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A recent review of the utilization of 3D printing in the development and manufacturing of pharmaceutical dosage forms

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ABSTRACT: Three-dimensional (3D) printing has paved the way in pharmaceutical applications. This innovative methodology presents novel and inventive remedies for patients and the pharmaceutical sector. Moreover, the benefits of this approach encompass the mitigation of adverse effects, customization of formulations for patients with rare medical conditions, and enhancement of therapeutic effectiveness. The objective of our review was to offer a comprehensive survey of the advancements observed in the drug delivery systems that were produced. A thorough inspection has assessed the diverse dosage forms developed using the three-dimensional printing technique (3DP), especially in the last five years. The pharmaceutical industry places significant emphasis on the benefits of developing dosage forms with intricate designs and geometries, incorporating multiple active ingredients, and tailored release profiles due to their versatility and related advantages. Drug delivery systems can be classified into different modalities, tablets, capsules, suppositories, transdermal delivery systems, microneedles, vaginal delivery systems, and nanoscale dosage forms. The utilization of our classification system facilitates researchers' task of evaluating publications and effectively pinpointing further opportunities for research exploration.

KEYWORDS: 3D-printing; Individualized medicine; Tablet; Capsule; Vaginal drug delivery; TTS; Suppository; Nanomedicine.

1. INTRODUCTION

Printing in three dimensions (3D) is a composition of additive fabrications bodied by successfully stacking or linking layers to breed an object [1, 2]. Three-dimensional printing, known as 3DP, has consistently grown over the last three decades. In that time, technology has been investigated for potential applications in the area of medication delivery, and those investigations culminated in the recent clearance by the FDA of a 3D-printed orally dispersible tablet containing levetiracetam [3, 4].

3D printing techniques utilized in manufacturing pharmaceutical dosage forms fall vastly into four categories [5]: extrusion-based [6], sheet-lamination-base [7], powder-based [8], and liquid-based systems [9]. Table lists these various techniques used within the categories and several advantages and disadvantages of each technique [10, 11].

The benefits of employing 3D printing products in dosage form development include accurately regulating the distribution of an active pharmaceutical ingredient (API) in a dosage structure's space, creating intricate shapes, incorporating small amounts of API, reducing waste, and allowing for quick production [12, 13].

3D printing is preferred over conventional manufacturing processes for formulation development because it accurately controls the spatial distribution of the API [14], is inexpensive [15], is easy to manufacture, and offers a one-step [16] and on-demand delivery in the drug development process [17, 18].

In addition, 3D printing has arisen as a promising technique for producing personalized dosage forms over the last decade [19, 20]. Instead of using conventional, mass-produced drugs that are ineffectual in treating large numbers of patients, personalized medicine depends on patient-specific or personalized dosages and combinations of them [21]. Inappropriate dose or dose compositions in drug therapy bring 75-85% of side effects[22]. It is necessary to change a dose to comply with the patient's needs due to differences in age, weight, and disease content, thus minimizing the potency for the side effects of a drug [23, 24]. In recent years, biopharmaceuticals, known as nanomedicines, in which 3D printing technologies are applied in production [25], have also been the focus of attention in academic society [26].

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This study focuses on the advances currently being implemented in 3D printing technology for creating customized medications and systems for delivering medications. This study highlights the 3D printing technologies currently being researched, offering an update on the most recent range of dosage forms created with these techniques. Additionally, the utilization of 3D-printed drugs, including nano pharmaceuticals and biomedicines, will be considered. Eventually, A forward-looking approach will be presented for its widespread adoption in clinical practice while presenting an insight into the barriers to the entry of 3D printing into pharmaceutical technologies.

Table. Comparison of 3D Printing Technologies in Pharmaceutical Application.

Classification		Method	Notion/Explanation	Benefit	Obstacle	Instance
Extrusion-Based System	Extrusion of Material	Fused Deposition Modeling (FDM)	When drug-loaded fibers are heated to a critical state, they become semifluid and can be ejected from the printing tip based on the model parameters.	• A wide selection of possible implements (several nozzles) • Reasonable cost of machinery • Effective printed dosage formulations with high mechanical qualities	•Scalability issues • Minimal drug load	The FDM technique is particularly suitable for addressing rare diseases and specific populations requiring customized dosages or release kinetics [27].
		Semi-Solid Extrusion (SSE)	SSE uses a syringe-based print head to uniformly extrude the paste under screw gear or pressure movement, depositing it on the printing surface in thin layers.	• Intense dosing • A gentle printing procedure/environment • Numerous Excipients Available	• Post-production • Low pixel density •Low productivity	SSE made a tool to help develop special methods for quickly making Orodispersible films (ODFs). The polymer of ODFs was hydroxypropyl methylcellulose (HPMC), and the sample drug was levocetirizine hydrochloride [28].
		Melt Extrusion Deposition (MED®)	Powder feedstocks are melted or softened using MED®, and then objects with the appropriate structures are deposited precisely layer by layer.	• No more editing is required. • Easily expandable • A wide selection of possible implements (several nozzles)	• Minimal drug load	The MED™ 3D printing technology is new, and the platform has great potential that involves the creation and advancement of changed drug release products [29].
Powder-based System	Binder Jetting (BJ)	Ink-Jet 3D printing	BJ puts together 3D objects by first making a 2D layer of powder and subsequently ejecting the binding solution into the powder bed to create a pattern and harden certain areas.	• Easily expandable • Extremely loud • Intense dosing	•Post-production •Ineffective powder utilization	Triastek, Inc. has recently obtained FDA approval for their Investigational New Drug (IND) application pertaining to a T19 dosage form that has been produced through Ink-Jet 3D printing technology [30].

