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Exploring the Impact of 3D Printing on Modern Drug Delivery Systems

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ABSTRACT
The use of 3D printing technology has completely changed how drugs are delivered. It is now used in oral controlled-release systems, transdermal patches, implants, microneedles, rapidly dissolving tablets, and dosage forms that release drugs in multiple phases. This technology has a lot of benefits over traditional methods. For example, it can make personalised medications with complex structures, specific drug release characteristics, and faster small-batch production while wasting less material. Even though it has medical and economic benefits, technical and regulatory issues are making it hard for it to be widely used in pharmaceuticals right now. This review explores various 3D printing techniques and their applications in drug delivery, further discussing the technological and regulatory challenges and proposed solutions to facilitate personalised healthcare and customised pharmaceuticals.
Keywords: *3D printing; pharmacy; nanomedicines; hydrogels; Computer aided drug design*

1. INTRODUCTION

Three-dimensional printing (3DP) is a process of 3D production of objects from digital designs wherein parts are integrated in layer upon layer so that items with varying geometries may be produced by a layer-on-layer procedure. This method is called advanced manufacturing, rapid prototyping, or solid freeform fabrication. 3D printing technologies have been in existence since the late 1980s and are predominantly employed in engineering and various non-medical manufacturing industries, including automotive, aerospace, and consumer products. Recent rapid improvements in three-dimensional printing techniques and the discovery of versatile biocompatible materials have facilitated their implementation in the pharmaceutical sector [1,2].

This method efficiently resolves specific problems related to conventional pharmaceutical unit operations. Simultaneously, advances in drug safety monitoring programs have significantly enhanced our ability to identify and characterise adverse event profiles associated with life-saving medications [1,3]. The evolving comprehension has also highlighted one limitation of classical targeted delivery systems, leading to a transition toward more flexible patient-centric therapeutic approaches. As a result, even traditional dosage schedules, such as the cumulative trough-only method, are no longer effective.

Because it is more cost-effective and yields better therapeutic outcomes, the trend towards personalised medicine—drug delivery catered to each patient's particular needs—has accelerated. The incorporation of 3D printing technology into medication delivery systems has been prompted by this need [4]. The implementation of 3D printing innovation in the healthcare sector has increased significantly in recent years, evidenced by the growing number of research publications and patents outlining its applications in pharmaceuticals [3,5-7]. 3D printing became prominent as a method for manufacturing pharmaceuticals [7]. This review aims to provide an in-depth overview and comparison of the latest findings and developments in this field of study. looking into the useful uses of 3D printing in pharmaceutical production, especially for producing intricate drug release patterns, patient-specific dosages, and modifiable drug compositions.

1.1 METHODOLOGY

This investigation studied renowned academic databases, namely PubMed, Google Scholar, and ScienceDirect, particularly on articles published mostly between 2018 and 2024**.** The search was conducted using the specific search phrases "3D printing",” Personalised medicines”, "Types of 3D printing”, “use of 3D in the pharmaceutical industry”, etc." These searches yielded substantial information regarding 3D printing and its applications in the pharmaceutical industry.

2. TYPES OF 3D PRINTING

A diverse array of 3D printing techniques is presently accessible in the market. The American Society of Testing and the International Organisation for Standardisation (ISO/ASTM) has created a uniform taxonomy of these technologies. The standard is AM ISO/ASTM 52900:2021 [8], which classifies the established additive manufacturing techniques into seven primary categories: Powder Bed Fusion, Fused Deposition Modelling, Direct Energy Deposition, Vat Photopolymerization, Binder Jetting, Sheet Lamination, Material Jetting, and Direct Energy Deposition. The concept of each category and its application to drug delivery are examined in the next section.

2.1. Fused Deposition Modelling

The FDM process is widely employed in pharmaceuticals due to its simple apparatus, economic efficiency, and enhanced product durability. 3D-printed objects are produced by computer-aided design software by sequentially depositing molten material in layers on printing surfaces [9,10]. Two rollers extrude the drug-infused polymer thread into a high-temperature sprayer, and the tip of the print moves along the Y and X axes while being controlled by programming to create the final product. When a layer is finished, the printing platform descends or the Z axis elevates by the dimension of the layer to start the following layer. This process is reiterated until the final product is achieved [11],[12]. Basic material extrusion processing parameters include layer thickness as well as extrusion sprayer diameter, where the layer thickness influences the printed object's resolution, and the extrusion tip diameter determines the printed lines' width. After printing, the printed product might demand post-processing, such as painting or sanding [12]. Layers may appear on the manufactured object's surface, which can be avoided by using a thinner layer. This technology has many benefits, such as ease of use, affordability, and quick accessibility, but it also has drawbacks, such as slow drug dissolution, insufficient drug loading capacity, and thermal degradation of componentry [13,14]. The principle of FDM technology and API incorporation techniques is shown in Figure 1.

