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Advancements in 3D Printing Technologies for Pharmaceutical and Biomedical Applications

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3D printing technology has become a revolutionary tool in the fields of pharmaceuticals and biomedicine, allowing for the development of customized drug delivery systems and intricate tissue structures. This review analyses the primary 3D printing methods, including Fused Deposition Modelling (FDM), Stereolithography (SLA), Selective Laser Sintering (SLS), Inkjet Printing, and Digital Light Processing (DLP). It focuses on their utilization in creating accurate, personalized medications and cutting-edge biomedical devices. The incorporation of these technologies in tissue engineering and drug formulation underscores their capacity to propel personalized medicine and enhance therapeutic results.
Keywords: 3D printing in medicinal device, Medicinal delivery, Biomedical application, Three-dimensional printing.

1. Introduction

The first medication made with 3D printing technology, Aprecia Pharmaceuticals' Spritam, was approved by the US Food and Drug Administration in 2015. Although 3DP is not a novel approach to pharma product production, many view it as such. It is a collection of well-known technologies that were first created to create engineering prototypes. Thus, important technological characteristics, development histories, and related intellectual property landscapes need to be taken into account when thoroughly assessing its potential for medicinal application [1]

Recent scientific and technical developments have brought forth a number of advances, including the successful implantation of artificial organs and patient-specific dosage forms that transport and/or modify active pharmaceutical ingredients (APIs) [2].

Concrete, metals, ceramics, polymers, resins, biomaterials, and other things can all be considered among these materials. The range of materials that can be printed via 3D printing

is still somewhat small, even with recent advancements in printing speed, processing efficiency, and print resolution. Advances in sectors like 3D printing of biomaterials, tissues, and high-viability cells depend on printing ink's compatibility and flowability with existing printing processes. This paper describes the advancements in 3D printing materials and their compatibility with current printing technology for novel biomedical applications [3]

Sequential deposition of cells and biomaterials forms cell patterns in the additive process of bio-printing, the application of bio-printing techniques is growing in the field of tissue engineering. This innovative, multidisciplinary discipline builds structures with improved biological performance by fusing biology and engineering principles. In clinical applications, one of the main objectives of tissue engineering is to get beyond the drawbacks of existing therapies, which mostly rely on organ transplants and biomaterial implants. Problems with organs and tissues are serious threats to human health and well-being and need for specialized medical care, particularly in cases where the body is unable to heal itself [4]

In many industries, 3D printing is a technology that is revolutionizing the game. With the help of CAD, it can build three-dimensional objects piecemeal. Because of its remarkable precision and versatility, 3D printing has attracted a lot of interest in the field of medicinal delivery [5]. With the use of this state-of-the-art technology, materials may be carefully deposited and solidified, creating complicated shapes and exquisitely precise structures [6]

Given the great potential of 3D printing to bring about transformation in different industries, its use in medicine, specifically in drug delivery and tissue engineering, is particularly noteworthy. 3D printing's accuracy and ability to be tailored to specific needs enables the production of intricate, personalized solutions that were previously impossible using conventional manufacturing techniques. As the advancement of this technology progresses, it is essential to investigate and comprehend the compatibility and efficiency of novel materials, while also addressing the intellectual property landscapes associated with these advancements. This article seeks to explore the latest developments in 3D printing materials and their incorporation into current technologies, emphasising their impact on innovative biomedical uses and the future of personalized medicine.

Technologies for 3D printing types

Fused Deposition Modelling (FDM)

Stereolithography (SLA)

Selective Laser Sintering (SLS)

Inkjet Printing

Digital Light Processing (DLP)

Fused Deposition Modelling (FDM)

Bioprinting is still a relatively new field. Fused deposition modelling is a particular method used in 3D printing that uses extrusion.

FDM equipment is inexpensive and simple to use. Fused Deposition Modelling (FDM) products have superior reproducibility and printing accuracy, facilitating the production of complex structures. Thanks to 3D printing technology, FDM has emerged as a major field of

study in pharmaceutical preparation recently.

The creation of medication-loaded filaments is a crucial stage in the drug production process utilising FDM technology. There are two different methods for creating drug-loaded filaments: passive drug loading and active drug loading. Using the passive drug loading approach, polyvinyl alcohol (PVA) is submerged in a drug solution that is saturated, allowing the PVA filament to absorb the drug solution and eventually turn into a drug-loaded flame that may be printed after drying.