Powder Bed Fusion (PBF)	Selected Laser Sintering (SLS)	PBF uses a directed power source, like a laser or an electron beam, to make solid things out of powder particles.	• Superb clarity • No further resources are required	• The potential for drug breakdown •Post-production	The natural hydroxyapatite (HA) and polyamide 12 (PA12) used in the SLS printing of porous components make it suitable for use in bone and other biomedical applications [31].
Vat Photopolymerization (VP)	Digital Light Processing (DLP), Stereolithography (SLA)	VP works by using an ultraviolet laser source to selectively photopolymerize liquid reactive resins.	• Superior clarity and precision • Capable of printing structures on the microscopic scale	• Post-production • Possible toxicity of the substance • There is a lack of light-sensitive resin	In order to create rigid tissue structures, a poly l-lactic acid (PLLA) resin that is in harmony with the DLP 3D printing process was produced [32]. Hydrogels of cross-linked polyethylene glycol diacrylate were created via SLA printing and then loaded with ibuprofen [33].
Material Jetting	Continuous or Drop on Demand (DOD)	The item is constructed layer by layer as material droplets are placed via a print head and then dried by solvent evaporation or solidification under UV radiation.	• Superb clarity • The superior tablet printing surface	• Post-production •Insufficient excipients	Three types of antiviral medications (hydroxychloroquine sulfate—HCS, ritonavir, and favipiravir) were dispersed evenly within 3D-printed multi-chamber tablets using the direct oral delivery (DOD) approach [34].
Sheet Lamination	Screen Printing Innovational Drug Technology (SPID®)	The principle behind 3D screen printing is that the printing paste is transferred from the printing screen via individual holes and onto the substrate.	• Simple to expand upon. • Faster than average printing speeds	•Post-processing	SL combines elements of both subtractive and additive production methods in order to speed up the construction process [35].

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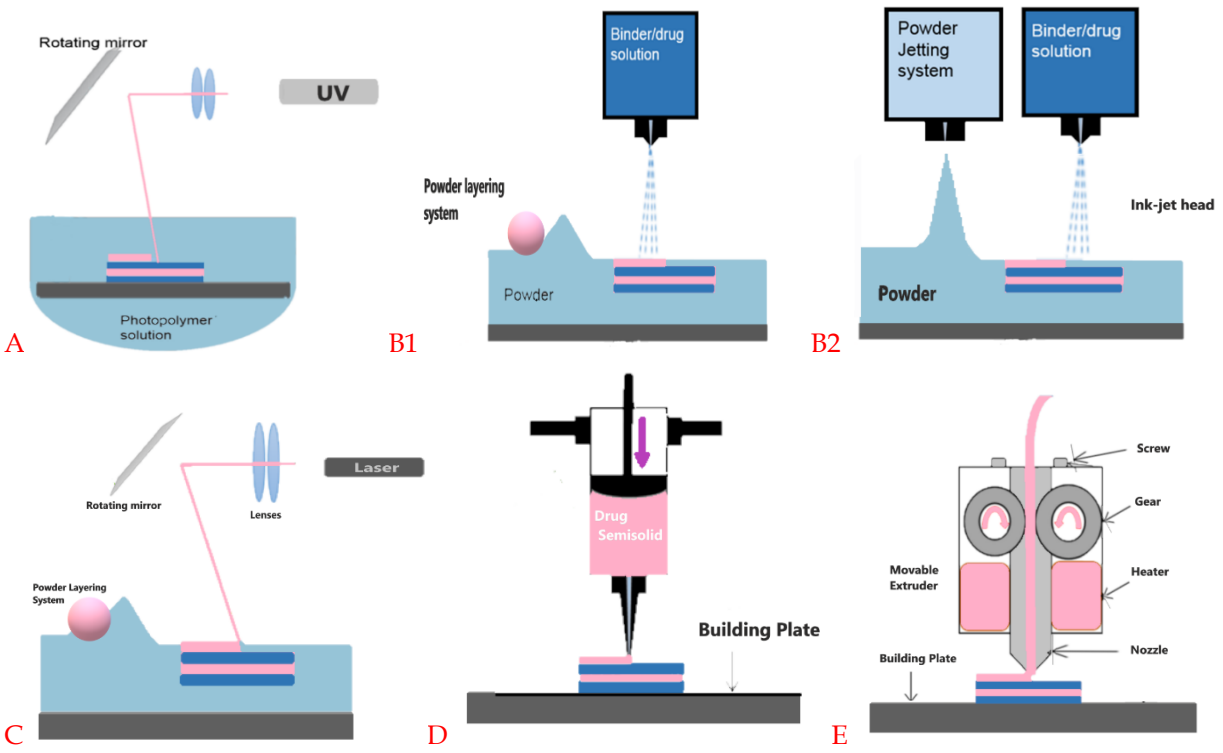

Figure 1. The mechanisms behind different 3D printing methods: A) Stereolithographic (SLA), B1) Powder bed, B2) Powder jetting, C) Selective laser sintering (SLS), D) Semi-solid extrusion (EXT), E) Fused deposition modeling (FDM).

