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Review Article

A Review on Recent Trends of 3D Printing Technology and Its Approaches in Current Drug Delivery

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ABSTRACT

Three-dimensional printing (3DP) is emerging as a groundbreaking technology in the pharmaceutical industry, promising transformative advancements in drug formulation and delivery. This innovative method enables the creation of personalized medications with precise dosages and tailored release profiles, addressing the limitations of traditional mass production. Despite its promising potential, the widespread adoption of 3DP in medicine faces several challenges. The primary issue is the lack of comprehensive regulatory guidelines, which creates uncertainty regarding standardization and quality control. Ensuring the quality and stability of 3D-printed drugs is another critical concern, with non-destructive evaluation methods like Near-Infrared and Raman spectroscopy being explored for real-time quality assessment. Additionally, current 3D printers often do not fully comply with Good Manufacturing Practice standards, which are essential for ensuring product consistency and safety. This study provides a comprehensive examination of recent trends and innovative approaches in 3DP technology applied to drug delivery systems, highlighting both the progress made and the challenges that need to be addressed. By examining current methodologies, materials, and applications, the research aims to elucidate the evolving landscape of 3D-printed pharmaceuticals. The study focuses on evaluating the feasibility, efficacy, and scalability of diverse 3DP approaches in developing personalized and precision drug formulations. These insights are intended to enhance the field of pharmaceutical sciences and support patient-centric healthcare by offering more customized and effective medication solutions. Through a comprehensive analysis of innovative 3DP techniques, the research seeks to contribute to the advancement of drug delivery systems, potentially revolutionizing the way medications are produced and administered.

Keywords: 3D printing technology, Inkjet printing, Extrusion-based printing, Powder-based binding method, Laser based 3D printing

1. INTRODUCTION

Three-dimensional printing (3DP) is regarded as a groundbreaking advancement in the pharmaceutical and biomedical industries (Li et al., 2023). This versatile technology facilitates

the precise manufacture of various devices, including novel dosage forms and engineered tissues, significantly impacting drug delivery, organ engineering, and disease modelling. As one of the fastest-growing fields in technology and science, 3DP continues to expand its applications (Li et al., 2023; Rani et al., 2023).

The International Standard Organisation defines 3DP as the fabrication of objects through material deposition using a print head, nozzle, or similar technology. Unlike traditional subtractive and formative manufacturing methods, 3DP is an additive manufacturing (AM) technique, building objects layer by layer from 3D models (Izdebska-Podsiadły, 2022). This approach enables the rapid and cost-effective design of personalized medications. Also known as layered manufacturing or rapid prototyping, 3DP originated in the early 1980s with Charles Hull's invention and gained prominence around 2012. Notably, the technology's pharmaceutical application began in the early 1990s at MIT, leading to innovations like the FDA-approved 3D-printed tablet "Spritam" in 2015 (Izdebska-Podsiadły, 2022; Jakus, 2019).

Since 2012, the application of 3DP in science and engineering has grown, particularly in creating solid dosage forms for individualized therapy, transdermal drug delivery, and biomedical devices, including implants and surgical models. The convergence of AM and bioprinting has been notable, with advancements in materials science facilitating the customization of medical products (Parhi, 2021; Jamróz et al., 2018). Various 3DP methods, such as extrusion-based printing, powder-based binding, and inkjet printing, have become vital to the pharmaceutical industry. This technology allows for customized drug formulations tailored to patients' specific needs. Such personalization extends to creating complex drug release profiles and unique dosage forms, offering an alternative to conventional manufacturing methods (Izdebska-Podsiadły, 2022).

The adaptability of 3DP in constructing personalized active pharmaceutical ingredient (API) combinations is remarkable. It is used in the pharmaceutical industry to develop digitally controlled and individualized products, transforming concepts into prototypes using 3D computer-aided design (CAD) or Magnetic Resonance Imaging (MRI). Research has demonstrated the application of 3DP in various areas, including buccal patches, implants, oral dosage forms, and transdermal delivery systems. Innovative companies like FabRx Ltd. are pioneering 3D-printed medications, further showcasing the technology's potential (Kalyan et al., 2023; Tatipamula and Annam, 2022; Muhindo et al., 2023).

The field of 3D bioprinting, which aims to create living tissue models, represents a new frontier in 3DP technologies. As research continues, 3DP's role in the pharmaceutical industry is poised to grow, offering more efficient, customized solutions for patient care (Muhindo et al., 2023). This review explores recent advancements in 3DP technology as applied to drug delivery systems. It provides a comprehensive analysis of current methodologies, materials, and applications, highlighting the innovative approaches shaping this field. The primary focus is on evaluating the feasibility, efficacy, and scalability of various 3DP techniques for developing personalized and precision drug formulations. By examining these aspects, the review aims to contribute to the advancement of pharmaceutical sciences and enhance patient-centric healthcare.

2. SEARCH STRATEGY

Publications on “3D bioprinting” from 1990 to August 2023, were retrieved and downloaded from the database of Science Citation Index Expanded of Web of Science. Citespace software was used for data analysis and visualization, including the Countries, academic institutions, journals, authors, subject categories, keywords (most frequently used), references and citations of these target literatures.

3. DIFFERENCE BETWEEN 3D PRINTING & 3D BIOPRINTING

3.1. 3D Printing

A research design for 3DP technology typically includes both qualitative and quantitative approaches. It starts with a literature review to identify gaps and establish theoretical frameworks. Experimental studies are central, involving material selection, prototyping, and performance testing under controlled conditions. Methodologies include additive manufacturing processes (FDM, SLA, and SLS) parameter optimization, and mechanical property analysis (Hieu et al., 2021; Izdebska-Podsiadły, 2022). 3DP technology addresses various medical challenges, such as creating artificial organs and skin. By directly constructing layers of material, this technology forms intricate 3D structures. It is utilized for printing a wide range of materials, including plastics, metals, polymer resins, and rubber. In the medical field, 3DP is employed to manufacture customized implants, surgical instruments, and other medical devices. It also allows for the creation of hard materials to produce precise 3D objects (Figure 1a). For example, 3DP can rapidly generate models of cancerous tumors using data from Computed Tomography (CT) and MRI scans. Beyond medicine, the applications of this technology extend to engineering, dentistry, architecture, aerospace, food, agriculture, education, product design, and research and development.

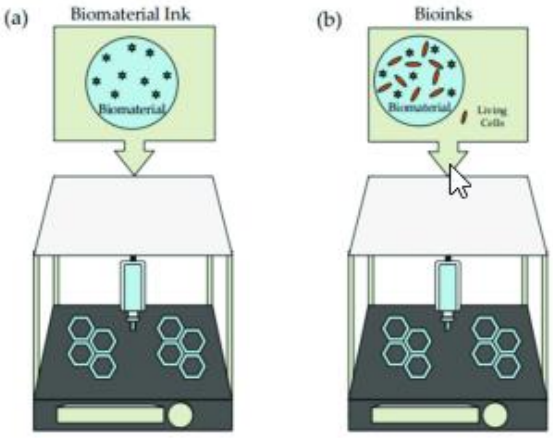

Figure 1. (a) 3D printing & **(b)** 3D bioprinting

3.2. 3D Bioprinting

3D bioprinting is an emerging technology for fabricating skin and is increasingly used for personalized wound treatment. This innovative approach has been successfully applied in regenerative medicine to address various medical issues (Zang et al., 2023; Chouhan et al., 2019). A 3D bioprinter employs bioink containing living cells to print biomaterials, and it can also incorporate scaffolds to form the required structure of target tissues. This technology is capable of printing liquid and gel-based materials, enabling non-contact droplet printing (Figure 1b). It has been utilized to develop tissue-like structures, including cardiac and vascular tissues, through the use of growth factors (Gungor-Ozkerim et al., 2018; Kalhori et al., 2022). 3D bioprinters can print biological materials such as bone particles, cells, organic molecules, and other extracellular matrices. Currently, tissues and organs created using this technology have shown improved success rates in surgeries. For instance, scientists have used 3D bioprinting to create skin layers with integrated blood vessels, reducing the likelihood of graft rejection (Rahimnejad et al., 2021; Diakuara et al., 2022; Thuan et al., 2023). Furthermore, the

application of 3DP technology offers a potential alternative for constructing effective and customized combinations of APIs tailored to individual patients. It is crucial to recognize that the field of 3DP in pharmaceuticals is rapidly evolving, with ongoing research focused on overcoming current challenges. As the technology progresses and regulatory frameworks become more accommodating, the benefits of 3DP in pharmaceutical applications are expected to outweigh its current limitations (Serrano et al., 2023; Polimati et al., 2022).

