REVIEW ARTICLE

An Overview of Three-Dimensional Printing in Pharmaceutical Technology

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ABSTRACT

Three-dimensional printing (3DP) in pharmaceutical technology is a new technique that can build the desired objects directly from CAD models using a layer-by-layer material build-up approach. This article presents an overview of the 3DP technique with a brief look into the history of the 3DP process and various methods like stereolithography, fused deposition method, hot melt extrusion, polyjet, etc., their merits and demerits, and applications of 3DP in pharmaceutical technology. The challenges 3DP has surmounted in the areas of pharmaceutical and biomedical research related to additive manufacturing are outlined in this review.. The use of 3DP has increased recently. Personalized medicine may now have access to a whole new range of options due to 3DP. The concept of specialists and researchers is to create customized oral pills using 3DP. Since technology is still developing, any regulations on security, safety, and privacy have yet to exist. Thus, these issues will be of more significant concern shortly. The applications of 3DP technologies in modern drug delivery are highlighted in this article, which expounds on using these technologies for forward-thinking advancements in pharmacy practice.

Keywords: Additive manufacturing; Computer-aided design (CAD); Drop on solid (DOS); Polymers; Selective laser sintering (SLS); Three-dimensional printing (3DP).

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INTRODUCTION

The first three-dimensional (3D) printing technology was created in 1980. Rapid prototyping (RP), solid free-form technology, and additive manufacturing (AM) are other synonyms for this technology. Three-dimensional printing (3DP) is described by the International Standard Organization (ISO) as the fabrication of objects through the deposition of a substance utilizing a print head, nozzle, or other printer technology 3DP can be extended in stages of drug development, from primary medical care to preclinical research. Using the data from a 3D model, different parts are prepared by layer-by-layer material joining for this approach. Rapid prototyping is the term of the implementation method for AM. The first step in 3DP technology is modeling, which uses programming and computer-aided design (CAD) to generate 3D objects by layering materials on a substrate. As a result, this 3DP provides manufacturing capabilities, maximum flexibility, and time savings for objects or pharmaceutical medicine products.[1]

Fast-dissolving tablets, micro pills, microchip medication implants, and oral controlled release systems are a few examples of pharmaceutical development techniques that involve 3DP. This method can identify problems early in the development of medicine, as it makes drug screening platforms more accurate.[2] This novel technology's advantages include reduced material waste, reduced simple modifications for a product at a designed level, the ability to manufacture small objects, prototyping time and cost, and precision and accuracy with drug loading. It is used in various health sector applications, including producing 3D-printed tissue, dental bridges, drug products, and artificial implants. Hence, developing new pharmaceutical dosage forms and medicinal/surgical products can be achieved using 3DP technology.[3]

3DP has existed in concept since 1945 and has proposed efficient methods and patents since 1971. The Teletype Corporation developed the inkjet technology method of "pulling" a drop from a nozzle in 1960. They also experimented with wax that had been melted and produced a metal object that was liquefied and solidified into a shape by ink jet movement with each subsequent layer, as described by Johannes F. Gottwald in 1971. 3DP stereolithography, a commercial rapid prototyping technology, was first invented by Charles Hull in 1984. Adrian Bowyer's RepRap Project later launched an open-source project to develop a 3D printer that builds its parts in 2005.[4] 3DP was first used as dental implants and

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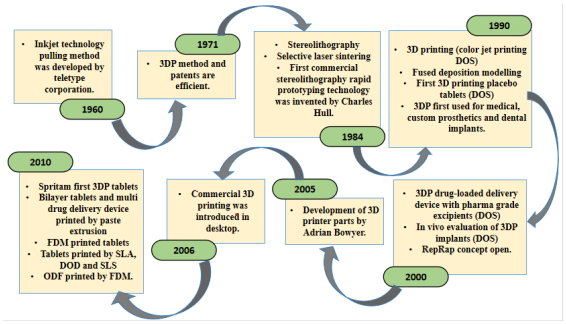

Figure 1: Timeline of 3DP technology

custom prosthetics in 1990 for medical purposes. Finally, desktop commercial 3DP was introduced in 2006. Aprecia is the first and only US-based pharmaceutical company to develop large-scale medication, and it has a Food and Drug Administration (FDA)-validated 3DP platform. Its main motto is to minimize the number of tablets patients need to take and make medications easier to consume.[5] Over the past 40 years, various approaches have been invented and enhanced with the development of 3DP technology. The timeline of 3DP technology, starting from its innovation year of 1960, is shown in Figure 1.

MATERIALS AND METHODS

Methodology

Making 3D objects using CAD is known as 3DP. 3D-printed items are usually built layer by layer and then allowed to solidify. We must first build a data file before printing on a 3DP object. Three phases are typically involved in 3DP, and Figure 2 shows the stepwise format for 3DP.

Modeling is the initial step of 3DP. Following CAD software modeling, a 3D printer was used to print the object. Manufacturing companies create object models using CAD programs. The object model is then saved in a file format called an additive manufacturing file (AMF) or standard tessellation language (STL). Most CAD packages can identify errors made during the modeling phase and model file errors like holes, self-intersections, manifolds, and face faults.

Printing is the second step of 3DP, in which the object is printed. The manufacturing company can upload AMF or STL files and instructions to the 3D printer. It will specify how and where the material is deposited if no errors are found. The 3D printer will build the bottom layer first and the next-highest layer. Thermoplastic is the substance that is used in this process the most frequently. The printed object is developed when thermoplastic pellets are extruded from the printer head and eventually settle on the bed. The third and last phase in 3D printing is finishing. Solvents may be added to the printed object in this final phase to smooth the surface and remove imperfections. Alternatively, any supports that hold the object during printing should be removed in this last phase. The classification of 3DP technologies is depicted in Figure 3. Various materials utilized for 3DP include ceramics, metals, powders, thermoplastics, and powders.

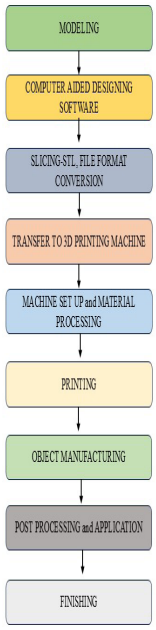

Figure 2: Stepwise format for 3DP process

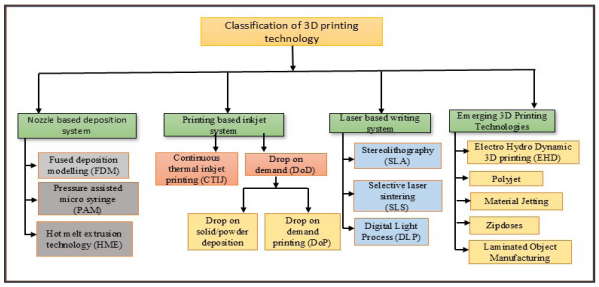

Figure 3: Classification of 3DP techniques

Nozzle-based deposition system

Fused deposition method (FDM)

S. Scott Crump developed the FDM in the late 1980s, and it was made commercially available in 1990 by Stratasys Company. The FDM process is done by heating the filament on the nozzle to a semi-liquid state and then extruding it into previously printed layers.[6] The filaments fuse during printing due to the thermo plasticity of the polymer filament, and they get solidified in less than seconds at room temperature. The production of medicines with customized dosages and delayed-release print mediums is made possible by FDM 3DP without an exterior enteric coating (Figure 4). It is the least expensive approach for 3DP.