2. DRUG DELIVERY SYSTEMS VIA 3D PRINTING

This section will highlight the diverse range of dosage forms that have been created through the utilization of 3D printing technologies. The focus of this inquiry is on research endeavors undertaken throughout the most recent quinquennium, spanning from 2018 to the present.

2.1. Tablets

For decades, 3DP has produced solid pharmaceutical dosage forms and others. Nevertheless, one formulation of levetiracetam (spritam) on the market was approved by the FDA in 2015. These tablets, which use the Patented ZipDose® technology [36]. As a production technique, it reaches Tmax in as little as 9 minutes, allowing for a fast onset of action. This technology has paved the way for treating epilepsy, especially in pediatric and geriatric populations with difficulty gulping tablets down [37].

In their study [38], Sadia and colleagues employed Hydrochlorothiazide (a BCS class IV medication) and used caplets with perforated tracks to speed up medication release from 3DP tablets, an innovative design method. They observed an increase in the surface area/volume ratio by including channels but emphasized that the width and length of the channel also influenced the broadcast pattern.

In 2018, By using FDM, Verstraete et al. planned to build ultra-drug-loaded dosage forms based on thermoplastic polyurethane (TPU) with a weight-to-weight concentration of more than 30% [39]. First, different particle sizes and the aqueous solubility of Theophylline and metformin were processed with various TPU ranks using filamentation using HME (hot melt extrusion). Thereafter, TPU-based filaments were printed into tablets and successfully refined into individualized doses rich in crystalline substances.

Furthermore, Goyanes et al., 2019 interpreted the first use of 3DP technology in a medical facility to evaluate personalized therapies to boost the reliance and admissibility of isoleucine supplementation in pediatric patients enduring Maple syrup urine disease (MSUD) [40]. Also, Chewable formulations printed

using the pectin polymer were approved by patients considering flavor and color; besides, they were shown to present a viable, rapid, and automated approach.

In 2019, the impacts of formulation and processing variability on the quality of tablets produced SLS 3DP utilizing the Box-Behnken response surface methodology were evaluated by Barakh Ali et al. Fourier-transformed infrared spectroscopy, X-ray powder diffractograms, Chemical images, scanning electron microscopy, and X-ray micro-CT scanning were among the tests used in the assessment. It was concluded that there was no chemical interplay between the formulation's ingredients pending the printing procedure and that the drug indicated a uniform distribution and showed a very porous microstructure in the printing parts with a porosity of roundly 37.89% [41].

In 2021, Xu et al. provided a report on the advancement of a portable 3D printer utilizing a mobile smartphone to streamline the manufacturing of point-of-care medicines. Working with stereolithographic principles, the printer produces the illumination emitted by the screen of a smartphone. The tablets containing Warfarin, which were printed in several sizes and shapes tailored to the needs of patients, demonstrated sustained release characteristics. The obtained results provide evidence for the prospective capabilities of a small, user-friendly, and networked smartphone-based system in the production of individualized pharmaceuticals [42].