This approach works best with low-dose medications since the filaments it produces usually have a limited capacity to carry pharmaceuticals. Using hot melt extrusion (HME) to generate a drug-loaded filament is the fundamental step in the active drug loading process. This process boosts the potential of FDM and significantly increases the drug loading capacity of filaments. The ongoing development of FDM technology has resulted in 3D printer upgrades in recent years. The potential of FDM technology is being further enhanced with the development of multi-head printers. Figure 1 shows the fused deposition modelling.

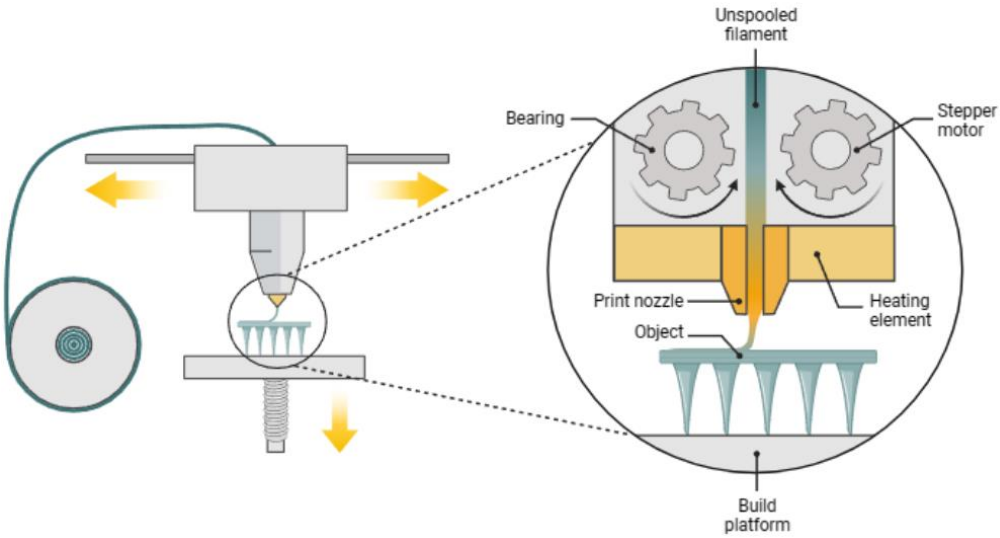

Figure 1 Fused Deposition Modelling (FDM)

Throughout the printing process, a multi-head printer can print simultaneously utilising various filaments. This development significantly raises the possibility of creating intricate structures using FDM 3D printing technology. Using FDM 3D printing, scientists have created a variety of oral tablet compositions with complex three-dimensional architectures. The preparations display unique releasing characteristics.

As a result of HC's superior thermal stability, researchers have used FDM to create customised HC oral tablet forms. The tablet's dimensions could be changed to vary the dosage, and it had a waif-like morphology. Furthermore, in an effort to maximise therapeutic efficacy for CAH patients, some researchers have developed HC sustained-release pills. Our inquiry into triple pulsatile HC pills was based on these studies.

In the current study, HC multi-pulsatile tablets were created using FDM [7]Figure 2 shows the Development of 3D Printed Drug Delivery Implants.

Giri et al. developed a novel method using hot melt extrusion (HME) to create drug-loaded filaments for use in fused deposition modelling (FDM) printers, enabling the production of printed in 3D tablets or gastro-retentive floating tablets (GRFT). GRFT can remain in the stomach for extended periods, preventing issues like inconsistent intestinal transit and metabolic degradation that commonly affect oral dose forms. Using a substance called cellulose (HPC) as the matrix and theophylline as the drug, the researchers produced drug-loaded the filaments through HME. They created tablets with varying shell thicknesses alongside infill densities, then assessed the medication content, dissolution rates, as physicochemical properties, and float behaviours of a resulting tablets.

Lamichhane et al. created floating gastro-retentive tablets with controlled release characteristics using FDM printing technology. Pregabalin-loaded filaments were made of hypromellose acetate succinate (HPMCAS) and polyethylene glycol (PEG 400). Using fused deposition modelling, cylindrical tablets with different infill densities were created (FDM). Thermogravimetric analysis (TGA), Fourier-transform infrared (FTIR) spectroscopy, an X-ray powder diffraction (XRPD), and distinct scanning calorimetry (DSC) were used to examine the properties of the resultant tablets. The results demonstrated that the printing and extrusion processes had no effect on the stability and crystallinity of the drug. It was demonstrated that the printed tablets' ability to float depended on the existence of a top and bottom layer.