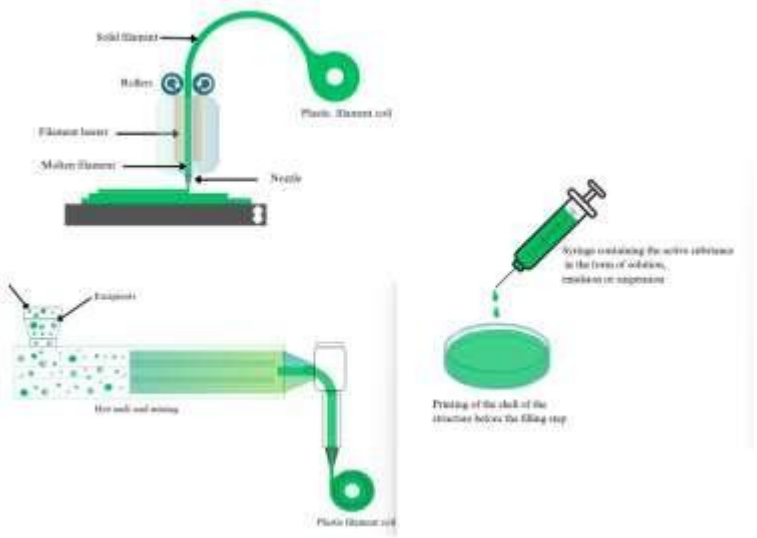


Fig 1. Schematic diagram of the principle of FDM technology and three methods of tablet preparation: (**A**) schematic diagram of the printing principle of FDM technology; (**B**) schematic diagram of the preparation of drug-containing filaments by the dipping-melting method; (**C**) schematic diagram of the preparation of drug-containing filaments by the HME-FDM method [15]

2.1.1 Incorporation of API into polymer filament

- **Dipping-melting method:** It is the initial technique for incorporating the medicine into the polymer strand. To create an API-infused filament for printing, the filament is submerged in a solution or dispersion that contains the API [9].
- **Hot Melt Extrusion-Fusion Deposition Modelling method**: The HME-FDM approach involves mixing the drug and excipients, like polymers, in a molten state initially, followed by the extrusion of a filament with the desired diameter at a specific velocity, pressure, and configuration [9]. The filament is processed to the heating area without being distorted or extruded, heated to a temperature just over its melting point, and then expelled via a nozzle to produce 3D-printed tablets [16]. Because the drug-containing filament must have a high degree of elasticity and strength to prevent fragmenting throughout the course of printing, which could affect the product's quality, the technique places significant restrictions on the choice of API and printable excipients [17,18].
- **Filling and forming method:** In this method, the empty shell was printed first, followed by filling in the API. Both the printing and filling processes can take place simultaneously or consecutively [19,20].

2.1.2 Polymers Used for FDM

FDM technology requires the use of thermoplastic polymers, with the most used materials being polylactic acid, polyamide, polycarbonate and acrylonitrile butadiene styrene [21]. Furthermore, polyvinyl alcohol, a biodegradable substance often employed as a support material, has demonstrated the potential to be enhanced into a significant filament material for personalised medicine due to its ability to dissolve into a colloidal solution [22]. Polymeric materials employed in Fused Deposition Modelling (FDM) are typically defined by parameters including glass transition temperature (Tg) and melting temperature (Tm) [23]. The polymer's Tg must be maximally distanced from its decomposition temperature [24]. The capability of the filament to pass through the sprayer at the temperature necessary for printing and to restore its structure after deposition are both influenced by viscosity, a critical rheological property [25]. In addition to external variables like ejection temperature, shear rate, nozzle diameter (usually narrow), and printing speed, intrinsic material properties like filament formulation, drug molecular weight, and solid-state also affect the shear viscosity of the filament during nozzle extrusion [26]. Moreover, the uniformity of the filament, including the elimination of lumps or air bubbles, is crucial for ensuring consistent layer-by-layer deposition without fluctuations in thickness [27].

2.2 Powder Bed Fusion

A laser beam or binder is used to fuse small powder layers in a process known as powder bed fusion, which is a form of additive manufacturing. The powders are spread out and packed tightly on a platform, and then fused or attached in a predefined pattern using a laser beam or binder. The procedure is performed layer by layer until the finished 3D component is constructed. After the surplus powder has been eliminated, the component may undergo additional processing or detailing if needed [28]. The predominant powder bed fusion technology utilised in pharmaceutical and medical applications is selective laser sintering (SLS). SLS is a rapid prototyping technique that employs a laser beam to harden powdered layers for the production of intricate 3D components. The SLS system comprises two essential components: a beam deflection mechanism that enables the beam to scan each layer according to specified CAD models, and a powder deposition system for applying thin layers of powder before laser sintering [29,30]. SLS is preferable to extrusion and FDM techniques. First of all, because of the laser's accuracy, it has a higher resolution (up to 100 µm). Second, unlike the extrusion process, which requires a drying period of approximately 48 hours after manufacture, it does not require solvents [31].

In general, powder bed fusion operations are considered to be the less appropriate methods for administering oral medications because the method's dependency on a heat source solidifies the powdered substance, which could cause the API to break down. However, there aren't many studies on powder bed fusion that have been published. A mixture of pharmaceutical and biopolymeric powder was combined into bespoke tablets using selective laser sintering. Paracetamol was added to the polymeric matrix at different concentrations. The results showed that producing oral medications that have immediate and controlled release properties is achievable [32]. In a different study, the researchers created SLS 3D-printed medicine tablets with gyroid lattice and cylindrical bi-layer structures that had tunable

drug release characteristics. According to the study, the designed gyroid lattice structures' improved porosity and surface area result in a shorter dissolving time. As a result, additional water entered the formulation, causing the medication to be released more quickly [33]. Modifying the internal parts to create the appropriate drug release profile is an additional benefit of adopting additive manufacturing in the production of oral dosage forms. The working principle of the powder bed fusion method is shown in Figure 2.