3.3. Advantages of 3D printing technology in pharmaceutical applications

3DP technology offers numerous advantages in pharmaceutical manufacturing. It enables the production of personalized and patient-specific dosage forms, tailoring drug delivery to individual needs. The technology facilitates the creation of intricate and complex drug structures that are difficult or impossible to achieve with traditional methods (Al-Dulimi et al., 2021; Nguyen et al., 2021; Nguyen et al., 2022). With precise control over drug composition, 3DP ensures uniform distribution of APIs within each dosage unit. It supports rapid prototyping, allowing researchers to quickly iterate formulations and reduce time-to-market for new medications (Al-Dulimi et al., 2021; Beg et al., 2020; Bozkurt and Karayel, 2021; Nguyen et al., 2021a). Additionally, 3DP enables polypharmacy by combining multiple drugs into a single dosage form, enhancing patient compliance. Taste-masking capabilities make medications more palatable, particularly for pediatric and geriatric patients. The resource-efficient process reduces material wastage compared to traditional methods and supports on-demand, small-scale production, offering flexibility and reducing the need for large-scale manufacturing facilities (Beg et al., 2020; Bozkurt and Karayel, 2021; Nguyen et al., 2020; Nguyen et al., 2020a).

3.4. Disadvantages of 3D printing technology in pharmaceutical applications

Despite its transformative potential, 3DP in pharmaceuticals faces several challenges. A limited range of pharmaceutical-grade materials restricts its versatility compared to traditional methods (Beg et al., 2020; Hieu et al., 2020; Bozkurt and Karayel, 2021). Regulatory frameworks struggle to keep pace with evolving 3DP technologies, posing challenges in standardizing and approving 3D-printed drugs (Thuan et al., 2022; Vyshnavi et al., 2023). The process can be time-consuming, particularly for complex or large-scale production, impacting scalability. Additional post-processing steps, such as coating or polishing, add complexity to manufacturing. Concerns about material stability under varying storage conditions remain under active research. High equipment costs limit adoption among smaller manufacturers, while quality control challenges demand robust measures to ensure dosage consistency. Additionally, the open-source nature of some 3DP technologies raises intellectual property concerns, as unauthorized sharing of drug blueprints could occur (Beg et al., 2020; Bozkurt and Karayel, 2021).

4. 3D PRINTING RECENT APPROACHES OF DRUG DELIVERY SYSTEM

3DP techniques involve the layer-by-layer deposition of material to create three-dimensional objects designed using computer software. The design process can be conducted using software like AutoCAD, 3D Slash, SketchUp, Fusion 360, and Solidworks. Once the design is completed, slicer software such as KISSlicer, Slic3r, OctoPrint, Simplify3D, and Cura converts the design file (STL format) into printer-readable G-code (Mohammed et al., 2021; Wang et al., 2021). This software sets essential printing parameters, including layer count, infill percentage, offset height, layer spacing, speed, and total print time. The generated G-code is then uploaded to the 3D printer, which utilizes various systems, such as inkjet, extrusion, and

laser-based technologies, to deposit material and form the object (Dine et al., 2021). In pharmaceutical applications, polymeric materials like Eudragit and ethyl cellulose are commonly used as binder inks to formulate targeted drug delivery and controlled release systems. Additionally, the use of ink formulations for color printing can enhance patient compliance, particularly among geriatric and pediatric patients, by making the medications more visually appealing and easier to differentiate (Mohapatra et al., 2022; Tatipamula et al., 2021; Tatipamula et al., 2022).

4.1. Extrusion-based printing

Extrusion printing technology, which began to gain traction in the 1980s and became operational in the 1990s, encompasses two primary methods: hot melt extrusion (HME) and fused deposition modeling (FDM) (Madla et al., 2018; Placone and Engler, 2018). In the HME technique, a homogeneous solid dispersion of pharmaceutical excipients, including polymeric materials and plasticizers, is prepared in a molten polymer form. A drug substance is then incorporated into this polymeric composition. The resulting formulation ink is extruded through a die under high pressure and elevated temperatures, and subsequently fused and solidified to produce a 3D object with uniform shape, high quality, and consistent drug content. This method allows for precise control over the drug's distribution within the final product (Repka et al., 2018; Prasad et al., 2019). FDM, also referred to as fused filament fabrication in some literature, differs from HME in that it typically results in products with lower mechanical properties and drug load. However, FDM is well-suited for home-fabricated manufactured goods, making it advantageous for personalized medication applications. One notable advantage of HME is its solvent-free nature and makes it an ecologically friendly production method (Prasad et al., 2019; Dumpa et al., 2021; Rao et al., 2015).

The late 1990s saw the introduction of thermoplastic polymers such as polylactic acid (PLA), polyvinyl alcohol (PVA), and ethyl vinyl acetate into the field, marking a significant advancement in pharmaceutical 3DP. In FDM, the drug substance is loaded into a thermoplastic polymeric filament and extruded through a heated printer head onto a surface, where it immediately hardens (Couți et al., 2024), Both extrusion methods have increased popularity for fabricating 3D products due to their flexibility in developing novel solid oral dosage forms with various geometries, complexities, and drug release profiles. Particularly, the extrusion technique is promising for producing amorphous form materials, which can enhance the bioavailability of poorly soluble drugs and improve dissolution rates (Auriemma et al., 2022; Gurunath et al., 2013).

4.2. Powder-based binding method

Rapid prototyping using powder-based methods is gaining significant interest in the pharmaceutical industry due to its alignment with existing manufacturing processes and potential for long-term efficiency (Sen et al., 2021; Tran and Wen, 2014). This technique involves constructing multilayer 3DP products by spraying a binder or drug solution along with excipients onto a powder bed using a small Y print head in a two-dimensional manner. The build platform is dropped along the Z-axis according to the elevation of each layer until the complete structure is formed. Layers are bonded through adhesion or welding in a liquid solution, and unbound powder and residual solvent are subsequently removed under appropriate conditions to ensure proper development of the 3D product. Droplets of the binder or drug solution are directed onto an electrically charged element to achieve the desired charge before being deposited onto the substrate to form the final product (Ngo et al., 2018; Warsi et al., 2018) (Figure 2).

The powder bed 3DP method is noted for its speed and compatibility with a wide range of pharmaceutical substances. It produces high-quality 3D products and offers significant cost reductions in production. This method is particularly advantageous for fabricating drug formulations, immediate-release and controlled drug products. The technique's flexibility and efficiency have led to its widespread adoption in pharmaceutical applications (Haritha et al., 2019; Jandyal et al., 2022). Key factors influencing the quality of the final product include the selection of an appropriate binder and its concentration, as well as the particle size of the powder used. Proper optimization of these variables is crucial for ensuring the integrity and performance of 3D-printed drug products (Ibrahim and Maslehuddin, 2021).