On the other hand, FDM 3DP highlights some system defects, such as a lack of suitable polymers, frequently insufficient drug release due to entrapment of drugs in polymers, and inadequate measurement of drug and additive compatibility with the utilized polymers. Some of the FDM pharmaceutical formulations are given in Table 1. FDM printers are budget-friendly and receive extensive filament materials and colors. 3DP of entire parts can be accomplished

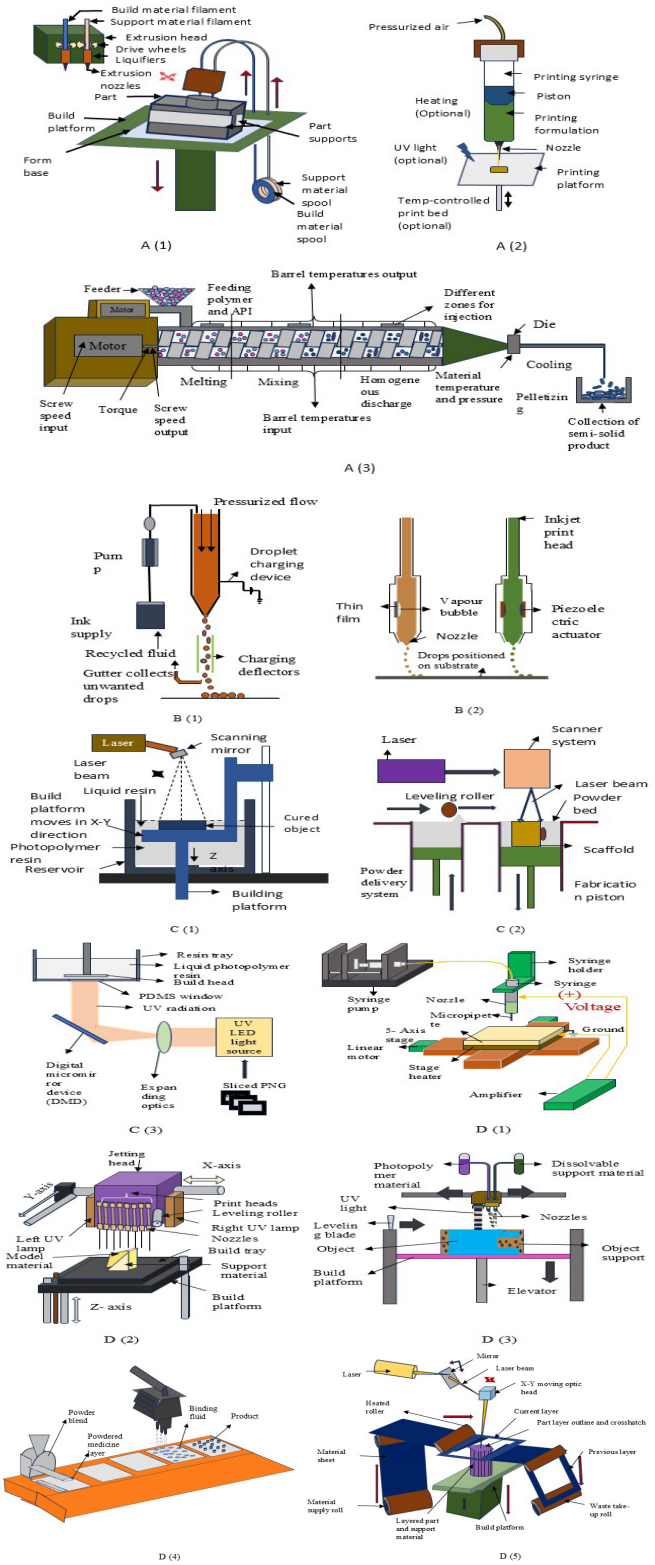

Figure 4: 3DP techniques: A(1)- Fused deposition modelling (FDM), A(2)- Pressure assisted microsyringes (PAM), A(3)- Hot melt extrusion technology (HME), B(1)- Continuous thermal inkjet printing (CTIJ), B(2)- Drop on demand printing (DoD), C(1)- Stereolithography (SLA), C(2)- Selective laser sintering (SLS), C(3)- Digital light process (DLP), D(1)- Electro hydro dynamic 3D printing (EHD), D(2) Polyjet, D(3) Material jetting, D(4) Zipdoses, and D(5) Laminated object manufacturing

in minutes or hours. Due to FDM's ability to print larger objects, they have a low cost-to-size ratio. The printer's easily scalable design speeds up prototyping and shortens lead times. However, it is only utilized when a few low-speed channels are required, and low resolution provides less thorough input; there is distortion due to intermodulation. FDM requires more hardware than TDM, and the circuitry for FDM is more complex than TDM.

Pressure-assisted microsyringe (PAM)

The PAM printing technique is also familiar as semi-solid extrusion. The starting material for this method must be a semi-solid formulation with the ability to construct a 3D object without collapsing during printing.[7] For instance, no melting of this material is required so that printing can be done below room temperature. PAM is suitable for thermo-sensitive drugs.[8] Since solvents are the foundation of printing formulations, solid objects must be dried to be produced. The formulation viscosity has the most significant impact on printability[9]. Printing becomes impossible if the viscosity is high due to nozzle clogging, and a substance with low viscosity cannot support the 3D structure. The PAM process image is shown in Figure 4 and the medications manufactured by PAM are listed in Table 1. The pressurized air is used to extrude the semi-solid formulation through the nozzle, which stresses the filament in the FFF process in the printing process. It functions at room temperature, is suitable for printing multi-drug pills, and achieves high drug loading. Nevertheless, polymer rheological properties impact structure formulation and printing techniques, so post-processing and drying are required. Organic solvents can lead to toxicity and drug instability, and printing resolution depends on nozzle size.

Hot melt extrusion technology (HME)

In the eighteenth century, HME was used to manufacture lead pipes and later in the rubber, plastic, pharmaceutical, and food industries[10]. Breitenbach was the one who first proposed the melt extrusion method for producing pharmaceuticals. It is a continuous process that involves melting drugs and polymers at high pressures and temperatures in order to combine them uniformly. Heating, mixing, feeding, and shaping are just a few of the numerous activities of this continuous manufacturing process[11]. The various steps for HME compaction include feeding the extruder through a hopper, followed by various operations such as mixing, grinding, reducing the particle size, venting, kneading, passing through the die, and then extruding from this and downstream processing. The image of the HME is shown in Figure 4 and the medications made by HME are listed in Table 1. Numerous medication delivery devices are produced using the robust HME technique. HME is a potential continuous process and may not apply to heat-labile drugs. Changes to the amorphous state of active pharmaceutical ingredients (API) should be moisture-free. Nonetheless, thermal degradation is possible for sensitive materials, leading to polymer or drug degradation and high start-up costs.

Table 1: Pharmaceutical formulations developed by different 3DP technologies

S. No	*API*	*Formulation*	*Category*	*Reference*
SLA Technique				
1	Amlodipine	Oral dosage form tablets	Antihypertensive	63
2	Atenolol	Oral dosage form tablets	Antihypertensive	63
3	Salicylic acid	Anti-acne patch	Psoriasis	65
4	Paracetamol	Oral-modified release tablets	Antipyretic	62
5	4-Aminosalicylic acid	Oral modified-release tablets	Antibiotic	64
CTIJ Technique				
1	Felodipine	Solid dispersion	Antihypertensive	66
2	Terbutaline	Solution	Bronchodilator	67
3	Prednisolone	Tablet	Anti-inflammatory or Immunosuppressant	12
4	Carbamazepine	Co-crystals	Antiepileptic	69
5	Levofloxacin, rifampicin	Muti-compartment tablet	Quinolone antibiotics, Anti-mycobacteria	70
6	Folic acid	Nano suspension	Anemia	68
FDM Technique				
1	Budesonide	Controlled release tablet	Ulcerative colitis	71
2	Amino salicylate	Tablet	Antibiotic	72
3	Captopril	Intermediate release tablets	Hypertension, CHF	73
4	Ibuprofen	Tablet	NSAID	74
5	Indomethacin	T-shaped (SC rods, IU)	Nonsteroidal anti-inflammatory	75
6	Hydroxyapatite	Implant	Carrier	76
7	Aripiprazole	Oral dispersible films	Anti- Psychotic	5
SLS Technique				
1	Ondansetron	Oral disintegrating printlets	Antiemetic drug	77
2	Paracetamol	Solid oral dosage form	Antipyretic	78
3	Paracetamol	Oral dispersible tablets	Antipyretic	79
HME Technique				
1	Ethylene Vinyl Acetate Copolymers	Subcutaneous rods	Nonsteroidal anti- inflammatory	75
2	Domperidone	Tablet	Treats PParkinson'sdisease	53
3	Rifampicin	Compartmentalized shells	Antibiotic	80
4	Hydroxypropyl cellulose	Tablet	Treats Keratoconjunctivitis	53
DLP Technique				
1	Atomoxetine hydrochloride	Tablets	Selective norepinephrine reuptake inhibitors	81
DOP Technique				
1	Ketoconazole	Oral dosage form tablets	Anti- fungal agent	82
2	Fluorouracil	Tablets	Anti-cancer drug	21
3	Levetiracetam	Anti-convulsants, Nontropic agent	Treats seizures	83
EHD Technique				
1	Paracetamol and cholorpheniramine maleate	Oral dosage form	Synergistic drugs	95
2	Ibuprofen and paracetamol	Films	Antipyretic treats pain alleviation or fever	30
3	Tetracycline hydrochloride	Patches	Anti- microial drug	84
4	Polycaprolactone	Scaffolds tissue	Cardiac tissue	85
PAM Technique				
1	Ramipril	Semi-solid extrusion	Angiotensin-converting enzyme inhibitors Controlled release oral drug delivery	9
2	Levetiracetam	Tablet	Anti-convulsants on demand manufacturing of immediate release	8