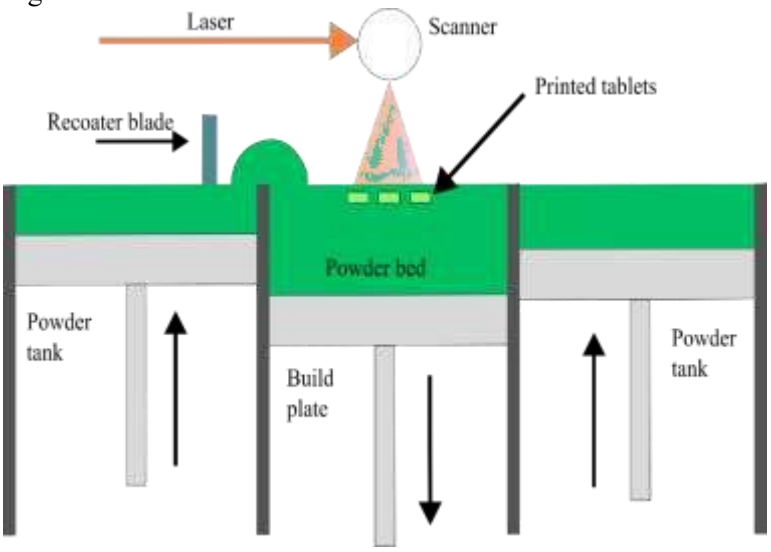


Fig 2. Schematic diagram of SLS-based PBF 3D-printing process [34]

2.3 Vat Photo Polymerisation

Vat polymerisation is the method where light is used to polymerise liquid photopolymer resin, thus creating three-dimensional objects. This process is known as photopolymerization or stereolithography (SLA). The vessel that holds the liquid photopolymer resin serves as the starting point for the vat polymerisation process. Later, a laser or projector is then used to selectively harden the resin in a tiny amount once a build platform has been lowered into the vat. After that, the build platform rises, and the process is repeated until the final product is achieved. The most popular laser for vat polymerisation 3D printing is the ultraviolet (UV) laser. UV lasers can penetrate liquid resin and cure it internally because their wavelength is shorter than that of visible light. This ensures that the cured layers are solid and adhere to one another. Both visible and infrared light can be used for vat polymerisation. The resolution of the prints produced by vat polymerisation 3D printing is affected by the light used. Prints with the highest resolution are produced by UV lasers, while those with lower resolution are produced by visible light and infrared lasers [35].

To start polymerisation, the process of creating a polymer through a chain reaction that requires at least three elements: an illumination device, a photopolymerizable monomer or oligomer, and a photoinitiator (PI)—a photon is frequently released during the printing process [36]. The photoinitiator undergoes a reaction when exposed to light during the polymerisation process, producing initiating species (cations, free radicals, anions etc.) that can interact with and incorporate more monomers or oligomers to produce cross-linking. Thus, the light-curing process can be divided into two categories: photo-crosslinking and photo-induced polymerisation [37]. While the latter indicates a process involving the creation of linkages within two macromolecular chains, the former indicates the sequential addition of monomers [38].

SLA is a non-thermal process that, in comparison with FDM technology, makes it easier to print tablets that contain thermosensitive drugs, hence preventing drug deterioration. Using the SLA technique, tablets containing paracetamol and four ASA were produced [39]. Additionally, SLA was used to create suppository moulds based on the specifications of each person's customised medications [40]. Diverse forms of transdermal and topical delivery systems, such as films and microneedles, have been developed utilising this technique. Choudhury *et al.* (2021) created a polymeric film for berberine (BBR) distribution utilising SLA 3D printing. The resin solution was formulated with PEGDMA as the photopolymer, PEG 400 to

promote hydrophilicity and penetration, and TPO as the photo initiator [41]. SLA was used to create the manufactured microneedles, and then inkjet printing was used to apply cisplatin to the top of the microneedles. The findings indicated that the fabricated microneedles exhibited superior piercing capability with an 80% penetration depth [42]. Figure 3 represents the schematic diagram of the printing principle of SLA technology.

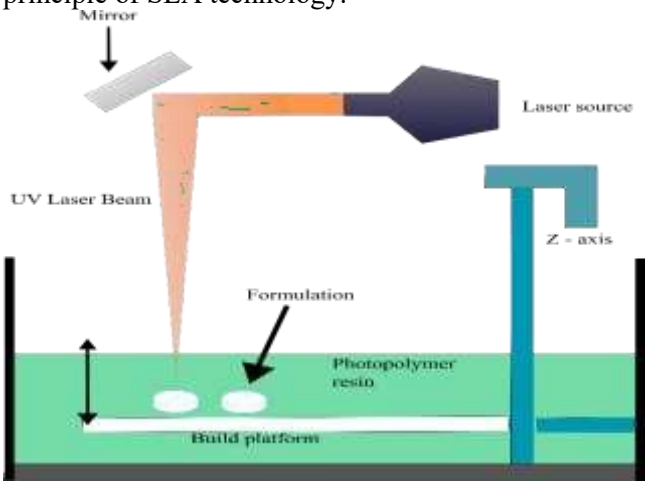


Fig 3. Schematic diagram of the printing principle of SLA technology [41]