Specifically, open systems failed to float, but closed systems maintain buoyancy for more than twenty-four hours.

Furthermore, compared to both open and closed systems with a high infill ratio, open systems with a low infill proportion demonstrated a faster drug release. They improved the formulation as a resultcreating a form of tablet having a top surface that is partially open and a bottom surface that is closed. For a full day, this formulation maintained its floating ability and demonstrated a zero-order drug release. This study shown that the fabrication of floating gastro-retentive tablets is a viable use for FDM printing technology [8]

Stereolithography

Stereolithography (SLA) is now on the market and have been investigated as possible drug delivery fabrication techniques. Martinez and colleagues, for instance, looked into the potential of SLA in the creation of sustained release dose forms and discovered how the rate of drug release could be changed by adjusting its aqueous content in a formulation.

Stereolithographic printing

A Formlabs Form 2 SLA 3D printer (Formlabs Inc., Somerville, MA, USA) with a 405 nm wavelength light source was used for all stereolithographic printing. The resolution of an SLA-style printer enables for the fabrication of items having layer thicknesses of 25, 50, or 100 µm. SolidWorks 2017 was used to create the oral dosage form, Afterwards, it was transmitted to the printing software, namely version 2.15.1, as an STL file. The printer's "Open Mode," which turns off the resin dispensing, heating, and wiping functions, was activated in order to print using the prepared photopolymer resin.

The stereolithographic print technique

Photocurable materials and concentrated ultraviolet (UV) radiation are used in stereolithography (SLA) to build solid 3D forms. This method is based on photopolymerization, in which UV light starts a chemical reaction that turns a liquid monomer into a solid polymers. The inclusion of light-sensitive substances known as photoinitiators starts the polymerization reaction. These substances become active at the right wavelengths and create radicals that are free from the light energy that was received.

The reaction that transforming a fluid monomers into a solid form—also known as a crosslinked hydrogel—then consumes these free radicals. It is a single-molecule that, when exposed to light of the right wavelength, photocleaves into radical fragments.

Photopolymer solutions have to be ready for loading into a SLA 3D printer in order to create the medication dosage forms. The ratios used were based on rheological profiling of earlier formulations as well as lab trials. The PCL Triol is a biodegradable, translucent aliphatic polyester containing a mild melting point and a small molecular mass. It has been intensively studied for its potential use in pharmaceutical delivery systems and as a biomaterial.

Additionally, the possibility for low molecular weight PCL Triols to function as plasticizers has been studied; Kanis et al. suggest that a group of hydroxyl groups that exist are what enable it to do so. Furthermore, while PCL Troise cannot crosslink on their own and do not natively have photopolymerizable terminal categories, PCL derivatives have been developed. Additionally studied to be utilised as a plasticizer and in pharmaceutical applications is poly(ethylene glycol) (PEG) which lacks the ability to crosslink like PCL Triol.

Poly(ethylene glycol) (PEG) is a man-made polymer substance that has been around for a while. PEG-based hydrogels have been extensively studied in the literature because of the remarkable qualities they provide, like nontoxicity, biocompatibility, and remarkable tunability. They are also FDA-approved for use in a range of clinical applications.

It was found that the model drugs, aspirin and paracetamol, easily dissolved within the respective photo polymer formulations. The solutions exhibited transparent hues, while the 3DP dosage forms displayed identical colours. Despite the model medications' low concentrations, the authors chose these concentrations based on Goyanes et al.'s previously reported contributions. Creating topical drug delivery systems that include salicylic acid, the main aspirin metabolite, at 2.00% w/w. Furthermore, paracetamol loadings of The concentrations are 5.90% weight/weight and 4.00% weight/weight were created in dosage forms by Martinez et al., and Wang et al., respectively. The formulations are meant to show off the AM technique's potential for customised batch manufacturing in a therapeutic setting, although the amounts used aren't instantaneously therapeutically significant. Martinez et al. utilised solid lipid extrusion (SLA) to create a multi-layered polypill by combining 10.00% weight by weight of two model medicines with four additional model drugs. This suggests that the scientists suspect that increasing the amount of drug is possible.