Drop on drop deposition				
1	Ibuprofen, cetirizine hydrochloride, diphenyl hydrazine	Mucosa thin films	Rapidly released NSAIDs	86
2	Ropinirole HCl	Tablets	Dopamine agonists. Fickian diffusion API release mechanism	87
3	Fenofibrate	Tablets	Anti-lipemic agents	52
Drop on solid deposition				
1	Diclofenac sodium	Tablets	NSAIDS fast drug release	88
2	Isoniazid	Implants	Anti-tuberculosis agents, sustained release	89
3	Captopril	Tablets	ACE inhibitors, Rapidly dispersing tablets	90
Polyjet				
1	Ropinirolehel and hyaluronic acid	Pills	Treats muscles pain associated with pparkinson'sdisease	91
Material jetting				
1	Naproxen and ibuprofen	Tablets	Hydrophobic drugs	92
2	Tripropylene glycol diacrylate	Ink	Difunctional acrylic monomer	93
Zipdose				
1	Levetiracetam	Tablets	Anti-convulsants	94

Printing-based inkjet system

Continuous thermal inkjet (CTIJ) printing

Thermal inkjet (TIJ) printing designs and loads drug-eluting stents. It is used for developing drug-loaded biodegradable microspheres and liposomes[12]. TIJ is a cost-effective method using a compact machine to create high-resolution codes on various substrates. Additionally, making biological films this way is practical and ensures that protein activity is not compromised. TIJ printers can only meet the needs of the modern production line by negotiating quality[13]. Some of the pharmaceutical formulations prepared by TIJ printing are reviewed in Table 1. There are four steps involved in TIJ technology, which include heating the ink using a heater, which causes the vaporization of ink-generating bubbles. In order to force an ink drop out of the nozzle, the bubble expands, which later collapses, causing the droplet to break off and imprint (Figure 4). TIJ printers are an inexpensive alternative to printing and can document quickly with a high-quality finish. Most printers do not require special training or practice to operate, and they can print on various materials, like ordinary and specialty papers, cartons, metals, and plastics. They are always ready for use because they have no warm-up or cool-down phases. However, they tend to be more expensive than regular printers, and they require purchasing thermal paper. They have color limitations, thermal labels fade over time, print heads can get damaged by heat, and they are expensive to replace.

Drop-on-demand printing (DOD)

DoD technology is subcategorized into drop-on-drop deposition and drop-on-solid deposition. Drop-on-drop deposition (Piezoelectric Technology): The process by which the printer head ejects the droplets onto one another creates a solid layer with excellent resolution. Only when thermally activated does a DoD inkjet printer release droplets.[14] Piezoelectric DoD produces an acoustic pulse for the ejection of ink because of the sudden volume change caused by the piezoelectric crystal's quick change in shape. They only provide a limited variety of inks because thermally sensitive materials cannot be processed, which reduces print head durability. The phases of the drop deposition process are the impact phase, the relaxation phase, and the capillary phase.[15] A piezoelectric membrane is deformed and squeezes the drop into the nozzle by changing the voltage using the inverse piezoelectric effect (Figure 4). Drop-on-drop placement was not accurate when using the catalyst mixture.[16] Because there are no deflection plates, DoD inkjet printers usually have a multi-nozzle configuration that allows them to print at a slightly higher resolution than CIJ.[17] The liquid material used in a DoD inkjet printer should typically have a viscosity and surface tension between 20 and 70 N/m and less than 20 mPas, respectively.[18] Some of the drugs prepared by drop-on-solid deposition are given in Table 1. These technological materials can only produce inexpensive electrical responses to dynamic mechanics. They can print directly over the surface of an item. It has a high resonance frequency, stability, and sensitivity. Nevertheless, they cannot be used for genuinely static measurements. It costs more than SLA/DLP.

Drop-on-solid deposition/drop-on-powder (DoP) was created in the 1980s at the Massachusetts Institute of Technology (MIT) and marketed by Z-Corporation to develop various 3D printers. Drop-on-powder Solid oral dosage forms that are highly drug-loaded can be created using 3DP.[19] It is acknowledged as the first application of 3DP technology to satisfy the demands of pharmaceuticals. DoP printing is primarily used for highly soluble compounds in high-dose

formulations.[20] In this method, a flattened powder bed is coated with a liquid binding solution through an inkjet head that can jet-dispense. Then, organic or inorganic binders can bind powder carrier particles together due to adhesive forces to create an agglomerated product.[21] This method is primarily restricted to less soluble medications.[22]

The USFDA approved the production of Spritam® (levetiracetam), the first instant tablet produced using DoP 3DP, according to an announcement by Aprecia Pharmaceuticals in 2015. The DoP deposition process image and manufactured drugs are shown in Figure 4 and Table 1, respectively. It has a low production cost and can recycle raw materials. It has high porosity, and various materials can be used. It is a room-temperature process and simple to scale up. On the other hand, these require post-processing and a specialized powder facility. It has insufficient mechanical properties and low material utilization, and it should have the properties of printing fluid.

Laser-based writing system

Stereo lithography (SLA)

SLA is a widely used 3DP technology invented by Japanese researcher Hideo Kodama in the 1980s. SLA is also referred to as resin printing, optical fabrication, photo-solidification, and vat photo polymerization. In this SLA technique, the liquid polymers are solidified by a computer-controlled laser beam. The pre-programmed design is drawn on the photopolymer vat surface with the help of CAD software and ultraviolet (UV) laser[23]. The thermoset polymers known as "resins" are the liquid components utilized for SLA printing, and models, prototypes, patterns, and production parts are all made using them.[24] A solid component can be created from a liquid using photo polymerization. SLA uses a digital mirroring device to trigger the gelation of the exposed area by initiating a chemical reaction in the photopolymer. The subsequent layer ensures adhesion and, thus, layer formation. This technique uses photopolymer resin, liquid UV light, and an ultraviolet laser to build the object layers one at a time[25]. The stereolithography process image is shown in Figure 4. In Table 1, a few of the medications created using SLA are listed. The functional parts can be manufactured daily, and SLA gives the highest accuracy and resolution. It is most suitable for micro-delivery devices. It creates prototype designs to master patterns for various metal casting processes and injection molding. Conversely, the high energy input may degrade starting materials. The photopolymers should be handled carefully because they are messy and sticky. Post-printing is required. It is often costly and takes a long time to print.

Selective laser sintering (SLS)

The SLS technology is a laser-based powder bed fusion method. It is a widely used method for the 3DP of metals. A laser is used in SLS to solidify the powder bed's powder particles into a 3D structure developed using CAD.[26] The sintered materials become part of the final item, and the unsintered materials become part of the supporting framework. The SLS technology is shown in Figure 4. 3DP with SLS combines pharmaceutical 3DP, a fabrication technique with high printing precision, with the capability to manufacture medications with unique engineering and functional properties.[27] It is also used to manufacture plastic, metallic, and ceramic objects for industrial use. Table 1 includes lists of some medications created using this technique. SLS enables various parameters such as hatch spacing, layer thickness, porosity, feed bed temperature, laser powder, etc., so the drug can be controlled according to the requirements. The SLS 3D printer enables easy batch printing without additional support, which is best for practical use. Printing costs are comparatively low, solvent-free, and have high dimensional accuracy—however, they have higher costs when compared to the other methods. Post-processing procedures are complex, and shifting from FDM/SLA to SLS is difficult. Material recycling is impossible, and large amounts of powder waste are generated.

Digital light processing (DLP)

DLP was first discovered by C. Clarke-Mark forged. It is used to create photopolymer parts quickly. This method uses a digital micromirror device (DMD) chip to reflect color and light onto a screen. It is similar to the SLA technique. By using ultraviolet light projection and a digital projector, DLP flashes a single image of a layer crosswise resin simultaneously. Highly detailed resin designs like figurines, toys, dental tools, molds, jewelry, and other intricately designed objects can be printed with DLP printing.[28] The digital light process image is shown in Figure 4. At the micron scale, this method's resolution is comparatively high. A complex structure can be printed with the DLP bio printer with a high resolution of 1 mm and a fast printing speed of 30 mm^3/s. The formulations prepared by DLP are given in Table 1. Rapid printing is possible for complex 3D structures with sub-500 nm features. It is a low-cost technology; the digital light process is relatively fast, has good accuracy, and has smooth surfaces. Still, these cannot be heat sterilized, and resin can cause skin sensitization. Higher-cost materials are used, and support materials must be removed.