2.4 Direct Energy Deposition

Direct energy deposition (DED) involves melting a material by focusing a laser or electron beam onto a focal area. The melted material is then deposited onto a heated substrate using a nozzle. At a focal point, a laser beam interacts with powdered or wired feedstock to create droplets of molten material on a substrate layer by layer along a predefined path. After that, the molten material is fused and bonded onto the substrate. The Directed Energy Deposition (DED) architecture comprises three separate processes: Wire and Arc Additive Manufacturing (WAAM), Laser Deposition Welding (LDW), and Laser Energy Net Shaping (LENS) [43]. This strategy primarily utilises metals, alloys, and their composites, including aluminium, nickel, stainless steel and titanium alloys. The approach stands out due to its high volumetric deposition rate, which for the WAAM process can reach up to 10 kg/h. Its large build capacity, which allows it to reach up to 6 meters in length, sets it apart. However, this approach's primary shortcomings are its lack of accuracy, low surface smoothness, and the need for reinforcement systems for drooping elements [44]. Consequently, the method has been applied to aerospace and gas turbine engine cladding, but it has not previously been studied for medication delivery systems. Nonetheless, the technique was applied to enhance the surface modification of biomedical implants [45].

Binder jetting 3DP (BJ-3DP) is the predominant 3D printing method employed in pharmaceutical manufacturing [46]. It is an additive manufacturing technique based on powder. Tiny ink droplets of the binder are injected into the powder using the printing nozzle, and they adhere to the powder to create a 3D printing structure [47]. The following parts make up the binder jet 3D printing system: printing nozzle, ink cartridge containing printing liquid, powder distribution roller, printing platform, powder collection device, and model design software. The following is the process for printing formulation: Computer-aided design (CAD) software is used to create 3D object designs, which are then converted to (.stl) or another printer-compatible format. The (.stl) file is sliced before printing, which turns the object into 2D layers and generates G-code printing instructions [47].

Additionally, the powder is evenly spread on the printer cabinet using an automated powder-distributing roller. The print head dispenses the binder or ink-laden medicament onto the powder bed at a predefined pace and in a targeted direction. After that, the console lowers, the printing nozzle shoots droplets, the powder-distributing roller moves to reorganise the powder, and the powder distribution platform rises [48]. The concept of "layered manufacturing and layer-by-layer superposition" is used to create the final preparations. Backing material for printed goods can be made from the unsprayed powder left over after printing. This powder can be taken out for further usage after printing is finished [49].

The active pharmaceutical ingredient and additional excipients are present in the powder bed, however printing inks are only present in the binder. The API can be added to the powder bed as a suspension of nanoparticles or as a solution [50]. Although there are few pertinent studies, the APIs that are amenable to BJ-3DP technology include both insoluble and highly water-soluble APIs, whose solubility can be improved with pretreatment [51].

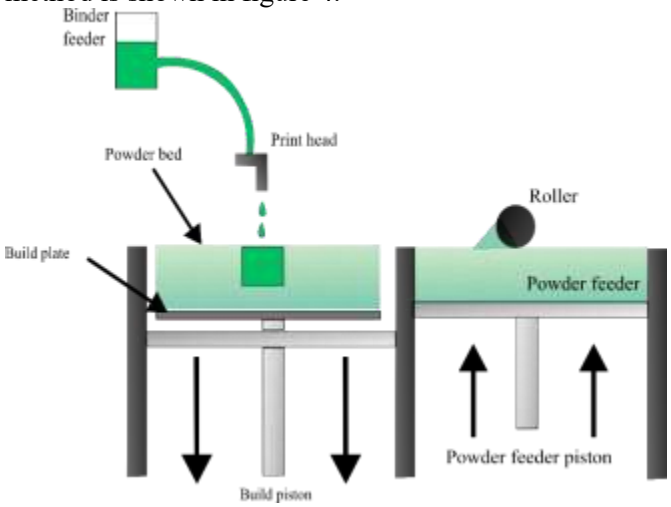
2.6 Material Jetting

Material Jetting (MJ) uses a print head to release material droplets that solidify through the elimination of solvent via evaporation or exposure to UV light, creating an item layer by layer. In 1999, Objet Ltd. created the technique, which fused inkjet and photopolymer technologies. In 2012, the two companies amalgamated. The technology offers high-resolution structures, a wide range of colours, and superior surface finish products [52].

IJP is a material jetting technique that uses a nozzle to discharge tiny liquid ink droplets. Based on how ink droplets are generated, they can be divided into two categories: Drop-on-Demand (DoD) Inkjet Printing (IJP) and Continuous Inkjet Printing (CIJP) [53].

CIJP creates a steady stream of ink by using a high-pressure pump to force the ink through a nozzle. Afterwards, surface tension forces cause the stream to break up into droplets. Droplet production can be controlled by altering the frequency [54]. Droplets pass through deflector plates that create an electrostatic field after being selectively charged by charging electrodes to produce a printed pattern. Uncharged droplets are recycled back into the system, while charged droplets are ejected onto the substrate.