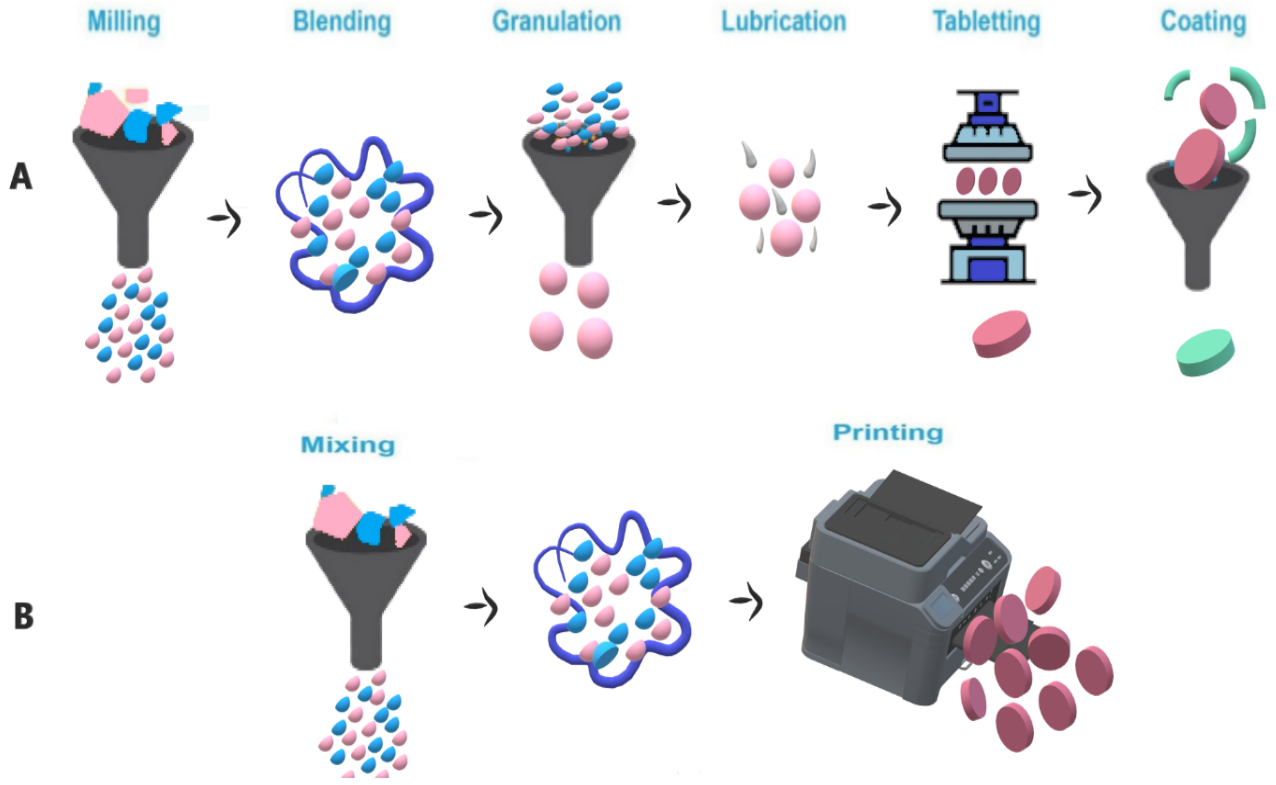

Figure 2. (A) The conventional procedure of tablet manufacture vs. (B) The manufacturing method of 3D printing

2.2. Capsules

The very first capsule to be made using 3D printing was produced in 2015 by Melocchi et al. For the manufacture of swellable abrasive capsules designed for the pulsatile delivery of drugs orally, filaments containing hydroxypropyl cellulose were formed by HME; subsequently, the filament underwent the process of 3D printing [43].

In 2018, Basit et al. produced four different polymer-based capsules to investigate gut behavior in rats. PVA-PEG, hydroxypropyl cellulose, ethylcellulose, and hypromellose acetate succinate were among the polymers selected, and FDM 3DP technology was used. The movement and disintegration of the produced capsules were followed by two types of tomography examinations after radioactive labeling with Fluorodeoxyglucose (18F-FDG). The EC constructs were not degraded within the gastrointestinal system of rats, while the PVA-PEG copolymer and HPC devices were degraded 60 min after oral administration and HPMCAS-based systems 420 min [44].

Individualized drug delivery studies continued to be explored in 2021 as drug efficacy and safety were improved for patients. Because existing gelatin capsules made using animal collagen protein release drugs too quickly and cause limitations, Gaurkhede et al. have created capsules that will advance personalized treatments. Capsule shells, consisting of mixtures of poly(vinyl) alcohol (PVA) and 5-25% hydroxypropyl methylcellulose (HPMC), were 3D printed and tested for acetaminophen delivery. Additionally, these shells provide a gelatin capsule substitute that does not involve the use of animals while also improving dissolution time compared to gelatin capsules. It was also observed that proportionately more HPMC was added to the blend, the release and dissolution were delayed, and the side effects of acetaminophen decreased [45].

A study by Rossi et al., also in 2021, involves the production and characterization of multi-compartment capsules made from FDM-processed PVA, considering a treatment strategy based on time-dependent release. Three different capsule types were made, each having a single reservoir, a double reservoir, and a triple reservoir. The dissolving periods fluctuated between around 180 and 390 minutes. Curcumin was used as a pharmacological model, and in vitro thermal evaluations were performed to determine how high temperatures might affect the polymer. Optical microscopy was also used to assess the uniformity of the dimensions. Results showed promise for using 3D-printed devices with little modifications for use as drug delivery items [46].

2.3. Vaginal Systems

One of the effective strategies for 3D printing, personalized and customized drug preparation, Vaginal rings are medical devices used for gynecological medicine administration purposes with a settled constitution, proportions, and drug doses [47]. Vaginal rings prepared by Fu J et al. consisted of a mixture of Progesterone, polyethylene glycol (PEG) 4000 combined with a blend of Tween 80 and Polycaprolactone (PCL) /Poly (lactic acid) (PLA) (2:8). The "O," "M" or "Y" shaped filament obtained by the hot melt method was used on an FDM printer to design the vaginal rings. The existence of progesterone in the rings was observed utilizing X-ray powder diffraction (XRD) and differential scanning calorimetry (DSC). While surface porosity and inner channel formation in the rings were observed due to PEG dissolution, thermal gravimetric analysis proved that progesterone did not deteriorate during the preparation. All three rings delivered continuous prolonged administration of progesterone for a duration beyond seven days, with the "O" one dissolving faster than the "Y" and "M" ones owing to its superior proportion and unusual form [48].