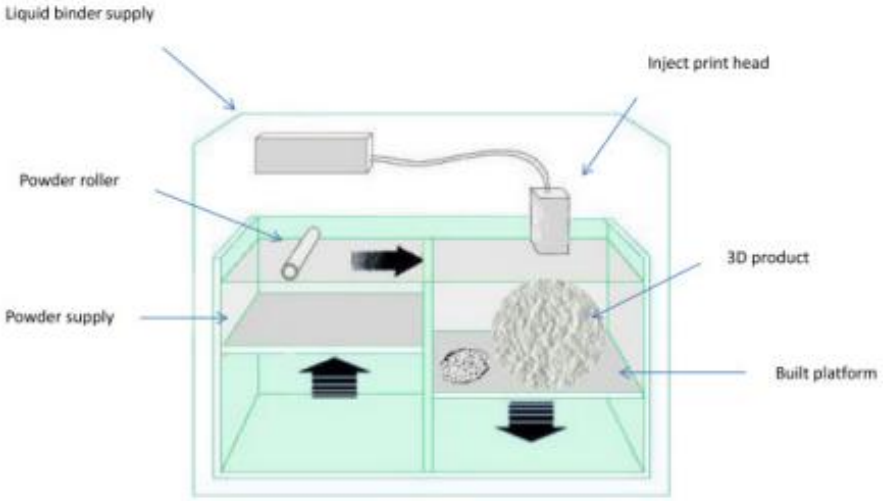

Figure 2. Schematic illustration of powder-based binding technique

4.3. Inkjet printing

Inkjet printing is an innovative adoption of 3DP technology in pharmaceuticals, particularly effective when the starting materials are in liquid form. This technique is classified into two main categories: continuous inkjet (CIJ) (Figure 3a) and drop-on-demand (DOD) printing (Figure 3b), based on the method of droplet formation (Castrejon-Pita et al., 2013; Park et al., 2019). In CIJ printing, droplets are continuously generated by droplet-loading apparatus or a transducer, which produces a steady stream of droplets. This method allows for high-speed printing and is suitable for applications requiring continuous material deposition. In contrast, the DOD printing system converts pharmaceutical-based ink into droplets by either applying a voltage to a piezoelectric crystal transducer, which causes the material to vibrate, or by heating the formulation above its boiling point to create droplets. These droplets are then driven from an orifice to the printer head's nozzle, where they are deposited and solidified drop by drop (Samiei, 2020). The key factor in developing a formulation for the inkjet printing system is the performance of the carrier formulation during printing, which is heavily influenced by rheological parameters such as fluid viscosity, velocity, and surface tension. Additionally, the release profile of the drug formulation can be tailored based on the deposition pattern of droplets onto the substrate. The primary advantage of inkjet printing in pharmaceutical applications is its high precision in creating 3D drug products (Daly et al., 2015; Tatipamula, 2022). This technology also opens new possibilities for utilizing novel APIs and personalizing drug formulations. Factors influencing the fabrication of 3D drug products, such as manufacturing processes and material properties, are critical for optimizing this technology (Carou Senra et al., 2024).

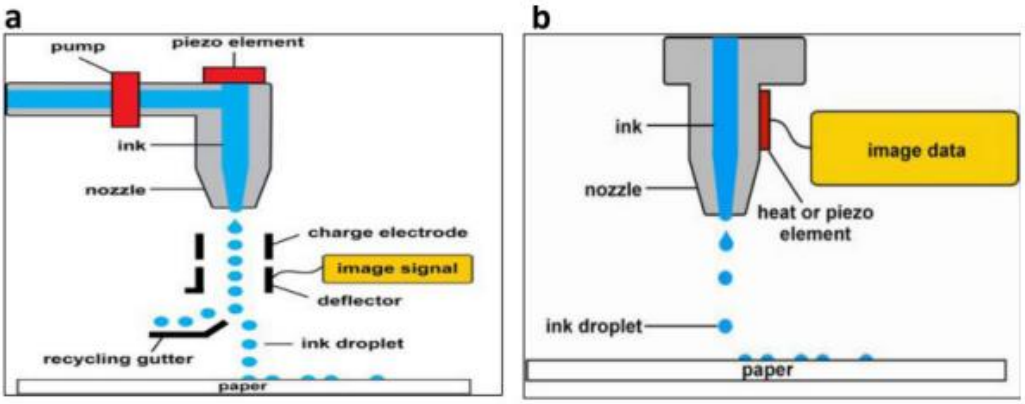

Figure 3. Inject printing technique **(a)** Continuous (CIJ) & **(b)** Drop on demand (DOD)

4.4. Laser based 3D printing

Both Stereolithography (SLA) and Selective Laser Sintering (SLS) techniques offer distinct advantages and face specific limitations in drug formulation and pharmaceutical 3DP. Despite their potential, challenges related to material selection, stability, cytotoxicity, and API degradation need to be addressed to fully exploit these techniques for pharmaceutical applications (Kafle et al., 2021; Awad et al., 2020).

SLA: SLA employs a UV laser beam to polymerize a photosensitive polymeric liquid, layer by layer, to build a 3D object. The technique is noted for its high resolution, achieving layer thicknesses as fine as 0.2 mm, which surpasses the resolution capabilities of other methods (typically 50−200 mm). The precision of SLA is influenced by the duration and intensity of laser exposure (Figure 4a). This high resolution makes SLA suitable for producing complex drug hydrogels and microstructures for transdermal drug delivery applications. However, SLA faces several challenges: there is a lack of FDA-approved photo-polymeric resins, instability of printed materials due to photosensitivity, and potential leaching of entrapped molecules (Huang et al., 2020; Skoog et al., 2014).

SLS: SLS is a powder-based technique where a laser beam selectively sinters a bed of powder material below its melting temperature. This process fuses the powder to form solid layers without the need for organic solvents or post-printing drying. SLS offers high resolution and a single-step printing process (Figure 4b). However, it has limitations, including potential degradation of APIs due to the laser melting process, a limited selection of compatible powders, and difficulty in printing hollow structures (Kruth et al., 2003; Kruth et al., 2005).

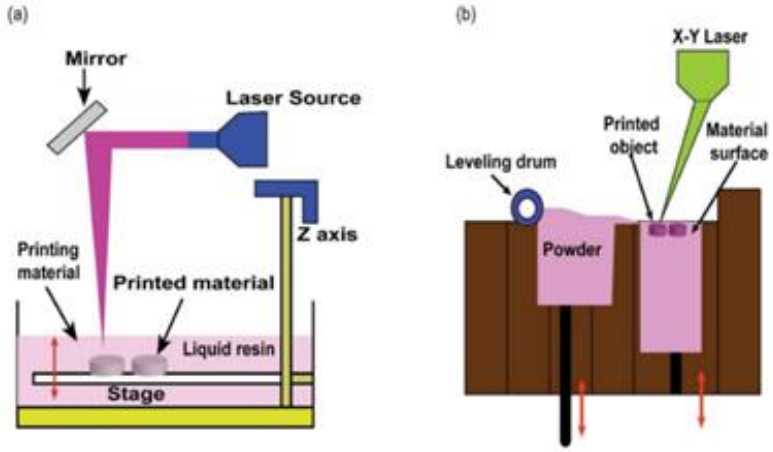

Figure 4. The laser-based 3D printing techniques. **(a)** Stereo lithography (SLA) technique, & **(b)** Selective laser sintering (SLS) technique

In summary, while SLA and SLS techniques present valuable tools for pharmaceutical 3DP, their respective advantages and limitations underscore the need for ongoing research and development to address material compatibility, stability issues, and other challenges to optimize their application in drug formulation.

5. 3D TECHNOLOGY OF FORMULATION OF ORAL DRUG DELIVERY

5.1. Tablets

The concept of 3DP for drug delivery systems was first explored in 1996, when solid samples were created using a desktop printer with polymers (polycaprolactone (PCL) and poly(ethylene oxide) (PEO)), incorporating colored dyes. This pioneering study showcased various construction methods and demonstrated that 3D-printed tablets could be designed to control drug release through erosion or diffusion mechanisms (Katstra et al., 2000; Lee et al., 2003; Sastry and Bharadwaj, 2018) (Figure 5). The research highlighted key considerations, including the choice of AM process, printing parameters, and the type of release profile – whether immediate or delayed, and whether following first-order or zero-order kinetics (Alhijjaj et al., 2016; Talluri et al., 2018; Bácskay et al., 2022).

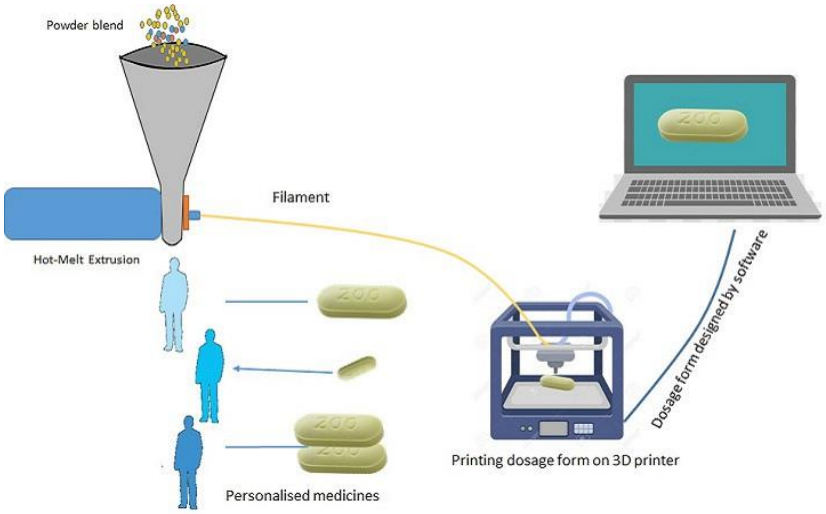

Figure 5. 3D printing of tablets

The advent of 3DP technology has significantly transformed the development of solid oral dosage forms, offering enhanced flexibility and customization in drug release profiles. Notable advancements in 3DP techniques, particularly extrusion-based methods, have enabled the creation of diverse oral drug delivery systems. These include immediate-release, delayed-release, polypills for complex regimens, gastro-retentive systems, and fast-dissolving films. By adjusting parameters such as layer thickness and filament composition, researchers have successfully tailored drug release profiles and developed sophisticated drug delivery devices. For example, studies have demonstrated the successful fabrication of bilayer tablets with distinct release characteristics for anti-diabetic medications. Additionally, polypills with customized immediate and sustained release profiles have been developed. These innovations illustrate the potential of 3DP to overcome limitations associated with traditional manufacturing methods, offering personalized medication solutions through tailored drug release profiles and novel dosage forms (Katstra et al., 2000; Lee et al., 2003; Wang et al., 2003; Alhijjaj et al., 2016; Bácskay et al., 2022; Thuan et al., 2024). Several key studies have further advanced the field (Table 1).