On the other hand, DoD methods react to an electrical trigger to release small amounts of liquid. DoD print heads fall into one of two categories: thermal or piezoelectric. An electrical signal is sent to a thermal component in the print head during thermal inkjet printing, raising the liquid's temperature to between 200 and 300 °C [55]. A droplet is created when the temperature rise causes bubbles to enlarge and release the fluid through the nozzle. A piezoelectric element in the print head of piezoelectric inkjet printing (PIJP) deforms in reaction to an electric current, causing droplets to be ejected. Because of its exceptional accuracy and automation capabilities, which enable precise control of ink deposition, DoD is widely used in pharmaceutical applications. Both thermal and PIJP have special benefits and drawbacks. Although they are less costly to manufacture, thermal printers may not work well with thermolabile materials. On the other hand, PIJP offers a more adaptable and scalable solution for pharmaceutical applications and is compatible with a wide range of pharmaceutical inks [55]. The schematic diagram of the Binder Jetting method is shown in figure 4.



3. SPRITAM® - FDA APPROVED FIRST 3D PRINTED PILL

Aprecia Pharmaceuticals developed the first 3D-printed drug, Spritam, which was approved by the U.S. Food and Drug Administration (FDA) on July 31, 2015, to treat seizures in people with epilepsy. Spritam is designed especially to help patients with dysphagia, including children, the elderly, and those dealing with similar issues. It contains levetiracetam, a frequently prescribed anticonvulsant [56].

Spritam features a distinctive porous formulation that enables the tablet to disintegrate swiftly, averaging 11 seconds (with a range of 2 to 27 seconds) when consumed with a sip of fluids, facilitating ingestion. This capability is enabled by the company's 3D printing technology, which consolidates doses of up to 1,000 mg of levetiracetam into a single tablet [7].

4. PERSONALIZED 3D-PRINTED COMBINATION DRUG TABLETS S

The term "polypill" denotes a single tablet containing a mixture of multiple medications. This notion is particularly advantageous for the elderly population, as individuals in this age group are susceptible to several illnesses and hence require different therapies [57].

The technique was created by Khalid *et al.*, who blended five different active pharmaceutical ingredients with different release patterns into an identical 3D dosage form [58]. The extended-release compartment included three prescription drugs: ramipril, atenolol, and pravastatin. A permeable barrier made of hydrophobic cellulose acetate physically separated the substances. Over the extended-release container was an immediate-release section that contained hydrochlorothiazide and aspirin [59].

5. DRUG DELIVERY BY 3D PRINTING TECHNOLOGY

Several drug delivery arrangements have been established using 3D printing technology by producing unique, creative, and specialised geometries that are tailored for unique drug release properties to provide customised drug delivery profiles. Utilising 3D printing technology is a creative way to deliver active pharmacological components in a variety of doses [60]. Both hydrophilic and lipophilic medications have been administered using 3D printing technology. The goal of BCS class IV and BCS class II medications is to improve both dissolution and bioavailability properties through the use of 3D printing technology [61]. This section will examine several drug delivery methods utilising 3D printing processes.

5.1. Oral drug delivery

The creation of solid oral dose forms using 3D printing technology has shown potential. This technology makes it easier to create novel formulations that circumvent many of the limitations of conventional pharmaceutical manufacturing methods. To satisfy the need for tailored medications, 3D printing may offer a range of sizes and complex shapes with unique release characteristics. When making oral dosage forms, extrusion-based 3D printing techniques are most commonly employed [60]. The drug release characteristics of active pharmaceutical ingredients (APIs) have been tailored to patient needs through 3D printing techniques for oral drug delivery. This led to the development of gastro-retentive drug delivery systems, immediate-release including delayed-release systems, and polypills, which comprise a complete dosing regimen to treat individuals suffering from diabetes or hypertension in a single pill. Modern 3D printing techniques for oral drug distribution are covered in this section [62].

Oral dosage forms provide the most traditional method for administering active pharmaceutical ingredients (API) and exhibit superior patient compliance relative to alternative routes of administration. Significant progress in traditional oral dose manufacture and an extensive array of excipients provide a flexible foundation for medication delivery. Nevertheless, the constraints of conventional production in terms of geometry and forms have restricted the adaptability of this technique. The idea of 3D printing, which involves layer-by-layer construction, enables the creation of geometric proportions unattainable by traditional technologies [63].

By employing three distinct manufacturing techniques to produce an oral tablet: injection moulding (IM), FDM, and direct compression (DC). Fuenmayor *et al.* contrasted 3D printing techniques with conventional production methods [64]. The same ingredients and proportions were used to make the pills. The tablets made using the three different procedures have statistically different physical and drug-release characteristics. In contrast to the direct compression (DC) tablet, which exhibited an immediate drug release profile, the injection-moulded (IM) tablet had a sustained release frequency over 48 hours. Likewise, depending on the printing conditions, the fused deposition modelling (FDM) tablet demonstrated both rapid and sustained release properties [64].

Matijasic *et al.* created a two-compartment capsular device, called the modular Super-H capsules, designed to deliver two different medications simultaneously with a delayed-release profile. Ascorbic acid and dronedarone hydrochloride served as API, while PVA was utilised for the creation of the filament through the FDM process. The device was fabricated using varying layer thicknesses. *In vitro* experiments showed

that the membrane thickness influences the lag time of the Super-H capsule in acidic conditions. After two hours in an acidic environment, the capsule released the medication in an alkaline setting, such as the small intestine. This study highlights the potential of 3D printing in encapsulating multiple drugs with delayed-release properties [65].