Emerging 3DP technologies

Electro hydrodynamic (EHD) 3DP

A developing 3DP process called EHD can fabricate fibrous materials by digitally controlling the layer-upon-layer material deposition to produce good-ordered free-form geometries. Based on this method, materials, including poly (ethylene oxide), polycaprolactone (PCL), polyvinyl alcohol (PVA), and cellulose acetate (CA), have been processed to manufacture the drug carriers.[29] Materials viscosities range from 1 to 10,000 mPas (PEO).[30] EHD provides a powerful method for developing small-scale pharmaceutical technologies to customize medications with specified therapeutic doses for the patient's needs (Figure 4).[31] EHD jet printing allows for far larger nozzle diameters (>100 m) than those used in thermal or piezoelectric inkjet printing (approximately 20 m), which minimizes the possibility of blockages and makes it simple to use a highly viscous liquid[32]. EHD printing is high-resolution inkjet printing and is cost-effective.[33] The products prepared by

the EHD 3D printing process are given in Table 1. EHD printing has a higher controllable resolution and non-conventional and ambient environment. This is a one-step process. EHD printing creates a thin, intact jet without the nozzle's reduced size. It is cost-effective and has a good surface finish. However, it has high requirements for solution properties and low efficiency. There is droplet charge accumulation, residual organic solvent, and in-site solvent drying.

Polyjet

The 3DP polyjet method creates items by spraying millions of photopolymer droplets on a build platform and curing the layers with ultraviolet light. This uses an inlet-style printing head to deposit different multi-materials from independent nozzles. The polyjet 3DP equipment generates highly detailed sculptures and multi-material components using a similar standard inkjet printer process. Depending on the type of design, the horizontal layer thickness can be as low as 16 microns and the ultra-thin walls as low as 0.6 mm (0.024"). Different polyjet 3D printers include objet30, j5 Medijet, and j5 Dentajet. Polyjet is used to create accurate molds in the dental industry and for surgical aids in the medical field [34]. The mechanism of the polyjet is shown in Figure 4. The formulations manufactured by the polyjet process are given in Table 1. This method is accurate, fast, and scalable, and it quickly manufactures the form, fit, and functional prototypes. However, it has poor mechanical properties and is costly.

Material jetting (MJ)

MJ technologies are the most accurate and fastest 3DP technologies, indicating high-speed deposition of micro-droplet liquid materials. The MJ process began by preheating the liquid resin to ensure a finer viscosity. Then, the print head moves above the build platform and deposits the first layer of material exposed to UV light. A print head can contain between 100 and 1000 nozzles.[35] Figure 3 displays an image of the material jetting process. The material is selectively deposited in successive layers and creates the end of a 3D object. MJ is commonly used for tooling and prototyping[36]. The preparations manufactured by the MJ process are given in Table 1. This technique can be used for multi-material and full-color 3D printing. It has a high level of accuracy and a thin layer that can be printed at around 0.013 mm. The material has flexibility, rigidity, and translucency. However, the objects developed by material jetting are weaker when compared to other 3DP techniques like SLS. Its printing part takes more time than other 3DP methods, and this technique can only successfully print the viscous material.

Zip doses

Zip dose is the first and only 3DP in new therapeutic areas that have been FDA-validated commercially. This technology can maintain rapid disintegration while holding a high dosage load. In order to formulate a tablet, Zip Dose employs a specific layering and zero compression method that is digitally coded. This process overcomes patient adherence and difficulty swallowing challenges.[37] Spritam (levetiracetam) is the first 3D-printed drug to obtain FDA approval, and it comes with four dosing strengths that range from 100 mg to 1,000 mg. Aprecia Pharmaceuticals marketed the oral-dispersible tablet Spritam. A layer-by-layer manufacturing method mainly comprises binder liquid, active ingredients, and excipients to create a matrix tablet. The zip dose process is shown in Figure 4, and the medications prepared by the zip dose method are given in Table 1. Zipdose allows the applications to enhance taste masking techniques and fast-dissolving. It has a higher dose load of up to 1,000 mg and rapid dispersion of highly porous products within seconds with liquid. Nevertheless, it requires access to a small amount of liquid.

Laminated object manufacturing

A solid-based method of additive manufacturing is laminated object manufacturing. Using adhesive or ultrasonic welding, sheets of material are laminated and joined together[38]. The components are fabricated by consecutive lamination of these adhesively bonded sheets. Before adding the next layer, each is laser-cut to the desired shape individually. A heated roller is used to activate the adhesives. Figure 3 shows an image of the laminated object manufacturing process. It has high production rates as a result of its fast-opening mechanisms. The technology of 3DP has advanced significantly. It is a quick and inexpensive manufacturing method for large parts, and no support material is needed. However, breaking out the parts is difficult; wooden parts absorb moisture and need a better surface finish.

Application of 3DP Technology

Three-dimensional printing primarily focuses on two potential directions: personalized medicine and the fabrication of a sophisticated drug delivery system. Architects utilize this technology to produce realistic models of complex structures and demonstrate their viability to clients[39]. It is also gaining interest from the academic and pharmaceutical sectors, and it has many medical applications, including artificial blood vessels, dental work, bone replacement, and prosthetic sockets (Figure 5). The innovative use of 3DP is personalized medicine, which can overcome the difficulties of treating heterogeneous

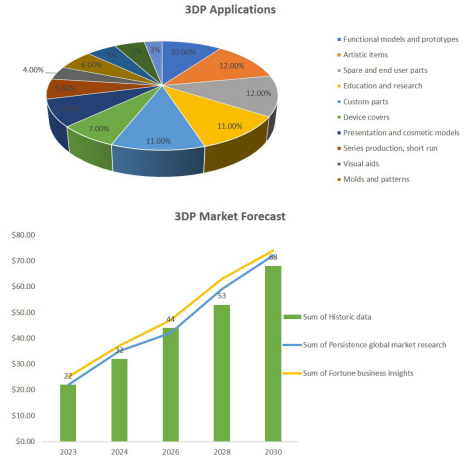

Figure 5: 3DP Applications and updated statistics

diseases. This 3DP technology enhances personalized drug dosing, bio printing of tissues and organs, complex drug release, and customized implants[40]. It has spread into the healthcare sector, where the development of dental implants necessitates more precise medication dispensing and tailored drug release to satisfy the individual needs of every patient. The pharmaceutical industry has made significant use of 3DP due to its potential benefits, which include increased productivity, single-step processes at low cost, complex drug dissolution profiles, and customization of drug delivery. It is cost-effective and environment-friendly, and materials production involves minimum wastage. A multi-drug implant release strategy is now a viable treatment option for bone tuberculosis. Formulations like oral solid dosage forms, films, implants, micro needles, and hydrogels are developed[41]. The American Society for Testing and Materials (ASTM) group created a set of standards in 2010 that categorizes the seven types of additive manufacturing techniques. These seven processes include sheet lamination, vat photo polymerization, powder bed fusion, binder jetting, and directed energy deposition.

Challenges of 3DP Technology

As a developing technology, 3DP faces some challenges, including process optimization, post-treatment techniques, enhancing the device's performance for multiple uses, selecting appropriate excipients, and improving their performance. Technical challenges can result in packing defects of printed tablets that cause the rejection of entire batches. The regulatory framework has a large gap as there need to be guidelines in the 3DP process. A massive scale of investment is required. Loss of Jobs and 3D printers cannot build components with the required precision and instead make objects with a virtually final shape. The main obstacle to creating specific dosage forms is the need for more excipients. Continuous modeling and slicing software updates should be necessary for design purposes[42]. The manufactured dosage form must meet the quality control parameters to ensure the reproducibility of the formulations.

The 3D printer manufacturers must meet Qualification standards according to GMP requirements. In 2017, the FDA introduced relevant regulations for 3D-printed medical devices, and pharmaceutical formulations using printing technology may advance from theoretical research to practical applications[43]. There are specific requirements for excipient properties in the preparation process for all 3DP technologies[44]. Compared to traditional pharmaceutical processes, excipients are limited to 3DP technologies. As 3D printers used to make pharmaceutical medicines do not meet GMP requirements, processes and products should be validated to ensure their efficacy and safety for human health.[45] Mechanical properties involve considering dosage from quality control factors. Equipment and product costs are high. It requires a post-treatment method and optimization[46].