Table 1. 3D printing technology in manufacture of tablets

Year	Type of 3D printing	Type of polymer	Type of API	Reference
2000	Droplet binding	Methacrylate copolymers	Chlorpheniramine	Katstra et al., 2000
	Droplet binding	Methacrylate copolymers	Chlorpheniramine and diclofenac	Rowe et al., 2000
2003	Droplet binding (TheriForm™ process)	None (mannitol)	Captopril	Lee et al., 2003
	Droplet binding (TheriForm™ process)	Kollidon SR (80% polyvinyl acetate, 19%)	Pseudoephedrine	Wang et al., 2003
2007	Bio-ceramic powder printing	Resomer RG502H (polylactide- polyglycolide 50:50)	Vancomycin, ofloxacin, and tetracycline	Gbureck et al., 2007
2009	Powder binding desktop 3D machine	PVP	Acetaminophen	Yu et al., 2009
	Powder binding desktop 3D machine	PVP K30	Acetaminophen	Yu et al., 2009
2015	Extrusion-based 3D printer (Fab@Home)	PAA	Guaifenesin	Khaled et al., 2015
2015	FDM	PVA	Budesonide, paracetamol and caffeine	Goyanes et al., 2015
	RegenHU 3D printer	HPMC	Nifedipine, captopril, and glipizide	Khaled et al., 2015
2016	FDM	Eudragit EPO, Soluplus and PVA	Felodipine	Alhijjaj et al., 2016
	FDM	Eudragit EPO	Theophylline, 5-ASA, captopril, and prednisolone	Sadia et al., 2016
	SLA	PEGDA	4-ASA and paracetamol	Wang et al., 2016
	FDM	PVA	Fluorescein	Goyanes et al., 2016
2017	Inkjet printing	PEG	Ropinirole	Acosta-Vélez et al., 2017
	FDM	PCL and Eudragit RL 100	Nanocapsules	Beck et al., 2017
	FDM	PLA	Acetaminophen	Zang et al., 2017
2018	Inkjet printing with piezoelectric nozzle	PEG and PEGDA	Naproxen	Acosta-Vélez et al., 2018
	UV-assisted crosslinking technology	PDMS	Prednisolone	Holländer et al., 2018
	Extrusion-based MAMII	HPMC K4M, HPMC E15, MCC PH101, and PVP	Dipyridamole	Li et al., 2018
2019	Zipdose	Unknown	Levetiracetam	Bhattacharya et al., 2019
2020	Semi-solid 3D extrusion printer	HPCM	Levetiracetam	Cui et al., 2020
	Desktop 3D printer	PCL and PEO	Yellow and blue dye	Huang et al., 2020

2021	Pressure-assisted microsyringe	PEG 400 and PEG 6000	Dapagliflozin	Mohammed et al., 2021
	FDM	PCL	Indomethacin and Theophylline	Viidik et al., 2021
	SLS	PVA	Indomethacin, Nifedipine, Tinidazole, Ibuprofen, and Metoprolol	Yang et al., 2021
2022	SLS	PEGDA	Warfarin sodium	Xu et al., 2022

Gbureck et al. (2007) utilized a unique 3D bio-ceramic powder printing process to manufacture drug delivery systems, subsequently adsorbing antibiotics over a week to create functional tablets. Yu et al., 2009 initially produced an acetaminophen-containing matrix tablet using a desktop 3D printer and later modified the design by orienting layers vertically to achieve a different dissolution mechanism. RegenHU's extrusion-based 3D printer was employed to create a polypill with distinct, fillable link cartridges for semi-solid API-containing materials, using inks manufactured from nifedipine, captopril, and glipizide combined with hydroxypropyl methylcellulose (HPMC). Beck et al. (2017) integrated AM with nanotechnology, exploring the potential of this combined approach to enhance drug delivery. Chai et al. (2017) designed an intragastric floating tablet by hot-melt extruding domperidone with hydroxypropyl cellulose (HPC) and then 3DP the filament using FDM. This method allowed for slow dissociation of HPC polymer chains, creating a rigid shell that supports sustained drug release. These advancements underscore the transformative impact of 3DP on pharmaceutical formulations, offering innovative solutions for personalized medication and enhanced drug delivery systems.

5.2. Capsules

In 2015, Melocchi group introduced the first 3D-printed capsular devices (Melocchi et al., 2015) (Table 2). This pioneering work utilized HPC-containing filaments produced through hot-melt extrusion, which were then employed in 3DP to create swellable, erodible capsules designed for oral pulsatile drug release (Melocchi et al., 2015). The fabrication process involved the use of inkjet printing and FDM to construct capsules. The final capsules consisted of three parts: two hollow sections with a rounded open end and a cylindrical closed end, and a middle section that functioned as a joint and partition (Figure 6). These capsules, varying in wall thickness and geometry, were filled with APIs, and the findings demonstrated successful pulsatile release of the APIs within 2 h (Maroni et al., 2017; Kolli et al., 2018).

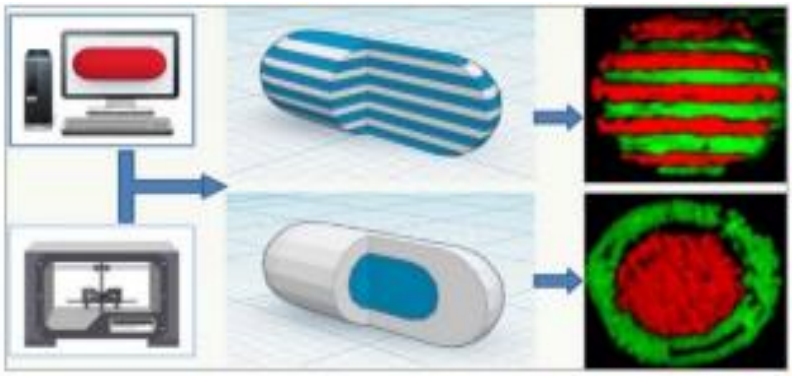

Figure 6. Cross-section of the designed capsules

Further research explored the combination of 3DP technology with the controlled release properties of nanocellulose hydrogels. This approach allowed for precise modulation of drug release by adjusting the inner geometry of the PLA capsules (Table 2). Notably, this method enabled the use of a wide range of APIs, including sensitive substances such as proteins and liposomes, as the API did not undergo heating during the manufacturing process (Phan et al., 2022; Thuan et al., 2022a). The advantages of 3D-printed capsular devices mirror those observed in personalized tablet formulations, including the ability to produce flexible, on-demand doses tailored to individual patient needs, which can lead to improved health outcomes. However, limitations have been noted, such as concerns regarding API stability and the limited availability of polymeric carriers. Despite these challenges, the integration of 3DP with advanced materials like nanocellulose hydrogels represents a significant advancement in the improvement of customizable drug delivery systems (Desu et al., 2021; Tatipamula and Ketha, 2020; Thuan et al., 2022b).