In 2021, an intravaginal ring was produced for Vulvovaginal candidiasis caused by a fungal pathogen, Candida albicans. Traditional treatment requires one or more applications per day with topical drug formulations (eg creams, gels, tablets), and daily use of oral antifungal medications for a duration of one month in case of relapse. Intravaginal rings, on the other hand, are superior to conventional drug formulations with their advantages, such as regulated vaginal medication delivery for a certain duration of time using a solitary application, enhancing patient adherence, and being flexible and biocompatible. With these advantages in mind, M Tiboni et al. fabricated a clotrimazole-loaded intravaginal ring by HME and FDM. Two distinct pharmaceutical substance concentrations (2% and 10% w/w) were printed on computer-designed rings. When their efficacy against C. albicans was evaluated in an agar diffusion test, the 10% loaded ring was chosen for further studies. Two distinct media, namely fifty percent ethanol and a vaginal analog fluid, were used to facilitate drug release. The researchers found a consistent and prolonged release of the medication over a duration of seven days. A time-kill investigation was conducted on Candida albicans in a simulated vaginal fluid medium, whereby full suppression of growth was seen over a period of 5 days. These results prove that these 3D-printed intravaginal rings are promising for treating vulvovaginal candidiasis and long-term treatment of relapses [49].

Another of the researchers working on vaginal rings was P Arany et al. FDM 3D printing was used to manufacture vaginal ring prototypes using thermoplastic filament. Subsequently, these rings were manually infused with gelled metronidazole or chloramphenicol for the purpose of treating vaginosis caused by bacteria. Thermogravimetric and heat flow tests assessed the requirement of filling by hand, while the dissolution profile was analyzed using the dissolving equipment. The non-toxicity of the polymer has been proven by long-term MTT testing on HeLa cells microbiological analysis was performed on E. coli and C. albicans. Samples containing only metronidazole or only chitosan showed a bacteriostatic effect, while samples containing metronidazole and chitosan showed a bactericidal effect. The samples had no fungistatic or fungicidal activity for C. albicans. As a result, 3D-printed vaginal rings filled with gelled metronidazole have been successfully produced [50].

Bacterial vaginosis (BV) is a condition characterized by an alteration in the vaginal microbiota, primarily attributed to the presence of Gardnerella vaginalis, a kind of permissive anaerobic bacterium [51]. The use of intravaginal tools composed of biodegradable and biocompatible polymers for the sustained release of metronidazole (MTZ) represents a significant improvement compared to existing antibiotic treatment options [52]. As a result, in 2023, E Utomo used SSE 3D printing to create intravaginal devices in two types (meshes and discs). For intravaginal devices, he also employed two distinct polymer layers consisting of PCL, as well as a mucoadhesive layer comprising a copolymer. Including this layer significantly enhanced the mucoadhesive properties of the absolute printed devices by around 5 times (from 0.52 to 2.57 N). The disc formulations, composed of a combination of high and low molecular weight PCL at a ratio of 50 percent each, exhibited a sustained release for a duration of nine days. In contrast, disc formulations containing ratios of 70 percent to 30 percent and 60 percent to 40 percent of high and low molecular weight PCL, respectively, demonstrated a release period of up to 72 hours. The results of the experiments show that changes in ratios didn't have a big effect on the release of MTZ. On the other hand, the form factor of the devices did have an impact on the introduction of MTZ, with those having a bigger area of contact. The antibacterial characteristics of intravaginal appliances incorporating MTZ were investigated, resulting within the observation of a zone of inhibition. The developed medication presents a viable alternative approach to the already established treatment based on the available data. This is attributed to its ability to provide a prolonged discharging MTZ, shortening the course of therapy and eventually improving the patient's outcomes [53].

2.4. Transdermal Therapeutic System (TTS)

Transdermal drug administration, also known as transdermal therapeutic systems (TTS), presents a compelling alternative to conventional oral and hypodermic insertion methods for administering drugs and is rapidly growing in influence on pharmaceutical drug design [54]. Microneedles (MNs), a novel invasive TDD method, are broadly utilized in cosmetology and medicine [55]. MNs establish a micro-scale canal into the dermis, allowing hydrophilic and macromolecules to be conveyed to the skin, although it cannot maintain a further impetus for drug transfer in tissue [56]. In the year 2022, a 3D-printed ultrasonic MN device will be used as a means to address this constraint. Ultrasound delivered through MNs has been observed to identify a motivating factor behind drug use penetration into the stratum corneum, hence significantly increasing modeling efficiency and reducing tissue damage caused by the insertion of MNs [57].

The use of artificial intelligence (AI) in the context of three-dimensional printing (3DP) eliminates the need for individual expertise since machine learning algorithms can accurately predict the ideal procedure characteristics [58]. Dissolvable MN patches employing ibuprofen (IBU) as a prototype medicine were effectively produced to distribute lipophilic API using DLP printing technology and AI algorithms. Enhanced printout accuracy and reduced needle accidents were achieved by implementing artificial intelligence techniques. The results of mechanical durability testing demonstrated that IBU MNs effectively formed porosity on human cadaver skin, hence maintaining drug permeability for a duration of seventy-two hours in subsequent skin permeability tests [59].

Biodegradable polymeric microneedle arrays (BPMNAs), a safe and painless method of drug delivery, can provide high drug charging capacity and elongated drug delivery once combined with a drug reservoir [60]. When preparing a BPMNA, A. Khosraviboroujeni et al. used estradiol valerate as the drug for the reservoir, while FDM used polylactic acid (PLA) for 3D printing and injection volume-filling techniques. As a result of the penetration, histological examination, and methylene blue staining tests, it was observed that 3D-printed PLA MNAs could penetrate the skin without achieving the dermal nerves and piercing the blood vessels [61].