Opportunities and Future Directions of 3DP

3DP technology has several benefits and opportunities in the pharmaceutical field. In orally disintegrating formulations, the preparation of direct compression, wet granulation, hot melt extrusion, and other methods are typically used to produce ODT dosage forms. However, the porosity of tablets needs to be improved. Therefore, 3DP is used instead of compression, a layer-by-layer method that exhibits high porosity and a fast disintegration rate. The binder was dropped on the inner selected region. In vitro test results showed that all the tablets disintegrated rapidly[47]. 3DP methods and improved drugs affect the speed with which older adults and children solve dysphagia problems[48].

Using 3DP technology in compound formulation preparations has several benefits, like high repeatability, an easy process, accurate drug loading, and great flexibility[49]. The first fixed-dose combinations (FDCs) to control cardiovascular disease were proposed by the World Health Organization (WHO) in 2001. Robles-M fabricated polypills containing six active ingredients through a commercial SLA 3D printer. It has good mechanical properties and a drug-release profile with six active components in dissolution studies[50]. 3DP in compound formulations can separate material conformations and adapt multi-active ingredients with specific pharmacokinetic properties in the product. High-loading formulation preparation involves many drugs with large doses in the pharmaceutical field. Traditional tablets only contain 30% to 40% of the active ingredients, making them difficult to swallow. So, 3DP technology is introduced[51]. Aprecia is the first printed preparation by Spritam, with four doses of 250, 500, 750, and 10000 mg. Levetiracetam was recently manufactured in a high-loaded, fast-release form using SSE technology[52]. High drug-loading tablets are manufactured using 3DP technology with less excipient addition. Tailored dose formulation preparation is based on the patient's age, gender, genetics, physiology, body mass index, and other parameters; the drug formulations are customized[53].

The manufacture of personalized medicine dosage systems will shift because of the great potential that 3DP has as a fabrication technique[54]. Compared to traditional manufacturing methods, prednisolone-loaded PVA filaments were successfully developed by Skowyra et al. by using an FDM 3D printer[55,56]. In personalized and innovative oral delivery device preparation, the traditional dosage form preparation method primarily controls drug distribution and release by selecting coating procedures and excipients. We can limit the design to unique structured dosage forms[57]. Kyobula et al. successfully created a fenofibrate medication using honeycomb-structured 3D-printed tablets and beeswax as a drug carrier. The ability to print tablets with highly customized structures is achieved using DOP technology with great potential, so the design feasibility of medication delivery systems will expand further[58]. The caplet structure is designed for implants to promote tablet drug release using FDM 3DP technology. Sadia et al. designed and prepared an innovative structure of caplets to accelerate drug release[59]. The core-shell structured tablets floated smoothly and behaved

well in dissolution tests. Li et al. printed and developed the dual chamber with polyvinyl alcohol and glipizide as the drug-loading filament using FDM 3DP technology[60]. Based on the internal structure of lattice, 3DP technology can prepare gastro-floating tablets over a long time using SSE 3DP as an innovative manufacturing method. For longer than eight hours, the manufactured tablets can remain floating. In Sandwich structure, the DOP 3DP technique was used to print sandwich-type gentamicin implants by Huang et al. in 2007. This structure achieves the long-term continuous release of implants by reducing the surface area of release, which inhibits burst release quantity.

Global 3DP Pharmaceutical Market

The market for 3D printed medications is developing as chronic diseases are becoming more common in dysphasia patients worldwide. The COVID-19 pandemic and quick increases in the pharmaceutical cycle are associated with the world's medicine scarcity. The FDA has investigated 3DP products by current regulations. FabRx Ltd. (M3DIMAKER), a company that uses specialized print-let technology to treat children with rare metabolic illnesses like polycythemia and organic syndrome, has completed the first clinical research in humans—the global adoption of personalized drugs[61]. The market for 3D-printed pharmaceuticals is expected to increase from USD 50 million in 2022 to USD 110 million in 2027. The USFDA has approved the first 3D printed medication ingredient (T19) for treating arthritis by Triastek, a Chinese pharmaceutical industry company that develops 3D printing technologies. In most national and international regulatory bodies, additional rules about 3D printing are necessary. Other reasons for increasing the 3D printed drugs market include the rising use of personalized medications and intensive scientific research.

CONCLUSION

3DP technology has the potential to manufacture and dispense medicines and help in drug and product development. It has significant flexibility in drug production and can progress drug frameworks, but it requires developing time. The numerous applications and unlimited potential of 3DP innovation in producing various medications for personalized medication administration and treatment are explained. It intends to demonstrate how this technology can be used in the tailored manufacture of pharmaceutical products. Much research has been done in this field since the introduction of 3DP in the 1980s, especially about creating materials for use in medical and pharmaceutical applications. 3DP can significantly reduce the drawbacks of traditional preparation technology. It can manufacture personalized precision medicines by selecting appearance, optimal doses, release profile, flavor, and dosage form. It has the potential to revolutionize clinical pharmacy practice. 3DP technology is cheaper, faster, and more extensive. 3DP will achieve new opportunities for drug discovery in the pharmaceutical industry.

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REFERENCES

1. Gross BC, Erkal JL, Lockwood SY, Chen C, Spence DM. Evaluation of 3D printing and its potential impact on biotechnology and the chemical sciences. Journal of analytical chemistry. 2014; doi.org/10.1021/ac403397r
2. Ursan ID, Chiu L, Pierce A. Three-dimensional drug printing: a structured review. Journal of the American Pharmacists Association. 2013 Mar 1;53(2):136-44. DOI: org/10.1331/JAPhA.2013.12217
3. Prasad LK, Smyth H. 3D printing technologies for drug delivery: A review. Drug Development Industrial Pharmacy. 2016; 42:1019–31.doi.org/10.3109/03639045.2015.1120743
4. Wu BM, Borland SW, Giordano RA, Cima LG, Sachs EM, Cima MJ. Solid free-form fabrication of drug delivery devices. Journal of Controlled Release. 1996 Jun 1;40(1-2):77-87.doi.org/10.1016/0168-3659(95)00173-5
5. Jamróz W, Kurek M, Łyszczarz E, Szafraniec J, Knapik-Kowalczuk J, Syrek K, Paluch M, Jachowicz R. 3D printed orodispersible films with Aripiprazole. International journal of pharmaceutics. 2017 Nov 30;533(2):413-20.doi.org/10.1016/j.ijpharm.2017.05.052
6. Parulski C, Gresse E, Jennotte O, Felten A, Ziemons E, Lechanteur A, Evrard B. Fused deposition modeling 3D printing of solid oral dosage forms containing amorphous solid dispersions: How to elucidate drug dissolution mechanisms through surface spectral analysis techniques?. International Journal of Pharmaceutics. 2022 Oct 15;626:122157. DOI:org/10.1016/j.ijpharm.2022.122157
7. El Aita I, Rahman J, Breitkreutz J, Quodbach J. 3D-Printing with precise layer-wise dose adjustments for paediatric use via pressure-assisted microsyringe printing. European Journal of Pharmaceutics and Biopharmaceutics. 2020 Dec 1;157:59-65. DOI:org/10.1016/j.ejpb.2020.09.012
8. El Aita I, Breitkreutz J, Quodbach J. On-demand manufacturing of immediate release levetiracetam tablets using pressure-assisted microsyringe printing. European Journal of Pharmaceutics and Biopharmaceutics. 2019 Jan 1;134:29-36.doi.org/10.1016/j.ejpb.2018.11.008
9. Mohammed AA, Algahtani MS, Ahmad MZ, Ahmad J. Optimization of semisolid extrusion (pressure-assisted microsyringe)-based 3D printing process for advanced drug delivery application. Annals of 3D Printed Medicine. 2021 Jun 1;2:100008. doi.org/10.1016/j.stlm.2021.100008
10. Zhang J, Yang W, Vo AQ, Feng X, Ye X, Kim DW, Repka MA. Hydroxypropyl methylcellulose-based controlled release dosage by melt extrusion and 3D printing: Structure and drug release correlation. Carbohydrate polymers. 2017 Dec 1;177:49-57.
11. Zhang J, Yang W, Vo AQ, Feng X, Ye X, Kim DW, Repka MA. Hydroxypropyl methylcellulose-based controlled release dosage by melt extrusion and 3D printing: Structure and drug release correlation. Carbohydrate polymers. 2017 Dec 1;177:49-57.doi.org/10.1016/j.carbpol.2017.08.058
12. Meléndez PA, Kane KM, Ashvar CS, Albrecht M, Smith PA. Thermal inkjet application in the preparation of oral dosage forms: dispensing of prednisolone solutions and polymorphic