Table 2. 3D printing technology in manufacture of capsules

Year	Type	Type of polymer	Type of API	Reference
2015	FDM	HPC	No (yellow and blue dye)	Melocchi et al., 2015
2016	FDM	PLA, EC, HPC, HPMC, HPMCAS, various Eugradit, PEO, PVA, Soluplus, PEG 400 and 8000	Acetaminophen and furosemide	Melocchi et al., 2016
2017	FDM and Inkjet	PLA, PVA, polymer formulations	No (yellow and blue dye)	Maroni et al., 2017
2020	FDM	PLA	Metoprolol and nadalolol	Auvinen et al., 2020

5.3. Oro-dispersible film

The advancement of 3DP technology has led to the creation of innovative oral dosage forms, including the development of 3D-printed oral films. One of the earliest examples of this technology was demonstrated using thermal inkjet (TIJ) printing, where salbutamol sulfate was dissolved in an aqueous solution (Arora and Chakraborty, 2017; Paidi et al., 2017). This solution was loaded into ink cartridges and printed onto a starch film, resulting in the production of oro-dispersible films (ODFs) (Figure 7). Similarly, various substrates, such as water-impermeable transparency films, were used to incorporate rasagiline mesylate (RM) as a low-dose API. By applying several layers of the printed solution on top of each other using a standard consumer TIJ printer, flexible doses of the API were achieved (Arora and Chakraborty, 2017; Paidi et al., 2017a; Salawi, 2022; Thuan et al., 2022c; Killari et al., 2023).

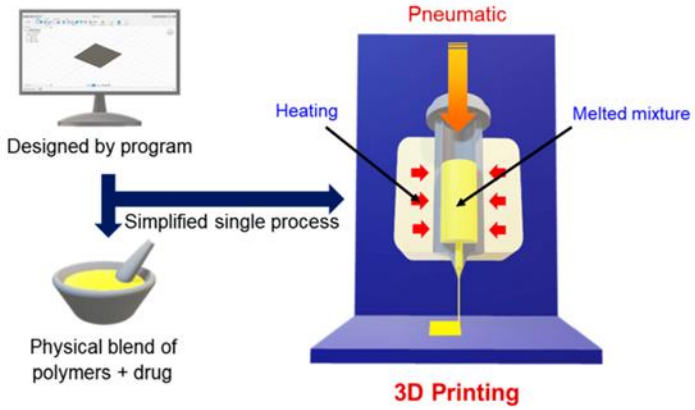

Figure 7. 3D printing in oro-dispersible films

Further advancements in 3DP techniques have incorporated multiple methods to enhance drug delivery systems (Genina et al., 2013; Killari et al., 2023a). For instance, Vakili et al., 2016 employed inkjet printing technology to produce ODFs containing propranolol hydrochloride. They designed these films with accelerating doses of the API across varied area sizes and three different substrates using TIJ printing (Vakili et al., 2016). Jamróz et al., 2017 utilized FDM technology to fabricate ODFs containing aripiprazole, employing PVA as the polymer matrix. The two-step hot-melt extrusion process resulted in the complete amorphization of aripiprazole, with the high strength of PVA helping to preserve this amorphous state (Jamróz et al., 2017). In another study, researchers explored semi-solid extrusion 3DP for the production of warfarin-containing ODFs. This approach aimed to overcome limitations associated with conventional manufacturing processes, making these oromucosal films particularly valuable for delivering potent APIs in treatments for cardiovascular disorders, schizophrenia, and migraines (Kean and Adeleke, 2023). For a comprehensive overview of the research on fabricated ODFs, please refer to below Table 3.

Table 3. 3D Printing technology in manufacture oro-dispersible films.

Year	Type of 3D printing	Type of polymer	Type of API	Reference
2011	Thermal inkjet printing	No need	Salbutamol Sulphate	Buanz et al., 2011
2012	Inkjet and flexographic printing	EC	Riboflavin and propranolol	Genina et al., 2012
2013	Thermal inkjet printing	Crospovidone (Kollidon CL-M)	Rasagiline mesylate	Genina et al., 2013
2017	FDM	PVA	Aripiprazole	Jamróz et al., 2017
2018	FDM	PVA, PEO, and PEG	Ibuprofen and paracetamol	Ehtezazi et al., 2018
2019	Semi-solid extrusion	Hydroxypropyl-β-cyclodextrin and cellulose	Carbamazepine	Conceição et al., 2019
2021	Multitool 3D printer	HPMC	Indomethacin	Germini and Peltonen, 2021

5.4. Intrauterine drug delivery system

3DP technologies have significantly advanced the development of drug delivery devices and implants, particularly for intrauterine and vaginal applications. These methods offer the flexibility to customize shape and size, enhancing both systemic and local delivery of APIs through these routes (Urbán-Morlán et al., 2021; Bao et al., 2019; Klein and Tietz, 2019; Killari et al., 2021). Holländer et al., 2016 pioneered the use of FDM for creating T-shaped intrauterine devices (IUDs). Their study demonstrated that 3D-printed devices made from PCL exhibited faster drug release of the model drug indomethacin compared to the drug-loaded extruded filament. The enhanced drug release was attributed to the drug polymer diffusion state in the 3D-printed devices, which facilitated a more efficient release profile compared to its crystalline form in the filament. Further advancing this field, the same research group utilized ethylene vinyl acetate (EVA) as a polymer for fabricating intrauterine systems (IUS) and subcutaneous rods (SR) using FDM-based 3DP. These custom-made T-shaped devices demonstrated a rapid drug release profile over a 30-day period, highlighting EVA as a suitable polymer for producing implantable devices through 3D extrusion techniques (Holländer et al., 2016).

In another notable development, Fu et al., 2018 applied FDM-based 3DP to create customized vaginal rings containing progesterone. They used poly(lactic acid) (PLA) and PCL for filament formation through HME. Various ring shapes, including O, Y, and M

configurations, were designed. The O-shaped ring, in particular, exhibited superior drug release characteristics due to its specific geometrical design. This approach underscores the potential of 3DP to produce tailored contraceptive devices with customizable shapes and sizes, optimizing drug delivery for individual needs. These advancements illustrate the transformative impact of 3DP on the design and production of drug delivery systems, offering personalized solutions that enhance therapeutic efficacy and patient compliance (Fu et al., 2018).

6. 3D TECHNOLOGY OF FORMULATION BASED ON NOVEL DRUGS

6.1. 3D Printing technology in nanomedicine

Personalized medicine aims to tailor drug treatments, drug combinations, dosing intervals, and drug release rates to meet the needs of individual patient, moving beyond the traditional 'one-size-fits-all' approach. In this context, nanotechnology has emerged as a transformative force, significantly advancing the development of novel drug delivery systems (Pyteraf et al., 2022; Zhu et al., 2018). By modifying the biopharmaceutical properties of poorly absorbable drugs, nanotechnology holds substantial promise for enhancing therapeutic efficacy and individualizing treatment strategies. Recent years have witnessed a surge in interest towards integrating nanotechnology with 3DP to develop multi-functional drug delivery systems, particularly solid dosage forms incorporating nano-pharmaceuticals. Nano-capsules, known for their physical stability over several months, often face challenges such as susceptibility to microbial contamination due to their high-water content. To address these issues, traditional methods such as spray-drying, freeze-drying, and wet granulation have been employed to enhance the stability, storage, and transportation of nano-capsules (Jain et al., 2021; de Oliveira et al., 2022; Sommonte et al., 2023). One significant advancement involves the conversion of liquid Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) into solid SNEDDS (Kazi et al., 2019). This transition improves the physical stability of the formulation and enhances patient compliance. The integration of 3DP technology into this field has opened new avenues for designing nanomedicine-based solid dosage forms, providing enhanced control over drug delivery characteristics and allowing for the production of complex and customized drug delivery systems. In the following sections, we will delve into the comprehensive development of nanomedicine-based solid dosage forms utilizing 3DP techniques, highlighting how this innovative approach addresses traditional challenges and paves the way for more effective and personalized drug delivery solutions (Kazi et al., 2019; Rehman et al., 2017; Hauptstein et al., 2015).

6.2. 3D Printed tablets loaded with polymeric nanocapsules

The application of FDM-based 3DP has marked a significant progress in the pharmaceutical field by enabling the transformation of polymeric nanocapsule suspensions into customized tablet dosage forms (Beck et al., 2017) (Figure 8). This approach is particularly notable for developing personalized drug delivery systems for medications like deflazacort. 3DP, a technique where products are constructed layer-by-layer from a digital model, has garnered increasing interest in the pharmaceutical industry since the FDA's approval of the first 3D-printed drug, Spritam (Serrano et al., 2023; Mohammed et al., 2021). This technology is not only revolutionizing drug discovery but is also being utilized for manufacturing drug delivery devices and biomanufacturing applications, such as bone and tissue engineering *via* scaffolds (Serrano et al., 2023; Shabbirahmed et al., 2023). The flexibility of 3DP allows for the production of products with a wide range of configurations, achieved through various processes

including SLS, SLA, FDM, SLS with Selective Extrusion (SSE), and powder bed-inkjet printing (Gioumouxouzis et al., 2020; Pradeep and Paul, 2022; Charoo et al., 2020).