Novel coverings with suitable bactericidal and biocompatible characteristics have been created for the purpose of facilitating healing and wound rejuvenation [62]. Manuka honey (MH) is a well-known natural antibacterial and also has favorable physiological consequences that have the potential to be advantageous in the context of regenerated wound care [63]. The research conducted in 2023 focused on the development and evaluation of antibacterial bandages made from Manuka-Gelatin in a three-dimensional format that provided high shape accuracy, structural stability, and controlled porosity. The addition of honey to the bandages, which are built on a combination of 3D Manuka and gelatin materials, facilitated the printing process and provided improvement. It has also been proven that the patches exhibit antibacterial activity and increase the promotion of angiogenesis [64].

2.5. Suppositories

Rectal drug delivery provides systemic and local therapeutic effects via suppositories [65]. While producing these dosage forms, systems with the exact dimensional requirements of the dosage form cannot be made in the traditional approach [66]. At the same time, this is avoided by using 3DP, patient-centered, and personalized drug therapy. In this context, in 2021, they used pressure support microsyringe technology to produce personalized lidocaine-laden suppositories by AT Chatzitaki. Similarities to nano-emulsifying drug delivery systems (SNEDDS) have been showcased in laboratory-generated efficiency and mechanical qualities. The potentiality of engaging in collaboration with 3D-printed personalized suppositories for local anesthesia with delayed lidocaine release was highlighted [67].

Ulcerative colitis is a state of inflammation placed inside the colon and is a worldwide medical issue impacting a vast number of individuals [68]. Rectal administration of immune-suppressive treatments, for instance, the drug tacrolimus, a narrow therapeutic index drug, offers some advantages [69]. While maximizing the drug concentration in the given area, systemic side effects are minimized [70]. Based on this, tacrolimus suppositories were produced in 2021 utilizing a pharmaceutical SSE 3D printer without the aid of mold. It has been published as two suppositories, Gel-44 and Gel-48, and both have been shown to let go of more than 80% of the drug within 120 minutes. The extrusion process of Gel-44 necessitated a lower energy input, disintegrated faster, and the ejection of tacrolimus was shown to occur at a slower rate in comparison to Gel-48 suppositories [71].

Acute severe ulcerative colitis (ASUC) is an inflammation localized in the rectum and colon that must be treated with multiple therapeutic agents, so topical administration using suppositories improves therapeutic outcomes [72]. Since (3D) printing allows the combination of multiple drugs and the formulation of individualized dose forms for each patient [73], a suppository was first produced in 2023 using SSE 3D printing to treat ASUC with two anti-inflammatory agents, budesonide and tofacitinib citrate. Performance enhancement for these two drugs, which are slightly water soluble, was achieved by the self-emulsification method of suppositories. Both suppositories exhibit similar disintegration and dissolution regardless of the drug ingredient, demonstrating the success and flexibility of 3D technology [74].

IBD, also called inflammation in the colon, comprises a group of systemic chronic inflammatory conditions that primarily impact the gastrointestinal tract [75, 76]. Infliximab, a kind of monoclonal antibody, has a significant role in the administration and therapy of IBD [77]. Infliximab has a macromolecular structure, and oral administration is not preferred because it prevents its passage through the digestive tract. In the rectal route, infliximab localized to the disease site preserves its bioactivity and integrity. In the study carried out in 2023 for the local treatment of IBD, SSE three-dimensional printing technology was employed in the manufacturing process of suppositories loaded with infliximab. Various printing inks containing Gelucire® (44/14 or 48/16) mixed with purified water and/or coconut oil were investigated. Infliximab reconstituted with water was incorporated directly into Gelucire® 48/16's writing ink as a solution, creating well-defined wicks and providing approximately sixty-five percent of the ability to bond. When the oil was introduced to the mixture, it enhanced the binding ability of infliximab, which rose to approximately 85%. The positive results of these studies provide evidence supporting the possibility of using 3D printing as a contemporary method for manufacturing administration forms [78].