5.2. Transdermal drug delivery

The technique of 3D printing is currently highlighted as a potential option for transdermal medicine distribution, as it produces detailed and customisable topologies for pharmaceuticals and medical devices. Several transdermal formulation techniques, such as microneedles, patches, and implants, have successfully demonstrated the use of 3D printing technology for the local and systemic delivery of active medicinal components that are customised to the patient's needs. Using 3D printing technology, Kempin *et al.* developed an implant whose geometry is customised for a particular application site and can be delivered there. This work showed how to create an implant with the fluorescent dye quinine as a prototype pharmacological agent. This implant was made by combining hot-melt extrusion of several polymers with extrusion-based FDM technology to produce a drug-loaded filament. The implant model that was printed was a hollow, cylindrical shape. According to the study's findings, PCL implants exhibited a 76% drug release within 51 days, but ethyl cellulose (EC) and Eudragit RS only produced a 5% release throughout 78 and 100 days, respectively [66].

5.3. Pulmonary Drug Delivery

Morrison *et al.* demonstrate how 3D printing can be effectively utilised for pulmonary treatment by developing bioresorbable airway splints to treat paediatric patients with tracheobronchomalacia. A strategy for developing customised devices for the management of fatal illnesses was made possible by the discovery that 3D-printed airway supports were a practical technique to keep patients' airways from collapsing [67].

5.4. Intrauterine drug delivery

Hollander *et al.* developed a 3D printing technique based on FDM to create a prototype intrauterine device in the shape of a T. When comparing the extruded filament to 3D printed devices made of poly-caprolactone, the model medication indomethacin had a faster drug release profile from the former. It was discovered that the medication was amorphous within the devices, as opposed to its crystalline structure in the filament, indicating that the drug release happened via polymer diffusion and that 3D-printed devices achieved an effective drug release profile [68].

The customised T-shaped 3D-printed prototype devices demonstrated an improved drug release profile over 30 days, laying the groundwork for the creation of implanted devices loaded with drugs using ethylene vinyl acetate (EVA), a polymer that can be manufactured using 3D extrusion [69]. The summary of 3D formulations in pharmaceutical drug delivery is elaborated in Table 1.

Table 1: Summary of the different 3D formulations proposed or researched in Pharmaceutical Drug Delivery

Product / Project Name	Drug / Compound	Developer / Institution	3D Printing Technique	Application	Status	References
Spritam®	Levetiracetam	Aprecia Pharmaceuticals	ZipDose® (Powder Bed Printing)	Epilepsy treatment	FDA-Approved (2015)	[7]
Triastek T19	GLP-1 receptor agonist	Triastek	Melt Extrusion Deposition	Type 2 Diabetes	Clinical Trials (China NMPA)	[70]
Polypill (Various Drugs)	Multiple APIs (e.g., aspirin, pravastatin, ramipril)	University College London	FDM, Inkjet Printing	Cardiovascular disease – multi-drug tablet	Research/Preclinical	[58]

Theophylline Chronopill	Theophylline	FabRx / UCL	Semi-solid extrusion	Chronotherapy for asthma	Research	[71]
Antibiotic-loaded Meshes	Ciprofloxacin, Gentamicin	University of Nottingham	Stereolithography (SLA)	Local infection treatment	Research/Preclinical	[72]
Orodispersible Films	Loratadine, Rizatriptan	ETH Zurich, UC San Diego	Inkjet Printing	Fast-acting oral drug delivery	Research	[73]
Drug-Eluting Stents	Paclitaxel, Sirolimus	Various research institutions	SLA / FDM	Cardiovascular stents with drug release	Research/Preclinical	[74]
Buccal Patches	Nicotine, Propranolol	University of Eastern Finland	Inkjet Printing	Transmucosal drug delivery	Research	[75]
Personalised Multi-Release Pill	Multiple APIs	National University of Singapore	FDM with polymer layering	Personalised medicine with controlled release	Prototype	[76]
3D-Printed Microfish	Drug-loaded nanoparticles	UC San Diego	Microscale 3D printing	Targeted drug delivery and detoxification	Proof-of-concept	[77]
E-jet Printed Breast Cancer Implant	5-FU and NVP-BEZ235	Chinese research team	Electrohydrodynamic jet (E-jet) printing	Localised chemotherapy for breast cancer	Preclinical	[78]
Dynamic Supramolecular Polyurethane Implant	Paracetamol	University of Reading & University of Nottingham	Hot-melt extrusion	Long-term implantable drug release	Research	[79]
3D-Printed Microneedles	Various (e.g., mesoporous iron oxide)	Multiple institutions	Digital Light Processing (DLP)	Transdermal drug delivery for conditions like alopecia	Experimental	[80]
Honeycomb-Structured Tablets	Fenofibrate	University of Nottingham	Inkjet printing with beeswax	Controlled drug release via tablet geometry	Research	[81]
3D-Printed Vaginal Rings	Paclitaxel and Cidofovir	Various research groups	Fused Deposition Modelling (FDM)	Localised treatment for cervical cancer	Experimental	[82]