A pioneering study by Beck et al. showcased the integration of 3DP and nanotechnology for the first time, producing tablet dosage forms containing polymeric nanocapsules tailored for personalized medicine (Beck et al., 2017). In this study, 3D-printed tablets (referred to as printlets) were manufactured using Eudragit RL100 filaments and mannitol. These printlets were subsequently drug-loaded by immersing them in a suspension of nanoparticles. The process demonstrated that drug loading was proportional to the volume of the nanocapsule suspension absorbed by the 3D-printed devices during the soaking process. By considering factors such as drug content, volume absorbed, and the final mass of the tablet, the study successfully converted nanocapsule fluids into solid dosage forms. This innovation represents a significant leap forward in 3DP technology, providing a novel and efficient method for developing personalized drug delivery systems based on nanomedicine. This approach not only facilitates the creation of customized drug delivery solutions but also highlights the potential of integrating advanced manufacturing technologies with nanotechnology to enhance the effectiveness and personalization of pharmaceutical treatments (Beck et al., 2017).

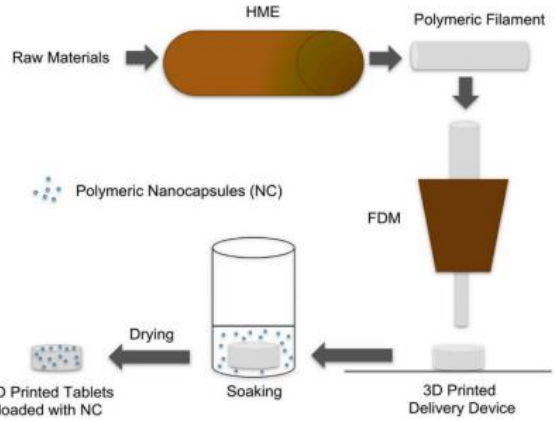

Figure 8. 3D printed tablet dosage forms loaded with polymeric nanocapsules

6.3. 3D Printing of self-nanoemulsifying tablets

Recent advancements in lipid-based formulation techniques (Table 4), particularly SNEDDS, have garnered significant attention for improving the oral bioavailability of poorly water-soluble compounds (Shetty et al., 2014; Kari et al., 2019). These formulations facilitate drug solubilization and enhance absorption by forming stable nanoemulsions upon oral administration. SNEDDS are designed to create self-emulsifying systems that disperse in aqueous media, resulting in nano-sized oil droplets that encapsulate poorly soluble drugs (Kari et al., 2019; Rehman et al., 2017). This nanoemulsion system significantly improves the solubility and bioavailability of the encapsulated drugs, as the small droplet size promotes better dissolution and absorption in the gastrointestinal tract. Traditionally, SNEDDS have been incorporated into soft gel capsules, which serve as an effective means for oral delivery. While this approach has proven beneficial for enhancing drug solubility and bioavailability, liquid-based nanoemulsion formulations face certain limitations, particularly concerning stability (Rehman et al., 2017). The stability of these formulations can be a significant challenge, often leading to issues such as phase separation or changes in droplet size over time, which can impact the efficacy and safety of the drug product. Addressing these stability concerns remains a critical focus in the development of lipid-based formulations to ensure the long-term efficacy

and reliability of SNEDDS in enhancing the bioavailability of poorly soluble drugs (Kari et al., 2019; Rehman et al., 2017).

Table 4. 3D printing technology based on self-nanoemulsiondrug delivery systems

Year	Drug delivery type	Type of 3D printing	Type of polymer	Type of API	References
2011	Nanosuspension	Inkjet-based micro dosing dispenser head	None	Folic acid	Pardeike et al., 2011
2011	Micron-sized dried deposits	Inkjet printing	PVP	Felodipine	Scoutaris et al., 2011
2012	Micropatterns	Inkjet printing	PLGA	Rifampicin	Gu et al., 2012
2012	Microparticles	Piezoelectric inkjet printing	PLGA	Paclitaxel	Lee et al., 2012

6.4. Transdermal drug delivery

The integration of 3DP technology into transdermal drug delivery systems represents a significant advancement in creating personalized and effective pharmaceutical products. This technology allows for the fabrication of complex and customized geometries that cater to specific patient needs, enhancing both local and systemic delivery of APIs (Prausnitz and Langer, 2008; Rastogi and Yadav, 2012). Here's a detailed look at the innovative approaches and applications of 3DP in transdermal drug delivery (Table 5).

Table 5. 3D printing technology in transdermal drug delivery system

Year	Type of 3D printing	Type of polymer	Type of API	References
2016	FDM and SLA	Flex EcoPLA and PCL	Salicylic acid	Goyanes et al., 2016
2016	Inhouse extrusion-based 3D printer – multi-head deposition system	PLA and PCL	5-Fluorouracil	Yi et al., 2016
2017	EHD	PCL and PCL/PVP	Tetracycline hydrochloride	Wang et al., 2017
2021	FDM	PVP	Quercetin	Chaudhari et al., 2021

3DP technology has demonstrated its versatility in advancing drug delivery systems through the development of implants, micro-needles, and masks tailored to specific therapeutic needs. Kempin et al., 2017 utilized extrusion-based FDM combined with hot-melt extrusion to create drug-loaded implants using polymers like PCL, Eudragit®RS, and ethyl cellulose. These hollow cylindrical implants provided tailored drug release, with PCL enabling the fastest release, facilitating extended and customized delivery (Kempin et al., 2017). Similarly, Allen et al., (2016) employed piezoelectric inkjet printing to fabricate dissolvable micro-needles for vaccines, such as the seasonal influenza vaccine. This approach improved compliance and efficacy by ensuring precise dosage and minimal waste during percutaneous administration. In dermatological applications, Goyanes et al. (2016a) created a custom nose mask for acne treatment using FDM technology, leveraging materials like Flex EcoPLA™ and PLC to enable controlled drug release and enhanced therapeutic effects. Muwaffak et al. (2017) further developed patient-specific wound dressing masks for the nose and ears incorporating antimicrobial agents such as zinc, silver, and copper. These masks provided superior fit, improved adherence, and localized antimicrobial treatment, outperforming traditional flat

dressings (Muwaffak et al., 2017). These innovations underscore 3DP's potential to enhance the precision, efficacy, and adaptability of medical treatments.

3DP technologies like FDM and inkjet printing, have significantly advanced transdermal drug delivery systems by offering innovative solutions. These technologies enable the creation of custom geometries, such as implants, micro-needles, and masks, designed to match patient-specific anatomical features. Additionally, they facilitate precise and controlled drug release profiles, ensuring that APIs are delivered in alignment with therapeutic needs. Furthermore, 3DP enhances patient compliance by providing targeted and efficient drug delivery systems, ultimately leading to improved treatment outcomes (Economidou et al., 2018). The continued evolution of 3DP technology holds promise for further innovations in personalized medicine, potentially transforming the landscape of transdermal drug delivery.

6.5. Microneedles

Recent studies underscore the transformative potential of 3DP technologies (Table 6), such as femtosecond laser two-photon polymerization and micro-SLA, in the fabrication of microneedles loaded with a range of pharmacologic agents, including amphotericin B, miconazole, dacarbazine, and insulin (Chu et al., 2018; Ge et al., 2020). These advancements highlight the versatility of 3DP in pharmaceutical applications. The use of specialized polymers, like Gantrez® AN 169 BF, has facilitated the development of microneedles designed for the transdermal treatment of cutaneous fungal infections, emphasizing the importance of material selection in tailoring drug delivery systems for specific therapeutic requirements (Ge et al., 2020). Moreover, the ability of 3DP to create dual-function microneedle arrays on personalized curved surfaces - combining drug delivery with splinting, offers a novel approach for personalized treatment (Figure 9). For instance, a microneedle splint for trigger finger treatment exemplifies how 3DP can enhance functionality without compromising hand mobility. The integration of pharmacologic agents with complex solubility profiles into microneedles through 3DP ensures precise dosing and maintains mechanical strength, presenting advantages over traditional metal microneedles. This technology also enables potential cell-targeted delivery due to the fine nano-scale tips. Overall, 3DP in microneedle fabrication shows significant promise for addressing diverse therapeutic needs, including localized drug delivery for skin cancer and transdermal fungal infections (Chu et al., 2018; Ge et al., 2020; Nugyen et al., 2020).