characterization by solid-state spectroscopic techniques. Journal of pharmaceutical sciences. 2008 Jul 1;97(7):2619-36. doi.org/10.1002/jps.21189
13. Li TH, Stachowiak JC, Fletcher DA. Mixing solutions in inkjet formed vesicles. Methods in enzymology. 2009 Jan 1;465:75-94. doi.org/10.1016/S0076-6879(09)65004-7
14. Hsiao WK, Hutchings I, Hoath S, Martin G. Ink jet printing for direct mask deposition in printed circuit board fabrication. Journal of Imaging Science and Technology. 2009 Sep 1;53(5):50304-1.
15. Fathi A, Kermani F, Behnamghader A, Banijamali S, Mozafari M, Baino F, Kargozar S. Three-dimensionally printed polycaprolactone/multicomponent bioactive glass scaffolds for potential application in bone tissue engineering. Biomedical glasses. 2020 Jan 1;6(1):57-69.doi.org/10.1515/bglass-2020-0006
16. Morita N. Acoustic Behaviors of a Continuous Inkjet Multi-Nozzle Printhead Driven by a Traveling Wave. Journal of Imaging Science & Technology. 2017 May 1;61(3).
17. Mohapatra S, Kar RK, Biswal PK, Bindhani S. Approaches of 3D printing in current drug delivery. Sensors International. 2022 Jan 1;3:100146.doi.org/10.1016/j.sintl.2021.100146
18. Latif M, Jiang Y, Kumar B, Cho HC, Song JM, Kim J. Three-dimensional printing of highly crosslinked and concentrated nanocellulose for environmentally friendly structural applications. ACS Applied Nano Materials. 2022 Apr 4;5(4):5680-7.doi.org/10.1021/acsanm.2c00151
19. Sen K, Mehta T, Sansare S, Sharifi L, Ma AW, Chaudhuri B. Pharmaceutical applications of powder-based binder jet 3D printing process–a review. Advanced drug delivery reviews. 2021 Oct 1;177:113943.doi.org/10.1016/j.addr.2021.113943
20. Gottschalk N, Burkard A, Quodbach J, Bogdahn M. Drop-on-powder 3D printing of amorphous high dose oral dosage forms: Process development, opportunities and printing limitations. International Journal of Pharmaceutics: X. 2023 Dec 1;5:100151. doi.org/10.1016/j.ijpx.2022.100151
21. Shi K, Tan DK, Nokhodchi A, Maniruzzaman M. Drop-On-Powder 3D Printing of Tablets with an Anti-Cancer Drug, 5-Fluorouracil. Pharmaceutics. 2019 Apr 1;11(4):150. doi:10.3390/pharmaceutics11040150. PMID: 30939760; PMCID: PMC6523964
22. Gharaie SH, Morsi Y, Masood SH. Tensile properties of processed 3D printer ZP150 powder material. Advanced Materials Research. 2013 Jul 10;699:813-6.doi.org/10.4028/www.scientific.net/AMR.699.813
23. Hutchings, Ian M., and Graham Dagnall Martin, eds. Inkjet technology for digital fabrication. Chichester, UK: Wiley, 2013. DOI:10.1002/9781118452943
24. Itoo AM, Raza SN, Khan A, Sarjohn B, Ubaid T, Khan NA. 3D DRUG PRINTING-A SWING FROM LABORATORY PRODUCTION TO COMPUTERIZED PRODUCTION. Journal of Drug Delivery and Therapeutics. 2019 Oct 22;9(5-s):201-7. https://doi.org/10.22270/jddt.v9i5-s.3255
25. Martinez PR, Goyanes A, Basit AW, Gaisford S. Fabrication of drug-loaded hydrogels with stereolithographic 3D printing. International journal of pharmaceutics. 2017 Oct 30;532(1):313-7. doi.org/10.1016/j.ijpharm.2017.09.003
26. Al-Litani K, Ali T, Martinez PR, Buanz A. 3D printed implantable drug delivery devices for wwomen'shealth: Formulation challenges and regulatory perspective. Advanced Drug Delivery Reviews. 2023 Jul 1;198:114859.doi.org/10.1016/j.addr.2023.114859
27. Saifullah Q, Sharma A, Kabra A, Alshammari A, Albekairi TH, Alharbi M, Abdalla M. Development and optimization of film forming non-pressurized liquid bandage for wound healing by Box-Behnken statistical design. Saudi Pharmaceutical Journal. 2023 Dec 1;31(12):101864.doi.org/10.1016/j.jsps.2023.101864
28. Krause J, Bogdahn M, Schneider F, Koziolek M, Weitschies W. Design and characterization of a novel 3D printed pressure-controlled drug delivery system. European Journal of Pharmaceutical Sciences. 2019 Dec 1;140:105060.doi.org/10.1016/j.ejps.2019.105060
29. Li X, Zhang C, Wu S, Chen X, Mai J, Chang MW. Precision printing of customized cylindrical capsules with multifunctional layers for oral drug delivery. ACS applied materials & interfaces. 2019 Oct 1;11(42):39179-91.doi.org/10.1021/acsami.9b13568
30. Wu S, Ahmad Z, Li JS, Chang MW. Fabrication of flexible composite drug films via foldable linkages using electrohydrodynamic printing. Materials Science and Engineering: C. 2020 Mar 1;108:110393.doi.org/10.1016/j.msec.2019.110393
31. Elele E, Shen Y, Boppana R, Afolabi A, Bilgili EA, Khusid B. Electrodeless electro-hydrodynamic printing of nano-suspensions for personalized medicines. InAPS Division of Fluid Dynamics Meeting Abstracts 2012 Nov (pp. A30-007).
32. Jaworek AT, Sobczyk AT. Electrospraying route to nanotechnology: An overview. Journal of electrostatics. 2008 Mar 1;66(3-4):197-219.doi.org/10.1016/j.elstat.2007.10.001
33. Ramos A, editor. Electrokinetics and electrohydrodynamics in microsystems. Springer Science & Business Media; 2011 Sep 20.
34. Patpatiya P, Shastri A, Sharma S, Chaudhary K, Bhatnagar V. ANN-predictive modeling and GA-optimization for minimizing dimensional tolerance in Polyjet Additive Manufacturing. CIRP Journal of Manufacturing Science and Technology. 2022 Aug 1;38:320-39.doi.org/10.1016/j.cirpj.2022.05.004
35. Yap YL, Wang C, Sing SL, Dikshit V, Yeong WY, Wei J. Material jetting additive manufacturing: An experimental study using designed metrological benchmarks. Precision engineering. 2017 Oct 1;50:275-85.doi.org/10.1016/j.precisioneng.2017.05.015
36. Gülcan O, Günaydın K, Tamer A. The state of the art of material jetting—a critical review. Polymers. 2021 Aug 23;13(16):2829. doi.org/10.3390/polym13162829
37. Hsiao WK, Lorber B, Reitsamer H, Khinast J. 3D printing of oral drugs: a new reality or hype?. Expert opinion on drug delivery. 2018 Jan 2;15(1):1-4.doi.org/10.1080/17425247.2017.1371698
38. Dermeik B, Travitzky N. Laminated object manufacturing of ceramic-based materials. Advanced engineering materials. 2020 Sep;22(9):2000256.doi.org/10.1002/adem.202000256
39. Ventola CL. Medical applications for 3D printing: current and projected uses. Pharmacy and Therapeutics. 2014 Oct;39(10):704.
40. Katakam P, Dey B, Assaleh FH, Hwisa NT, Adiki SK, Chandu BR, Mitra A. Top-down and bottom-up approaches in 3D printing technologies for drug delivery challenges. Critical Reviews™ in Therapeutic Drug Carrier Systems. 2015;32(1).DOI: 10.1615/CritRevTherDrugCarrierSyst.2014011157
41. Saifullah, Q., & Sharma, A. (2023). Current Trends on Innovative Technologies in Topical Wound Care for Advanced Healing and Management. Current Drug Research Reviews.doi.org/10.2174/0125899775262048230925054922
42. Annaji M, Ramesh S, Poudel I, Govindarajulu M, Arnold RD, Dhanasekaran M, Babu RJ. Application of extrusion-based 3D printed dosage forms in the treatment of chronic diseases. Journal