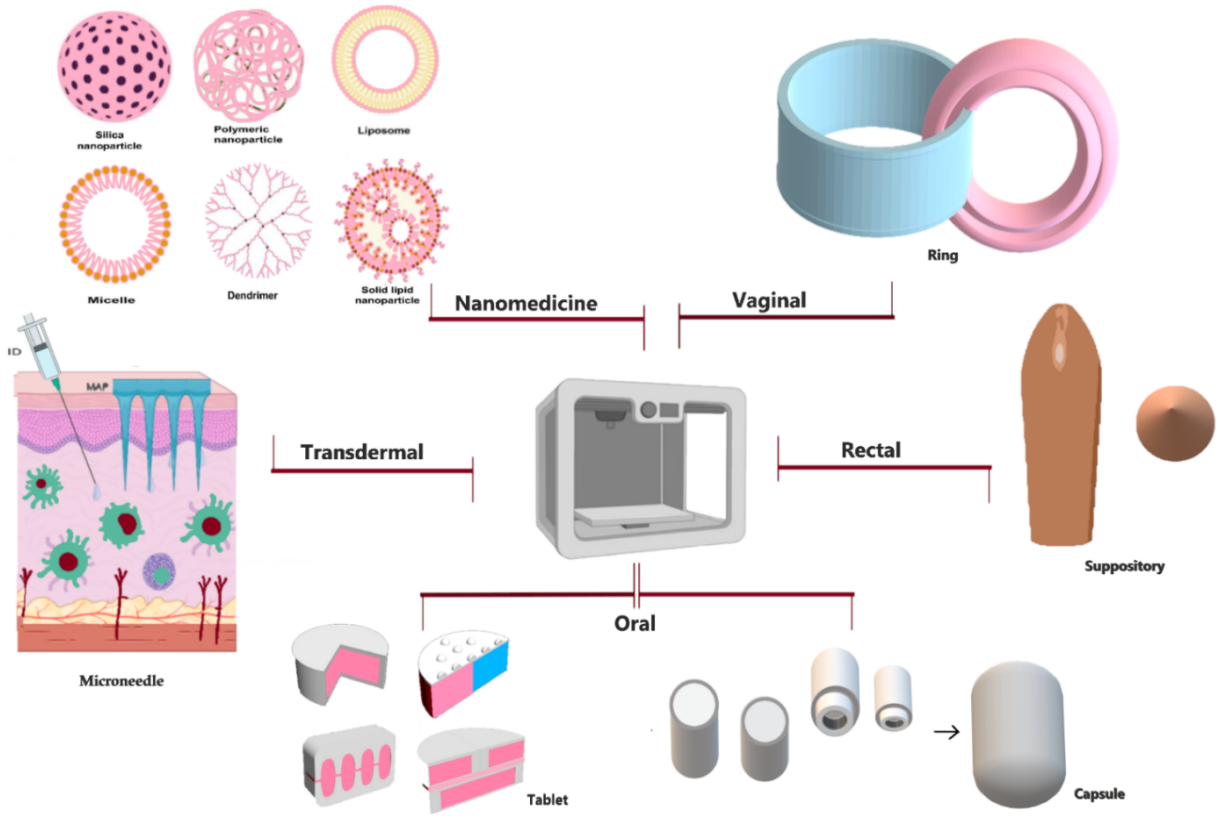

Fig. 3. Possible Structures of 3D Printed Dosage Forms.

2.6. Nanotechnology and 3D-Printed Medicine

Nanomedicine refers to using nanotechnologies in several areas of medical treatment, such as medication repurposing, specific drug administration, and developing theragnostic instruments [79]. Nanomedicine is a relatively new area that has garnered attention from researchers across all fields because of its potential for advancing scientific knowledge and fostering novel ideas [80]. Nanomaterials are currently employed in the field of composition as mixed substances to explore new possibilities, such as multimodal targeting, theranostic operations, and stimuli response releases [81]. Three medical fields that potentially benefit from the use of nanomaterials are nanodiagnostics, nanotherapy, and regenerative drug. Because of the disproportionately large amount of surface space that they possess to their overall volume, these tiny particles have a lot of surface energy and are very reactive, making them well-suited for a diverse range of therapeutic uses. Numerous nanomedicines exist, including carbon nanotubes, liposomes, micelles, liposomes, nanofibers, and nanoparticles. These may be further divided into organic and inorganic nanomedicines. There are several organic nanomedicines on the market; most of them are liposomes used to treat cancer and infectious diseases like Doxil, Onivyde, DepoCyte, and AmBisome. Moreover, inorganic nanomedicines, such as NanoHSA, Nanocoll, and SPIONS, perform the main part of the diagnostics.

2.6.1. Nanofibers

Nanofibers are a novel class of substances created of fibers with a nanometer diameter and display surface-to-volume ratio and high porosity [82]. These technologies have found applications in several domains, including medication delivery and the engineering of tissue, nanocomposites, and wound healing [83]. The utilization of 3D printing technology is a promising avenue for tailoring systems to meet specific demands. Consequently, researchers are now exploring its potential applications in the development of precision healthcare and nanomedicine designs [84]. In the research of R Olmos-Juste et al. in 2021, alginate-cellulose nanofibers (A-CNF) with CNF amounts up to 5% by weight were produced, and their printability was evaluated. It was observed that nanofibers containing less than 3% wt of CNF could not provide shape accuracy after printing, the selected ones were 3D printed and then freeze-dried to obtain porous scaffolds. CNF contributed to reinforcing the scaffolds and modulating their porosity. The A-CNF formulations were

then loaded with curcumin and successfully 3D printed in patches. The requirement of CNF for degradation of the scaffold was demonstrated in the in vitro evaluated release kinetics, and the importance of alginate and CNF for the stabilization of curcumin was also emphasized [85].

The integration of 3D-printed scaffolds with nanofibers presents a potential avenue for applications in the field of bone tissue engineering [86]. A structure composed of a biodegradable polymer was fabricated using 3D printing technology. This structure is designed to release deferoxamine, a substance crucial for promoting bone regeneration. Additionally, the structure was internally filled with gelatin nanofibers, and a scaffold was finally produced. Nanofibers facilitate cell adhesion and migration of 3D-printed scaffolds. In the in vivo study, it was observed that the DFO-loaded NGP scaffold provided vascularization and osteogenesis [87].