6. DEVELOPMENT OF 3D PRINTING IN CUSTOMISED BIOPHARMACEUTICALS

Tiny molecules have been the focus of much 3D printing research. The biopharmaceutical industry is expanding at an exponential rate, and the use of 3D printing, particularly in PAM, is creating novel

opportunities to integrate this technology and produce reliable organ-on-chip systems. In 3D printing for tissue engineering, peptides and proteins are primarily used, especially for bone and cartilage regeneration. Incorporating biopharmaceuticals, such as peptides produced from BMP-2 and bioactive peptides derived from mussels, into the bioprinting of cell-based scaffolds has been shown to improve the production of cartilage and bone [83]. BMP-2-derived peptides coupled to dopamine have been used to wrap PLA scaffolds, resulting in scaffolds with enhanced osteogenesis. Osteopontin, osteocalcin, and alkaline phosphatase are among the genes linked to osteogenesis whose expression was boosted by the scaffold [84]. Since water is the only medium used in this case, hydrogels are created without the need for heating during the printing or post-processing stages. To create a perfect arrangement of lipophilic and hydrophilic units that promote spontaneous physical gelation, peptide hydrogel design places a strong emphasis on adjusting the amphiphilic equilibrium within the backbone sequence. Native protein folding initiates the interactions, which mainly involve hydrogen bonding, electrostatic interactions, and π-stacking. Diverse secondary structures, including α-helices, hairpin motifs, and β-sheets, are produced as a result of these interactions [85,86].

7. PERSONALISED NANOMEDICINES VIA 3D PRINTING

A nanomaterial is defined by The European Commission as "a natural, incidental, or manufactured material containing particles, either in an unbound state or as an aggregate, where one or more external dimensions fall within the size range of 1 nm to 100 nm for 50% or more of the particles" [87]. Three different areas of medicine can benefit from the use of nanomaterials in nanomedicine: regenerative medicine, targeted drug delivery (nano therapy), and diagnosis (nano diagnosis) [88]. Their small size confers 18 out of 30 distinguishing characteristics in medicine, owing to the increased specific surface area relative to volume, resulting in significant particle surface energy and, as a result, reactivity.

Nanomedicines have been produced using 3D printing technology. However, because particle aggregation acts as a defects and jeopardises the quality of the 3D-printed structure, nanoparticle concentration is an important factor. Increased drug-loading nanoparticles inside a polymer matrix are generally difficult to accomplish due to Van der Waals-induced aggregates and nanoparticle interactions. A pretreatment step, such as ball milling, surfactant addition, ultrasonic application, and other techniques to reduce attractions, including Van der Waals-induced aggregations, may be required to improve the homogeneity of particles within liquid suspension [89].

Polymeric PCL nanocapsules were used to encapsulate re-dispersible 3D-printed solid dosage forms that contained polyphenols (curcumin and resveratrol). Using PAM, the latter was integrated into a hydrogel that was 3D printed from carboxymethyl cellulose. One recurring issue is that not all of the active components were removed from the nanocapsules, despite the polyphenols being partially released over eight hours [90]. Liposome-encapsulated curcumin was added to tissue scaffolds that were 3D printed. Although curcumin has strong anti-cancer, antioxidant, and osteogenic properties, its lipophilicity limits its bioavailability [91].

8. MICRO-SCALE 3D PRINTING IN PHARMACEUTICS

8.1. Microneedles

When oral consumption of medication is inappropriate, hypodermic needles are commonly used; nevertheless, this method is intrusive. Through the creation of microneedle arrays, additive manufacturing provides novel techniques for less invasive distribution.

Since 1979, when the first transdermal drug delivery system was introduced, these systems have evolved to include arrays of microneedles [92]. Compared to hypodermic needles, microneedle arrays improve patient compliance, lessen tissue damage and suffering, eliminate the requirement for skilled medical personnel to administer them, and stop microbial infiltration [93]. Additionally, drugs that are applied transdermally may increase immunogenic response and improve absorption [94].

Targeting highly accurate, fully dissolvable microneedle arrays is an effective strategy for achieving sustained long-term release. Polymer moulding, which is not an additive manufacturing process, is typically used to create these arrays [95]. The additive manufacturing of such needles is hampered by the limited printing capacity of stereolithography and the resolution limitations of alternative methods. Novel

materials are being developed for drug delivery applications that require high-precision targeting, such as in cancer therapeutics.

Luzuriaga *et al.* advanced the technology of material extrusion by demonstrating a new technique for producing microneedles [96]. However, as anticipated, sharp peaks could not form due to the printer's limited resolution. Since the minimum achievable tip diameter was more than twice the ideal size, postprocessing in a simple solution was necessary to produce functional microneedles. This explains why stereolithographic methods are so common in these applications. Notably, compared to the CAD model, the final printed features in stereolithographic printing with typical resolution show distortion [97]. Despite challenges, microneedle array additive printing can speed up prototyping and enable the production of complex structures [98].