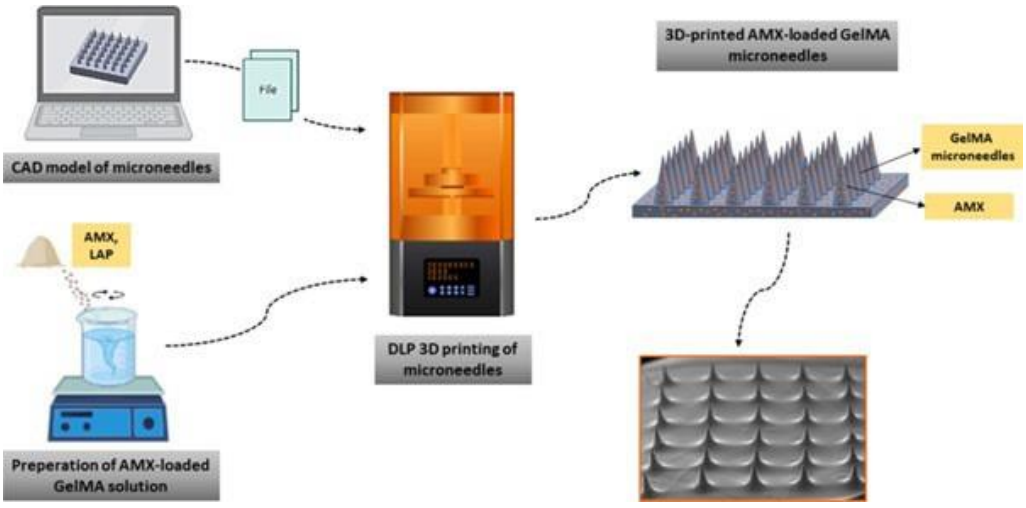

Figure 9. 3D printing of preparation of microneedles

Table 6. 3D printing technology of microneedles

Year	Type of 3D printing	Type of polymer	Type of API	References
2007	Femtosecond laser two photon polymerization	Ormocer®	None	Ovsianikov et al., 2007
2013	Piezoelectric inkjet printing	PDMS and PMMA	Amphotericin B	Boehm et al., 2013
2014	Piezoelectric inkjet printing	Gantrez® AN 169 BF (poly(methylvinylether-co-maleic anhydride))	Miconazole	Boehm et al., 2014
2015	Multi-material microstereolithography (μSL)	Poly(propylene fumarate)	Dacarbazine	Lu et al., 2015
2015	Inkjet printing	Soluplus®	5-Fluorouracil	Uddin et al., 2015
2017	DLP	3DMCastable resin	Diclofenac sodium	Lim et al., 2017
2018	SLA	Medium viscosity alginate	Blue dye, HepG2 cell encapsulation	Farias et al., 2018
2018	FDM	PLA	Fluorescein	Luzuriaga et al., 2018
2018	Inkjet printer	Dental SG	Insulin	Pere et al., 2018
2019	SLA	Dental SG	Insulin	Economidou et al., 2019

6.6. Implants

The intersection of healthcare and 3DP technology has ushered in transformative advancements in the fabrication of medical implants. Leveraging the principles of AM, 3DP has revolutionized implant design and production, providing unparalleled customization, precision, and patient-specific solutions. This technology enables the creation of implants with intricate and complex geometries, which is especially beneficial for devices that must integrate seamlessly with specific anatomical structures. Additionally, 3DP facilitates rapid prototyping, allowing for accelerated development processes and timely adjustments based on individual patient needs. From dental implants to orthopedic devices, 3DP offers tailored solutions for a wide range of medical requirements (Nagarajan et al., 2018; Tian et al., 2021). A summary of recent innovations in 3D-printed drug delivery implants highlights their diverse applications and capabilities. For instance, Levofloxacin-containing PLA implants with complex release profiles were designed using inkjet printing, achieving a steady-state drug release over 100 days. Multi-layered concentric cylindrical implants containing rifampicin and isoniazid demonstrated controlled drug liberation, with peak concentrations occurring between 8 and 12 days. Tailored drug delivery platforms containing dexamethasone, fabricated via extrusion printing, exhibited continuous API release for over 4 months, making them suitable for long-term implantation (Wu et al., 2009; Hatami et al., 2024).

IUDs and SR loaded with indomethacin, created from EVA copolymer using FDM printing, provided a long-acting, 3D-printed implantable system. Implantable meshes for hernia repair, loaded with ciprofloxacin, showed improved wound healing and maintained body temperature stability in animal studies. Moreover, 3DP has been applied to fabricate implants for localized drug delivery, including gentamicin and methotrexate-loaded devices such as screws, pins, and bone plates. PLLA samples, printed and immersed in various anticancer drugs, demonstrated effective local chemotherapy, multidrug delivery, and sustained drug release for osteosarcoma treatment. Additionally, 3D-printed ciprofloxacin-containing PLA implants were found to be more effective for treating bone infections compared to conventional methods. Collectively, these studies underscore the immense potential of 3DP in creating personalized,

complex drug release implants tailored to individual patient needs (Abdelgader et al., 2024; Fanse et al., 2022).

Applications of 3D-printed implants is revolutionizing medical implant fabrication by enabling the production of highly customized solutions across various medical fields. In orthopedics, 3DP allows for the creation of tailored implants, such as hip and knee replacements, ensuring a precise fit, reducing complications, and improving patient outcomes. In dentistry, the technology is employed to fabricate dental implants and prosthetics with exceptional accuracy, ensuring both functionality and aesthetic appeal. For cranial implants, 3DP provides precise matching to the skull's contours, catering to patients recovering from trauma or surgical interventions. Additionally, the versatility of 3DP extends to cardiac applications, enabling the creation of patient-specific stents and heart valve replacements, highlighting its transformative potential in personalized medicine (Ho et al., 2015; Wong, 2016; Daikuara et al., 2022).

7. CONTRIBUTIONS OF 3D PRINTING TECHNOLOGY

Maintaining healthy skin is essential for overall well-being, particularly in the context of burns, non-healing cuts, accidents, and severe wounds, which require prompt and effective skin therapy. Traditionally, skin injuries have been treated with transplants sourced from either donors or the patient's own body. However, 3D bioprinting represents a revolutionary advancement in generating skin transplants quickly and affordably. This cutting-edge technology facilitates the creation of functional tissue that performs essential biological functions, enabling significant innovations in both therapy and surgery. Researchers are continually developing viable skin tissues through 3D bioprinting, which can significantly aid in the recovery of individuals with severe skin conditions and burn injuries, thus streamlining the skin grafting process (Olejnik et al., 2021; Cubo et al., 2016). Steps involved in 3D bioprinting of skin were illustrated in Figure 10.

