients	3dp Printed Technology	References
1.	Tablets	Paracetamol	Kollicoat IR or Eudragit L, candurin gold sheen	Selective Laser Sintering (SLS)	[34]
2.	Tablets	Captopril	Maltitol, maltodextrin, water, polyvinylpyrrolidone (PVP)	Drop on Solid (a type of Drop on Demand (DoD))	[35]
3.	Tablets	Theophylline	Hydroxypropyl cellulose, triacetin, crospovidone, sodium starch	Extrusion-based Fused Deposition Modelling (FDM)	[36]
4.	Tablets	Paracetamol and 4-Aminosalicylic acid	Polyethylene glycol diacrylate (PEGDA), PEG 300 and diphenyl-(2,4,6-trimethyl benzoyl) phosphine oxide (DPPO)	Stereolithography (SLA)	[37]
5.	Multicompart ment tablet (polypill)	Hydrochlorothiazide, Aspirin, Atenolol, Pravastatin and Ramipril	D mannitol, Polyethylene glycol (PEG) 600, cellulose acetate	Semi-solid Extrusion (SSE) or Pressure assisted micro syringe	[38]
6.	Micro needles	insulin	Dental SG resin Xylitol, Mannitol, Trehalose	Stereolithography (SLA)	[39]
7.	Soluble Micro needles	Human immunoglobulin (IgG)	Maltose and stainless steel	Inkjet printing	[39]
8.	Dissolving Micro needles	Bovine serum albumin and lysozyme	Carboxymethylcellulose	Stereolithography (SLA)	[39]
9.	Coated Micro needles	Desmopressin (synthetic peptide hormone)	Titanium screen microneedles + desmopressin coating	Stereolithography (SLA)	[39]
10.	Biodegradable microneedle	Cy3-labeled plasmid DNA encoding luciferase	PDMS, PLGA, poly (β -amino ester) (PBAE)	Stereolithography (SLA)	[39]
11.	Buccal wafers	Famotidine (20, 40 mg)	Mannitol, aspartame, mint flavor, gelatin, red ferric oxide and xanthan gum	Fused Deposition Modeling (FDM)	[40]
12.	Buccal wafers	Metopimazine (7.5 mg)	Aspartame, xanthan gum, sodium docusate, dextran 70, mannitol	Fused Deposition Modeling (FDM)	[40]

13.	Buccal wafers	Paracetamol (500 mg)	Polysorbate 60, mono hydrous lactose, Aspartame, xanthan gum, dextran 70, orange flavouring,	Fused Deposition Modeling (FDM)	[40]
14.	Buccal wafers	diazepam	Diazepam, Hydroxyl propyl β -cyclodextrin, Hydroxy propyl methyl cellulose E3, E5, E15 and Glycerin, PEG 400, Propylene glycols	Fused Deposition Modeling (FDM)	[41]
15.	Buccal wafers	Selegiline (1.25 mg)	Citric acid, gelatin, mannitol, grapefruit flavor, glycine, aspartame, yellow iron oxide.	Fused Deposition Modeling (FDM)	[40]

XI. BENEFITS

1. Higher drug loading capacity compared to traditional dose forms. [42]
2. Precise and accurate dosage of powerful medications that are given in small doses. [42]
3. Minimizes manufacturing costs because there is less material wastage. [42]
4. Based on genetic variances, ethnic differences, age, gender, and environment, medication can be specially formulated or tailored for a patient in a certain situation. [42]
5. Due to the variable design and production of this dosage form, immediate and controlled release layers may be integrated, which helps in choosing the best treatment plan for an individual. [42]
6. Prevents batch-to-batch variations that occur when conventional dosage forms are manufactured in bulk. [43]

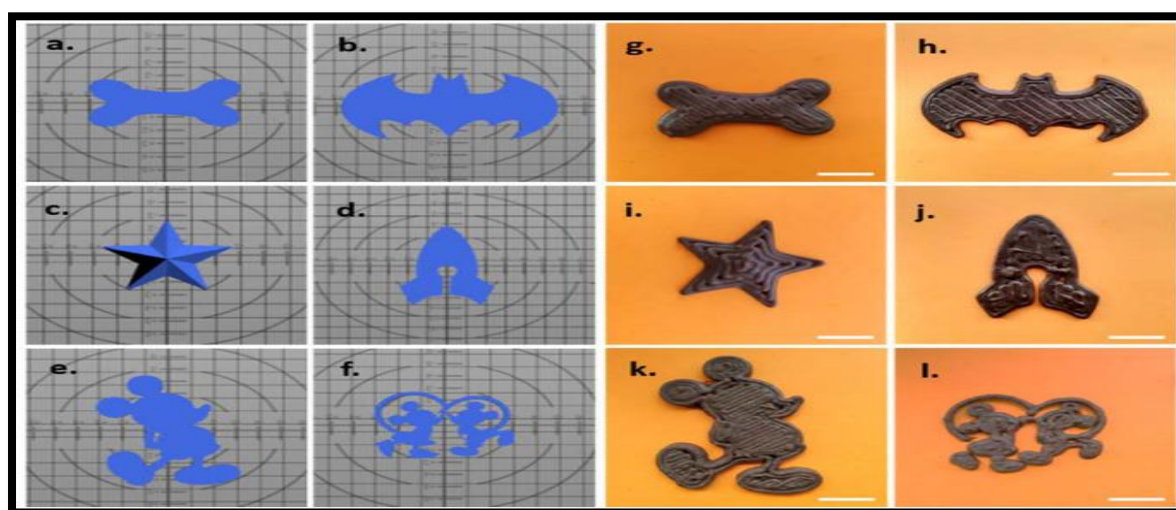


Figure 7: Different Shapes of 3DP Dosage Form. Computer Aided Design (Left), Final Printed Chocolate 3DP Dosage Form (Right).