8.2. Micro implants

Furthermore, high-precision release and targeting can be achieved with non-mobile drug delivery devices. These drug delivery techniques, sometimes known as micro-implants, can restore tissue function, encourage sustained release patterns, and fix tissue abnormalities. Conventional medicine has long depended on implants, and the application of additive manufacturing in implant production is also well-recognized [99]. Both inert and drug-eluting implants have important design considerations. Both can be solved with additive manufacturing. Because it controls interactions with resident cells, the microstructure is an essential feature of implanted materials [100]. The type of tissue determines the ideal pore size. The perforations in bone implants range in size from 200 to 400 microns Pore size is a prime example of important micro-geometry that affects differentiation, cell perfusion, and nutrient exchange. One of the unique properties of additive manufacturing is its ability to simultaneously create macrostructures and micro-geometries. Various additive manufacturing techniques, including binder jetting and selective laser sintering, have been employed in the fabrication of implant materials and tissue scaffolds [101,102] and material extrusion (including fused deposition modelling and semi-solid extrusion) [103,104]. Since the microstructure of many scaffolds is more than 200 microns, most printers can create biomimetic holes of that size. Materials for bone implants should be biodegradable, bacterially resistant, osteoconducting, osteoinducting, and angiogenic [105]. The development of these traits can be aided by the assimilation and controlled release of chemicals into the scaffold. Studies show that the combination of growth factors, specifically vascular endothelial growth factor (VEGF) and recombinant human bone morphogenetic proteins (rhBMP), improves bone response and proliferation. Additionally, antibiotics can be effectively absorbed. Controlled release can provide therapeutic alternatives in addition to improving the scaffold's properties. As seen in oral dosing, the spatial arrangement of the drug layers in these systems has a crucial role in the release profile. Because of their design, Martinez-Vazquez *et al.* were able to establish first-order kinetics [106]. Scaffolds often exhibit biphasic drug release characteristics, with a quick initial release followed by a persistent release [101]. Up to 80 days may pass during the extended-release. Consequently, integrating medications with additive manufacturing in implants offers distinct advantages [107].

9. QUALITY CONTROL ANALYSIS OF 3D-PRINTED MEDICINES

Over the past decades, substantial advancements have occurred in 3D printing (3DP) owing to its capacity for medicine personalisation. Ensuring the safety and efficacy of pharmaceutical products requires quality control, or QC. Recent years have seen the development of the current regulatory framework for pharmaceutical production, which focusses on large-scale batch production. Conversely, 3D printing for customised dosage forms functions on a demand-driven, small-scale model, resulting in negligible to no surplus completed items for quality control assessments. Thus, conventional testing procedures for end products, which are intrinsically damaging and labour-intensive, are inadequate for the personalised manufacturing capabilities provided by 3D printing [108].

10. POLICIES AND REGULATIONS IN THE FIELD OF 3D PRINTING

3D printing is a new technology with several benefits for the healthcare industry. Thanks to the initiatives of leading companies and the proactive assistance of government organisations like the Drug Review Centre, the 3D-printed pharmaceutical industry is getting closer to contemporary tailored medicine With the expectation that 3D printing will hasten the development of customised and intelligent drug

administration, the China CDE released an assessment in 2019, admitting its awareness and concerns about the 3D-printed medication industry [109].

Triastek's MED 3D printing technology was approved and included in the FDA's Emerging Technology Program in 2020, indicating that the technology has regulatory recognition. T19, the second 3D printing device in the world, received FDA IND certification in January 2021. Triastek helped develop pharmaceutical technology that year by attending the Q13: Continuous Manufacturing conference hosted by CDE in China. According to a 2021 report on drug manufacturing advancements published by the National Academies of Sciences, Engineering, and Medicine at the request of the Centre for Drug Evaluation and Research, 3D-printing technology is a new manufacturing technique that is set to replace conventional drug production methods.

The creation of regulatory guidelines for 3D-printed goods is critically needed, as no regulatory body has yet to guide these formulas. As technology develops and more study is conducted, 3D printing technology is expected to be able to create a thorough framework of scientific guidelines for the pharmaceutical industry that covers theory, practice, manufacture, and regulation [10].

11. CONCLUSION

3D printing is quickly becoming popular in pharmaceutical formulation as a cutting-edge technique that meets the demands of targeted drug manufacturing, patient-specific therapies, and personalised medications. More efficient, secure, and customised treatment options are becoming possible thanks to ongoing research and technology developments. Despite its infancy, 3D printing has the potential to revolutionise pharmaceutical manufacturing because it provides more flexibility than conventional techniques. This method enables the creation of intricate drug delivery systems that can administer multiple medications with varying release profiles—something that traditional batch processes often struggle to achieve. Because of their large-scale production limitations, traditional drug manufacturing methods hinder the delivery of personalised therapies. Conversely, 3D printing can create dosage forms with novel structures that are difficult to produce using conventional methods. To enhance the viability and accessibility of personalised medicine, researchers have spent the last ten years refining 3D printing techniques and tools. Polypills, which contain several drugs with controlled release properties in one dose form, are one example of this. As a result, 3D printing is being used more and more by pharmaceutical businesses to improve precise and effective drug delivery.

In the future, it is anticipated that 3D printing will transform into integrated digital pharmaceutical platforms, through which drug production will be real-time and on-demand in hospitals, clinics, and also in homes. With the use of AI and machine learning, it is meant that the algorithms will help create personalised doses of the medication based primarily on genetic data. Additionally, the integration of smart materials and biosensors shall facilitate the development of localized drug delivery systems that are able to change in accordance with the patient's body. The process of developing the regulations has also started in regards to which the 3-D technology will be the source of drug production, and such medications will be used as a part of primary healthcare. The technological option of personalized treatment can greatly benefit certain segments of the population who have special needs, e.g. kids, old people, or those who suffer from rare diseases. Poly-pills that come with immediate and sustained release compartments indicate a significant change in the drug design concept. Undeniably, despite several hiccups, it is anticipated and received wisdom that 3D printing is soon to be the focal point of precision medicine, catering to patient's needs and thus reducing therapy time and costs. The big question, however, is whether this technology can be successful in addressing individual medical care requirements at a mass and affordable level.

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Conflict of Interest

The authors declare no conflict of interest.

Ethical Statements

Not applicable

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