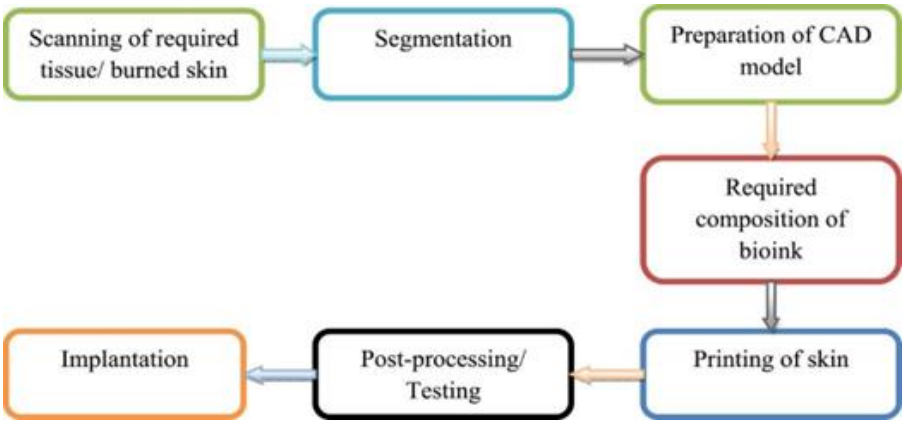

Figure 10. Steps involved during the printing of skin using 3D bioprinting

Applications of 3D bioprinting in skin therapy are revolutionizing skin regeneration and reconstruction by offering advanced solutions for various medical applications. It enables the rapid production of functional skin that closely resembles human skin, with a natural layered structure suitable for transplantation, providing a reliable and long-term solution for patients (Kérourédan et al., 2018). The technology also facilitates the printing of skin grafts, incorporating blood vessels to mimic natural living skin and allowing for biological scaffolds tailored to the specific shape and size of patients (Ghidini, 2018; Biedermann et al., 2013). For burn injury treatment, tissue-engineered skin created through 3D bioprinting serves as an

effective substitute, supporting wound closure and improving burn patients' quality of life (Ma et al., 2018; Zhang et al., 2019). Additionally, 3D bioprinting provides innovative solutions for nose wing reconstruction by enabling the fabrication of full-thickness skin grafts customized for individual needs and offering controlled tissue analogue creation (Khoo et al., 2018; Tatipamula et al., 2020). In summary, 3D bioprinting represents a transformative approach in skin therapy, offering rapid, customizable solutions for a range of medical needs. Its ability to create patient-specific, functional skin tissue opens new avenues for effective treatment and improved patient outcomes.

8. APPLICATION OF 3D PRINTING TECHNOLOGY

3DP technology is transforming healthcare by revolutionizing drug delivery systems and enabling personalized medicine. It facilitates the development of tailored drug delivery systems with customized release profiles, improving therapeutic precision and efficacy (Goyanes et al., 2014; Goyanes et al., 2019). By considering factors such as patient weight, age, and specific health conditions, 3DP enables the fabrication of personalized medications that enhance treatment outcomes and adherence (Norman et al., 2017; Trenfield et al., 2018; Bharadwaj, 2019). The technology also allows for the production of intricate printed dosage forms and complex drug formulations, offering innovative solutions for drug delivery. Additionally, 3DP is instrumental in manufacturing customized medical devices, such as implants and transdermal drug delivery tools, tailored to therapeutic requirements (Goyanes et al., 2014; Bharadwaj et al., 2018; Trenfield et al., 2018). Its rapid prototyping capabilities streamline pharmaceutical development by accelerating the testing and optimization of formulations. For orphan drug production, 3DP provides a cost-effective approach to manufacturing rare medications in small quantities. Taste-masked formulations produced *via* 3DP improve palatability and patient compliance, especially for pediatric and geriatric populations (Chitturi et al., 2016; Trenfield et al., 2018; Trenfield et al., 2019). Lastly, 3DP enables patient-specific medication, ensuring that treatments are personalized to unique medical needs, further enhancing therapeutic outcomes (Goyanes et al., 2014; Norman et al., 2017). Overall, 3DP is revolutionizing healthcare by advancing drug delivery, personalization, and patient care across diverse applications.

9. OPPORTUNITIES AND CHALLENGES FOR IMPLEMENTING 3D PRINTING IN MEDICINE

3DP represents a transformative advancement in personalized medicine by enabling the production of small batches with customized doses and release profiles. This technology overcomes the limitations of traditional mass production methods, allowing for the creation of drug formulations tailored to individual patient needs. The FDA approval of Spritam by Aprecia in 2015 and Triastek's recent FDA clearance for a 3D-printed dosage form for rheumatoid arthritis mark significant milestones in integrating 3DP into mainstream medical practice, underscoring its growing acceptance and potential for wider application. Additionally, 3DP offers a unique advantage in the production of orphan drugs, facilitating the creation of small batches for rare diseases and thereby addressing the challenge of medication shortages. This approach contrasts sharply with conventional industrial methods, providing a promising solution for the delivery of specialized therapies (Liaw and Guvendiren, 2017; Nguyen et al., 2021b; Nguyen et al., 2021c).

The widespread implementation of 3DP in medicine faces several significant challenges, primarily stemming from the lack of comprehensive regulatory guidelines. Without established standards and protocols, integrating 3DP technology into healthcare systems is fraught with difficulties. Regulatory bodies such as the FDA’s Emerging Technology Team, the Centre for

Drug Evaluation and Research, and Health Canada are actively addressing these challenges by focusing on 3DP in pharmaceutical research (Shahrubudin et al., 2020; Tatipamula et al., 2021a). Their ongoing efforts are essential for developing frameworks that can facilitate the technology's integration into clinical practice. A major concern in the field is ensuring the quality and stability of 3D-printed drugs. To tackle this, non-destructive evaluation methods such as near-infrared and Raman spectroscopy have been proposed for real-time assessment of drug product quality during production. These techniques aim to address concerns related to the consistency and reliability of 3D-printed medications. Furthermore, while various 3D printers have been explored for pharmaceutical dosage forms, none of the current models fully comply with Good Manufacturing Practice standards. Achieving Good Manufacturing Practice compliance is important for safeguarding the consistent safety, quality, and efficacy of 3D-printed medical products. In summary, although 3DP has substantial potential to revolutionize drug formulation and delivery, overcoming regulatory, quality, and compliance challenges is essential for its successful integration into the healthcare system (Palo et al., 2017; Lim et al., 2018; Quanjin et al., 2020; Shahrubudin et al., 2020).

10. CONCLUSIONS AND FUTURE PERSPECTIVE

3DP is emerging as a transformative technology in the pharmaceutical industry, promising groundbreaking advancements in drug manufacturing and delivery systems. By bringing production closer to patients and enabling customized therapies, 3DP offers a novel approach that enhances treatment efficacy through tailored drug formulations. The continual advancements in technology and research hold the potential to revolutionize drug delivery systems, making them safer, more effective, and adaptable to individual needs. The capability of 3DP to create innovative drug delivery systems, with varying release rates and personalized dosing, underscores its impact on the future of medicine. Over the past decade, significant research efforts have focused on optimizing printers and processes to produce unique dosage forms, setting the stage for personalized medicine. The technology's versatility allows for the administration of a wide range of medications with different release profiles, offering unparalleled flexibility in drug design. As the pharmaceutical industry continues to explore new formulations and delivery methods, 3DP is increasingly recognized for its potential to manage medication release rates and create novel drug delivery solutions. The technology's ability to rapidly prototype various dosage forms, including mucoadhesive films and layered structures, highlights its promise for advancing medicinal administration systems. In summary, 3DP holds great promise for transforming drug manufacturing and delivery, positioning itself as a pivotal technology with the potential to shape the future of the pharmaceutical industry.

3DP stands at the forefront of revolutionizing drug delivery systems, offering unprecedented capabilities for creating personalized medications. This modern technique not only enhances cost-effectiveness and simplifies production but also enables the development of complex formulations with precise control over release profiles and designs. The high flexibility of 3DP allows for the production of a wide variety of drug products, tailored to meet specific patient needs. This adaptability is crucial for advancing personalized medicine and addressing individual therapeutic requirements with greater accuracy and efficacy. Despite these advancements, regulatory challenges remain a significant hurdle. Although the FDA approved Spritam in 2015, which utilized ZipDose technology similar to traditional powder compaction, there is still a lack of comprehensive guidelines for the regulation of 3D-printed pharmaceutical dosage forms. This regulatory uncertainty poses challenges for researchers and manufacturers as they navigate the complexities of bringing 3D-printed drugs to market. Another promising area is bioprinting, which involves printing living cells, tissues, or organs. Early exploratory studies in bioprinting have demonstrated significant potential for

pharmaceutical applications, offering new avenues for tissue engineering and regenerative medicine. As 3DP technology continues to evolve, it holds the promise of further transforming drug delivery systems and medical treatments, paving the way for innovations that could enhance patient care and expand therapeutic possibilities.

Conflict of Interest
The authors declare no conflicts of interest.

Author Contribution Statement
Heera Battu: Supervision, Conceptualization, Methodology, Software, Writing- Reviewing and Editing. Mandala Hari Prasad, Seranti Lokesh and Yalamarthi Reenu.: Data curation, Writing- Original draft preparation. Seranti Lokesh and Yalamarthi Reenu.: Visualization, Investigation. Paridala Pravallika, Dhanikonda Ganesh, and Madiki Manasa Angel.: Software, Validation.

Data Availability Statement
The authors confirm that the data supporting the findings of this study are available within the article.

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