2.6.2. Nanoparticles

By utilizing 3D printing technology, pharmaceuticals can be manufactured, including personalized structures possessing predetermined architectural arrangements, porosity, porous dimensions, and exceptional repeatability [88]. However, nanoparticles have been employed to enhance similar scaffolds' surface area and physiological features [89]. In 2021, 3D PCL structures were fabricated without the inclusion of solvent using fused deposition modeling. The surface of the scaffolds was modified using plasma deposition and immobilization of silver nanoparticles techniques, thus maintaining the porosity and mechanical integrity of the scaffolds. While good biocompatibility was observed in scaffolds functionalized with nanoparticles, no enhanced angiogenesis and foreign body reaction were observed for in vivo studies [90]. In 2022, a new antimicrobial system was developed for the study on implant infection associated with Resistant Staphylococcus aureus. A scaffold including shell-core nanoparticles was developed using 3D printing technology. The nanoparticle was loaded with a plasmid containing an antimicrobial peptide, and its surface was subjected to grafting. The cells that continue to form as a result of the translation of the LL37 plasmid maintain the production of antimicrobial peptides, thus creating a long-lasting antibacterial effect [91].

Systems with high bioactivity and antibacterial properties are being developed for bone tissue regeneration [92]. In the research carried out in 2023, nanocomposites consisting of porous bioactive glasses (MBGs) embedded with metallic silver nanoparticles (AgNPs) were synthesized. The biological properties of Ag/MBG nanocomposites were investigated in accordance with preosteoblastic cell culture and bacterial tests. As a result of antimicrobial experiments, it was observed that bacterial growth inhibition and biofilm destruction increased as AgNPs increased in MBG matrices. 3D-printed scaffolds doped with AgNPs have demand applications for bone tissue regeneration [93].

2.6.3. Nanocapsules

Nanocapsules exhibit a spherical morphology and are liquid formations characterized by an internal hollow enclosed by a polymeric outer shell. These nanocapsules possess a size range spanning from 10 to 1000 nm [94]. Nanocapsules act as smart carriers, increasing bioavailability, safety, and efficacy, as well as being able to load a combination of hydrophilic and hydrophobic medicines [95].

3D printing of multi-component materials offers advantages over traditional methods [96]. In 2020, Rupp et al. Nano- and micro-filled PCL composites were produced by using two printing systems (FDM and a liquid inkjet print head). Composites with a core-shell capsule structure showed thermal stability up to 176 (°F) degrees Fahrenheit [97].

In the year 2022, a further instance of 3D-printed nanomedicines using drug-loaded nanocapsules was successfully implemented. The process included the encapsulation of resveratrol and curcumin into nanocapsules, which were then incorporated into a hydrogel made from carboxymethyl cellulose. The study revealed that full release of resveratrol and curcumin from solid oral forms occurred after a duration of 8 hours, notwithstanding their encapsulation in nanocapsules [98].

2.6.4. Hydrogels

Hydrogels are 3-dimensional structures that contain water networks in the construction of super absorbent and flexible hydrogels that offer high tension and self-healing properties [99]. Examples of current research in hydrogel using 3D printing technology are evaluated below.

It was produced by Extrusion-based 3D printing for a hybrid hydrogel bioscaffold in 2021 using different ratios and concentrations (3%, 5%, and 7%) of gelatin and alginate. As a result of the texture profile analysis, it was seen that the most suitable formula for 3D printing was the bio-scaffold produced with 7% 1:2 G/A hybrid gels and had the highest stiffness and stickiness. The application of scanning electron microscopy (SEM) has shown the capacity of 3D-printed scaffolds to encapsulate and provide several bioactive substances, including antioxidants and probiotics [100]. Owing to their favorable biological and structural properties, chitosan hydrogels are preferred in biomedical applications. 3D printing of chitosan-based hydrogels has attracted attention in the scientific world more recently. Chitosan hydrogels may now be used as a covering for ink or scaffolds in 3D printers [101].

3D printing of hydrogels offers great opportunities for the development of innovative systems as it can design custom shapes and structures [102]. Research on printable hydrogel materials with 3D printing techniques still continues [103]. In the study conducted in 2023, after the Hydrogel precursor resin was produced for 3D printing, it was cured using Pluronic P123 diacrylate and N-isopropyl acrylamide monomer, and a robust heat-sensitive hydrogel was formed. Thus, hydrophilic drugs are loaded at refrigerator temperature, and drug release continues at body temperature. The heat-sensitive hydrogels were then 3D-printed by loading hydrophilic drugs into a medical hydrogel mask large enough to fit and adhere to the human face [104].

3. CONCLUSION

Customized medication delivery methods rely heavily on three-dimensional printing due to its cost advantage, simplified manufacturing process, and ability to accommodate complex geometries. The efficacy of varied release profiles and designs is a contributing factor in the development of personalized dosage formulations. For the drug formulations generated using this technology to effectively align with future expectations, enhancements in factors such as solubility and speed are imperative. Furthermore, there is a need for enhancement in the printing process of nano-sized formulations. There is an anticipation that there will be a diversification and renewal of materials, such as ink and polymer, which currently impose limitations on the production of 3D printing. Spritam® was approved by the FDA in 2015; however, ongoing guidance is necessary to ensure the proper inspection of manufactured formulations. The bioprinting of living cells, an area of research within the field of pharmacy, holds great promise for future advancement.

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