Challenges

It produces encouraging results in medication delivery applications. It confronts several problems, including the optimization process; enhancing device performance for varied usage; selecting appropriate excipients; post-treatment methods; and so on.

1. Problems with the nozzle provide a significant issue since they prevent the printer head, which affects the structure of the finished output. [44]
2. Another difficulty is clogging in powder printing. [44]
3. The potential to alter the final structure in response to mechanical stress, impacts of ink Compositions And Storage Condition Adaptations. [44]
4. The Effects Of Various Printer-Related Variables On Printing Quality And Printer Cost. [44]

Applications

Dental implants and custom prosthetics were the first items made using 3D printing in the field of medicine. The creation of tissues and organs, the development of prostheses, implants, and anatomical models, and pharmaceutical research into drug discovery, delivery, and dosage forms are some of the current medical uses of 3D printing.

1. These technologies enable the fabrication of almost infinite dosage forms, which is predicted to pose a challenge to traditional medication manufacturing. Previously, 3D printers were used to manufacture a variety of novel dosage forms, including microcapsules, hyaluronan-based synthetic extracellular matrices, antibiotic-printed micropatterns, mesoporous bioactive glass scaffolds, nano solution, and multilayered drug delivery devices. [45]
2. Potential uses in industrial design, aerospace, medical engineering, tissue engineering, architecture, and pharmaceuticals for process improvement and performance improvement.
3. It primarily focuses on two possible places for expanding the scope of pharmaceutical product development by producing complex delivery systems and customized medication.
4. Helps with organ printing, biomaterials, and cell-laden materials. In the healthcare industry to create dental implants. On making an organized release multi-drug implant for bone TB treatment. [46]
5. Complex medication production procedures may also be standardised using 3D printing, making them easier and more practical. 3D printing technology has the potential to be highly useful in the development of customised medicine.

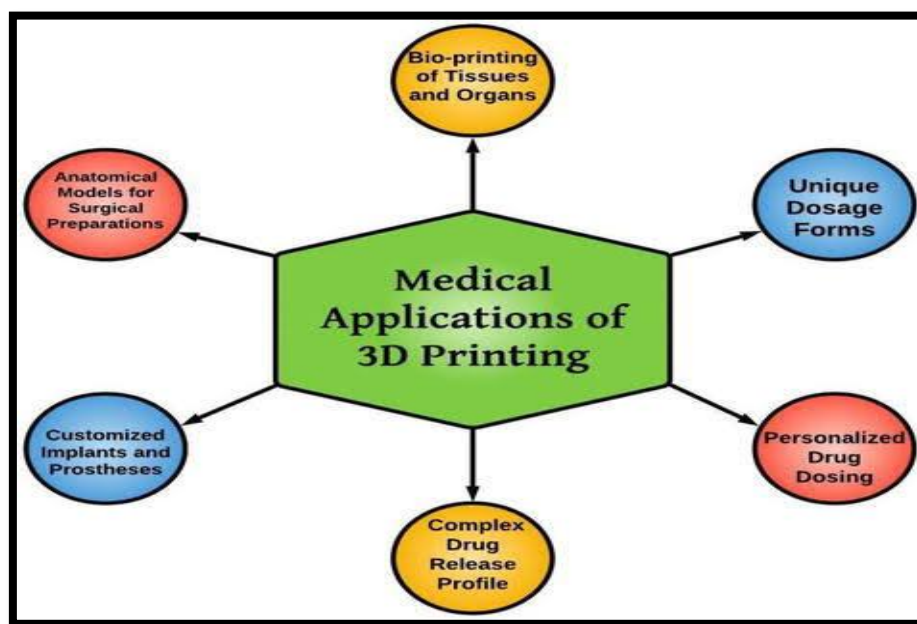


Figure 8: Application of 3D Printing in Medicine.

XII. DISCUSSION

This niche technology appears to be a breakthrough tool in pharmaceutical production, providing greater flexibility. 3D printing, a complicated layer-by-layer technology, can immediately build complex, customizable objects. The application of 3D printing in medication delivery systems is an intriguing technology for the manufacture of personalized items. In a few years, the concept of 3D-printed drug formulation has fast grown under the supervision of patient-centric medicine in an attempt to enhance therapy. The FDA authorized the first pharmaceutical produced utilising 3D printing technology, resulting in an incredibly speedy development. The ability to construct multifunctional drug delivery systems, multidrug devices, and drug formulations with fast release qualities for personalised therapy is another advantage of 3D printing. To achieve the best therapeutic index, future research should focus on producing pediatric and geriatric dosage forms in individual dose and dimensional-specific medication formulations. A growing number of drug development studies have demonstrated the clear benefits of this approach, but leading complex innovative dosage forms on a large scale will yield the greatest outcome.

XIII. CONCLUSION

The application of 3D printing technology in the pharmaceutical business enables the production of individualised medication that is focused on the needs of the patient. It has many benefits, including improving production and cost-effectiveness. The speed of manufacturing has undergone a transformation because of 3D printing. It decreases lead time and tooling costs, and enhances the design and manufacturing of products. This chapter summarized how the drugs are printed using 3D printing technology and its different dosage forms, its benefits and challenges, and also the application of 3DP in the medical field. Hence, 3D printing of drugs has more benefits when compared to challenges, it is therefore a beneficial one. The pharmaceutical industry uses a wide range of technical aspects of 3D

printing to create novel drug delivery systems, create new excipients, increase medication compatibility, and create personalized dosage forms. It is believed that 3D printers will eventually replace pharmaceutical shelves once the proper printing platform is built, launching a new era of digital health. As a result, it is expected that more 3D-printed pharmaceutical drugs and medical devices will be available on the market sooner than expected.

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