of Pharmaceutical Sciences. 2020 Dec 1;109(12):3551-68.doi.org/10.1016/j.xphs.2020.09.042
43. Pham DT, Gault RS. A comparison of rapid prototyping technologies. International Journal of machine tools and manufacture. 1998 Oct 1;38(10-11):1257-87.doi.org/10.1016/S0890-6955(97)00137-5
44. Yu DG, Zhu LM, Branford-White CJ, Yang XL. Three-dimensional printing in pharmaceutics: promises and problems. Journal of pharmaceutical sciences. 2008 Sep 1;97(9):3666-90.doi.org/10.1002/jps.21284
45. Zheng F, Huang SW. Advances in study on three-dimensional printing in pharmaceutics. Chinese Herbal Medicines. 2016 Apr 1;8(2):121-5.doi.org/10.1016/S1674-6384(16)60020-5
46. Fedor JA, Gaylo CM, Materna PA, inventors; AFBS Inc, assignee. Apparatus, systems and methods for use in three-dimensional printing. United States patent US 7,073,442. 2006 Jul 11.
47. Comoglu T, Dilek Ozyilmaz E. Orally disintegrating tablets and orally disintegrating mini tablets–novel dosage forms for pediatric use. Pharmaceutical Ddevelopmentand technology. 2019 Aug 9;24(7):902-14.doi.org/10.1080/10837450.2019.1615090
48. Liu Y, Li P, Qian R, Sun T, Fang F, Wang Z, Ke X, Xu B. A novel and discriminative method of in vitro disintegration time for preparation and optimization of taste-masked orally disintegrating tablets of carbinoxamine maleate. Drug Development and Industrial Pharmacy. 2018 Aug 3;44(8):1317-27.doi.org/10.1080/03639045.2018.1449854
49. McDonald S, Comrie N, Buehler E, Carter N, Dubin B, Gordes K, McCombe-Waller S, Hurst A. Uncovering challenges and opportunities for 3D printing assistive technology with physical therapists. InProceedings of the 18th International ACM SIGACCESS Conference on Computers and Accessibility 2016 Oct 23 (pp. 131-139).doi.org/10.1145/2982142.2982162
50. Khaled SA, Burley JC, Alexander MR, Yang J, Roberts CJ. 3D printing of tablets containing multiple drugs with defined release profiles. International journal of pharmaceutics. 2015 Oct 30;494(2):643-50.doi.org/10.1016/j.ijpharm.2015.07.067
51. Khaled SA, Alexander MR, Wildman RD, Wallace MJ, Sharpe S, Yoo J, Roberts CJ. 3D extrusion printing of high drug loading immediate release paracetamol tablets. International journal of pharmaceutics. 2018 Mar 1;538(1-2):223-30.doi.org/10.1016/j.ijpharm.2018.01.024
52. Cui M, Pan H, Su Y, Fang D, Qiao S, Ding P, Pan W. Opportunities and challenges of three-dimensional printing technology in pharmaceutical formulation development. Acta Pharmaceutica Sinica B. 2021 Aug 1;11(8):2488-504.doi.org/10.1016/j.apsb.2021.03.015
53. Herrada-Manchón H, Rodríguez-González D, Fernández MA, Suñé-Pou M, Pérez-Lozano P, García-Montoya E, Aguilar E. 3D printed gummies: Personalized drug dosage in a safe and appealing way. International Journal of Pharmaceutics. 2020 Sep 25;587:119687.doi.org/10.1016/j.ijpharm.2020.119687
54. Cui M, Yang Y, Jia D, Li P, Li Q, Chen F, Wang S, Pan W, Ding P. Effect of novel internal structures on printability and drug release behavior of 3D printed tablets. Journal of Drug Delivery Science and Technology. 2019 Feb 1;49:14-23.doi.org/10.1016/j.jddst.2018.10.037
55. Alomari M, Mohamed FH, Basit AW, Gaisford S. Personalised dosing: Printing a dose of oone'sown medicine. International journal of pharmaceutics. 2015 Oct 30;494(2):568-77.doi.org/10.1016/j.ijpharm.2014.12.006
56. Cui M, Li Y, Wang S, Chai Y, Lou J, Chen F, Li Q, Pan W, Ding P. Exploration and preparation of a dose-flexible regulation system for levetiracetam tablets via novel semi-solid extrusion three-dimensional printing. Journal of Pharmaceutical Sciences. 2019 Feb 1;108(2):977-86.doi.org/10.1016/j.xphs.2018.10.001
57. Kyobula M, Adedeji A, Alexander MR, Saleh E, Wildman R, Ashcroft I, Gellert PR, Roberts CJ. 3D inkjet printing of tablets exploiting bespoke complex geometries for controlled and tuneable drug release. Journal of Controlled release. 2017 Sep 10;261:207-15.doi.org/10.1016/j.jconrel.2017.06.025
58. Sadia M, Arafat B, Ahmed W, Forbes RT, Alhnan MA. Channelled tablets: An innovative approach to accelerating drug release from 3D printed tablets. Journal of controlled release. 2018 Jan 10;269:355-63.doi.org/10.1016/j.jconrel.2017.11.022
59. Li Q, Wen H, Jia D, Guan X, Pan H, Yang Y, Yu S, Zhu Z, Xiang R, Pan W. Preparation and investigation of controlled-release glipizide novel oral device with three-dimensional printing. International journal of pharmaceutics. 2017 Jun 15;525(1):5-11.doi.org/10.1016/j.ijpharm.2017.03.066
60. Cui M, Pan H, Su Y, Fang D, Qiao S, Ding P, Pan W. Opportunities and challenges of three-dimensional printing technology in pharmaceutical formulation development. Acta Pharmaceutica Sinica B. 2021 Aug 1;11(8):2488-504.doi.org/10.1016/j.apsb.2021.03.015
61. Gioumouxouzis CI, Karavasili C, Fatouros DG. Recent advances in pharmaceutical dosage forms and devices using additive manufacturing technologies. Drug discovery today. 2019 Feb 1;24(2):636-43.doi.org/10.1016/j.drudis.2018.11.019
62. Wang J, Goyanes A, Gaisford S, Basit AW. Stereolithographic (SLA) 3D printing of oral modified-release dosage forms. International journal of pharmaceutics. 2016 Apr 30;503(1-2):207-12.doi.org/10.1016/j.ijpharm.2016.03.016
63. Xu X, Robles-Martinez P, Madla CM, Joubert F, Goyanes A, Basit AW, Gaisford S. Stereolithography (SLA) 3D printing of an antihypertensive polyprintlet: Case study of an unexpected photopolymer-drug reaction. Additive Manufacturing. 2020 May 1;33:101071.doi.org/10.1016/j.addma.2020.101071
64. Wang J, Li S, Yi F, Zi Y, Lin J, Wang X, Xu Y, Wang ZL. Sustainably powering wearable electronics solely by biomechanical energy. Nature communications. 2016 Sep 28;7(1):12744.doi: 10.1038/ncomms12744 (2016).
65. Goyanes A, Det-Amornrat U, Wang J, Basit AW, Gaisford S. 3D scanning and 3D printing as innovative technologies for fabricating personalized topical drug delivery systems. Journal of controlled release. 2016 Jul 28;234:41-8.doi.org/10.1016/j.jconrel.2016.05.034
66. Scoutaris N, Alexander MR, Gellert PR, Roberts CJ. Inkjet printing as a novel medicine formulation technique. Journal of controlled release. 2011 Dec 10;156(2):179-85.doi.org/10.1016/j.jconrel.2011.07.033
67. Sharma A, Rong X. Establishing Standards for Color and Print Quality in Large Format Inkjet Printing. Journal of Imaging Science & Technology. 2014 May 1;58(3).
68. Pardeike J, Strohmeier DM, Schrödl N, Voura C, Gruber M, Khinast JG, Zimmer A. Nanosuspensions as advanced printing ink for accurate dosing of poorly soluble drugs in personalized medicines. International journal of pharmaceutics. 2011 Nov 25;420(1):93-100.doi.org/10.1016/j.ijpharm.2011.08.033
69. Cooley P, Wallace D, Antohe B. Applicatons of iinkjet printing technology to BioMEMS and microfluidic systems. JALA:

Journal of the Association for Laboratory Automation. 2002 Oct;7(5):33-9.doi.org/10.1016/S1535-5535-04-00214-X
70. Ballard DH, Tappa K, Boyer CJ, Jammalamadaka U, Hemmanur K, Weisman JA, Alexander JS, Mills DK, Woodard PK. Antibiotics in 3D-printed implants, instruments and materials: Benefits, challenges and future directions. Journal of 3D printing in medicine. 2019 Jun;3(2):83-93.doi.org/10.2217/3dp-2019-0007
71. Okwuosa TC. *On Demand Manufacturing of Solid Dosage Forms via Fused Deposition Modelling (FDM) 3D Printing* (Doctoral dissertation, University of Central Lancashire).
72. Goyanes A, Buanz AB, Hatton GB, Gaisford S, Basit AW. 3D printing of modified-release aminosalicylate (4-ASA and 5-ASA) tablets. European journal of pharmaceutics and biopharmaceutics. 2015 Jan 1;89:157-62.doi.org/10.1016/j.ejpb.2014.12.003
73. Sadia M, Sośnicka A, Arafat B, Isreb A, Ahmed W, Kelarakis A, Alhnan MA. Adaptation of pharmaceutical excipients to FDM 3D printing for the fabrication of patient-tailored immediate release tablets. International journal of pharmaceutics. 2016 Nov 20;513(1-2):659-68.doi.org/10.1016/j.ijpharm.2016.09.050
74. Yang Y, Wang H, Li H, Ou Z, Yang G. 3D printed tablets with internal scaffold structure using ethyl cellulose to achieve sustained ibuprofen release. European Journal of Pharmaceutical Sciences. 2018 Mar 30;115:11-8.doi.org/10.1016/j.ejps.2018.01.005
75. Genina N, Holländer J, Jukarainen H, Mäkilä E, Salonen J, Sandler N. Ethylene vinyl acetate (EVA) as a new drug carrier for 3D printed medical drug delivery devices. European Journal of Pharmaceutical Sciences. 2016 Jul 30;90:53-63.doi.org/10.1016/j.ejps.2015.11.005
76. Water JJ, Bohr A, Boetker J, Aho J, Sandler N, Nielsen HM, Rantanen J. Three-dimensional printing of drug-eluting implants: preparation of an antimicrobial polylactide feedstock material. Journal of pharmaceutical sciences. 2015 Mar 1;104(3):1099-107. doi.org/10.1002/jps.24305
77. Allahham N, Fina F, Marcuta C, Kraschew L, Mohr W, Gaisford S, Basit AW, Goyanes A. Selective laser sintering 3D printing of orally disintegrating printlets containing ondansetron. Pharmaceutics. 2020Feb;12(2):110.doi.org/10.3390/pharmaceutics12020110
78. Gueche YA, Sanchez-Ballester NM, Bataille B, Aubert A, Leclercq L, Rossi JC, Soulairol I. Selective laser sintering of solid oral dosage forms with copovidone and paracetamol using a CO2 laser. Pharmaceutics. 2021 Jan 26;13(2):160.doi.org/10.3390/pharmaceutics13020160
79. Fina F, Madla CM, Goyanes A, Zhang J, Gaisford S, Basit AW. Fabricating 3D printed orally disintegrating printlets using selective laser sintering. International journal of pharmaceutics. 2018 Apr 25;541(1-2):101-7.doi.org/10.1016/j.ijpharm.2018.02.015
80. Genina N, Boetker JP, Colombo S, Harmankaya N, Rantanen J, Bohr A. Anti-tuberculosis drug combination for controlled oral delivery using 3D printed compartmental dosage forms: From drug product design to in vivo testing. Journal of controlled Release. 2017 Dec 28;268:40-8.doi.org/10.1016/j.jconrel.2017.10.003
81. Krkobabić M, Medarević D, Pešić N, Vasiljević D, Ivković B, Ibrić S. Digital light processing (DLP) 3D printing of atomoxetine hydrochloride tablets using photoreactive suspensions. Pharmaceutics. 2020 Aug 31;12(9):833.doi.org/10.3390/pharmaceutics12090833
82. Gottschalk N, Burkard A, Quodbach J, Bogdahn M. Drop-on-powder 3D printing of amorphous high dose oral dosage forms: Process development, opportunities and printing limitations. International Journal of Pharmaceutics: X. 2023 Dec 1;5:100151. doi.org/10.1016/j.ijpx.2022.100151
83. Wojtyłko M, Lamprou DA, Froelich A, Kuczko W, Wichniarek R, Osmałek T. 3D-printed solid oral dosage forms for mental and neurological disorders: recent advances and future perspectives. Expert Opinion on Drug Delivery. 2023 Dec 10:1-9.doi.org/10.1080/17425247.2023.2292692
84. Yao ZC, Wang JC, Wang B, Ahmad Z, Li JS, Chang MW. A novel approach for tailored medicines: Direct writing of Janus fibers. Journal of Drug Delivery Science and Technology. 2019 Apr 1;50:372-9.doi.org/10.1016/j.jddst.2019.02.006
85. Lei Q, He J, Li D. Electrohydrodynamic 3D printing of layer-specifically oriented, multiscale conductive scaffolds for cardiac tissue engineering. Nanoscale. 2019;11(32):15195-205.doi.org/10.1039/C9NR04989D
86. Cader HK, Rance GA, Alexander MR, Gonçalves AD, Roberts CJ, Tuck CJ, Wildman RD. Water-based 3D inkjet printing of an oral pharmaceutical dosage form. International journal of pharmaceutics. 2019 Jun 10;564:359-68.doi.org/10.1016/j.ijpharm.2019.04.026
87. Clark EA, Alexander MR, Irvine DJ, Roberts CJ, Wallace MJ, Sharpe S, Yoo J, Hague RJ, Tuck CJ, Wildman RD. 3D printing of tablets using inkjet with UV photoinitiation. International Journal of Pharmaceutics. 2017 Aug 30;529(1-2):523-30.doi.org/10.1016/j.ijpharm.2017.06.085
88. Goole J, Amighi K. 3D printing in pharmaceutics: A new tool for designing customized drug delivery systems. International journal of pharmaceutics. 2016 Feb 29;499(1-2):376-94.doi.org/10.1016/j.ijpharm.2015.12.071
89. Wu W, Zheng Q, Guo X, Sun J, Liu Y. A programmed release multi-drug implant fabricated by three-dimensional printing technology for bone tuberculosis therapy. Biomedical Materials. 2009 Nov 9;4(6):065005. DOI: 10.1088/1748-6041/4/6/065005
90. Lee KJ, Kang A, Delfino JJ, West TG, Chetty D, Monkhouse DC, Yoo J. Evaluation of critical formulation factors in the development of a rapidly dispersing captopril oral dosage form. Drug development and industrial pharmacy. 2003 Jan 1;29(9):967-79.doi.org/10.1081/DDC-120025454
91. https://3dprintingindustry,com/news/new-3d-bioink-polyjet-3d-printed-pills-105087/
92. Acosta-Vélez, G. F., Zhu, T. Z., Linsley, C. S., & Wu, B. M. (2018). Photocurable poly (ethylene glycol) as a bioink for the inkjet 3D pharming of hydrophobic drugs. International journal of pharmaceutics, 546(1-2), 145-153.doi.org/10.1016/j.ijpharm.2018.04.056
93. He Y, Zhang F, Saleh E, Vaithilingam J, Aboulkhair N, Begines B, Tuck CJ, Hague RJ, Ashcroft IA, Wildman RD. A tripropylene glycol diacrylate-based polymeric support ink for material jetting. Additive Manufacturing. 2017 Aug 1;16:153-61.doi.org/10.1016/j.addma.2017.06.001
94. https://www.pharmaceuticalonline.com/doc/zipdose-technology-0001
95. Li Z, Al-Milaji KN, Zhao H, Chen DR. Electrohydrodynamic (EHD) jet printing with a circulating dual-channel nozzle. Journal of Micromechanics and Microengineering. 2019 Jan 31;29(3):035013.DOI: 10.1088/1361-6439/aafd9e
96. Singh C, Yashwant, Gupta AK, Garg V. Formulation Development and Evaluation of Divalproex Sodium Extended-release Tablets. International Journal of Drug Delivery Technology. 2022;12(4):1769-1773.DOI:10.25258/ijddt.12.4.46