The two active components in aspirin and paracetamol have different pKa values (3.5 and 9.5, respectively).

The geometry to be printed was chosen to be a rectangle. It demonstrates the potential of 3D printing in personalized medicine by showing that 28 tablets can be produced in a single

print [9]

Selective laser sintering

The SLS technique, referred to as quick three-dimensional printing technology, provides a method of manufacture that is free from solvents and may be completed in a single step. This technique employs a beam of laser energy to precisely fuse powdered substances together, resulting in the formation of three-dimensional objects arranged in layers. Up till now, SLS has demonstrated remarkable adaptability, allowing it to create a vast range of dose forms with various forms and delivery properties, such as immediate and modulated release dosage forms and orally disintegrating tablets. Due to the laser's exceptional accuracy, it is feasible to produce complex lattice shapes with customisable internal designs that would be unachievable by conventional production methods. The SLS 3DP system's excellent resolution might make it a good choice for developing multi-particulate drug delivery systems.

It was successful to use SLS 3DP to produce miniprintlets with two distinct diameters—1 mm and 2 mm. The primary polymer matrix used was ethyl cellulose, while the model medication used was paracetamol. It was discovered that a scanning velocity of 50 mm/s using a laser could effectively bond successive printing layers while preserving the miniprintlets' intended size and shape. For this reason, that speed was chosen. A single set of 100 miniprintlets measuring 1 mm each required around two minutes for printing, but a set of miniprintlets measuring 2 mm each took around two minutes and forty seconds to print. In addition, two miniprintlets were developed for the purpose of multi-drug therapy, with distinct layers containing ibuprofen and paracetamol. The double miniprintlets were produced in two separate dimensions, specifically one millimetre and two millimetres, mirroring the size options of the one miniprintlets. The double miniprintlets were created using 2 drug combinations. One medication was dispersed in Kollicoat IR, which is an immediate release polyethylene glycol/polyvinyl alcohol graft copolymer. The second medication is evenly distributed within ethyl cellulose. Ibuprofen along with paracetamol were selected for the test drugs due to previous studies indicating that their combined use yields a greater synergistic effectiveness compared to using them alone.

A set of 100 dual mini print-lets measuring 1 mm required roughly two minutes and 30 seconds for printing, whereas a set of mini print-lets measuring 2 mm took approximately three minutes and forty seconds to print. The powders were added by hand, requiring extra surface heating, thus the duration was a little longer than for the single mini print-lets. The option to combine various APIs with distinct release profiles within a single mini print-let is provided by the use of dual mini print-lets. The use of both instant and extended release forms in the composition of the mini print-lets may have advantages, such as easier dosage and less frequent ingestion. while offering analgesic and antipyretic benefits that are more durable. As a result, medication combinations with varying dosages and the same ratio of active pharmaceutical ingredients might be created to meet the needs of patients in various age groups.

When it comes to paediatric and elderly patients, where dose changes are necessary because of differences in pharmacodynamic and pharmacokinetic features, the creation of a patient-centric platform may be especially helpful. The usage of the mini print-let platform is far

easier and more effective than previously suggested methods for personalised drugs since it eliminates the need to change the dosage form's dimensions or shape, both of which could have an impact on the drug release. By using this innovative strategy, the treatment plan may be improved and shifted from a "one size fits all" strategy to customised medications, which are safer and more efficient. Mini print-lets created with SLS 3DP offer a distinctive method of delivering medication that provides excellent flexibility and precise control over the drug content and release characteristics. The combination of two rate-controlling mechanisms in small and intricate pharma dose forms enables the distinct construction of each drug. This highlights the technology's worth and sets it apart from other commercial fabrication techniques used in the manufacturing of medications [10]

Digital light processing (DLP)

The light source that is utilised to cure the resin is the only real distinction between DLP and SLA, making it a "sister technology" to SLA Digital light processing 3D printing machines utilise a custom digital lighting projectors screen as the light source, while SLA printers employ lasers and galvanometers to solidify the resin. Because of its screen, Digital Light Processing is commonly regarded as more efficient and faster than SLA. Both DLP and SLA technologies face limitations because to the scarcity of photo cross linkable polymer that are appropriate for medical purposes and the exclusion of certain chemicals from the generally recognised to be harmless (GRAS) category of additions. Figure 2 shows the process of DLP 3Dprinting.

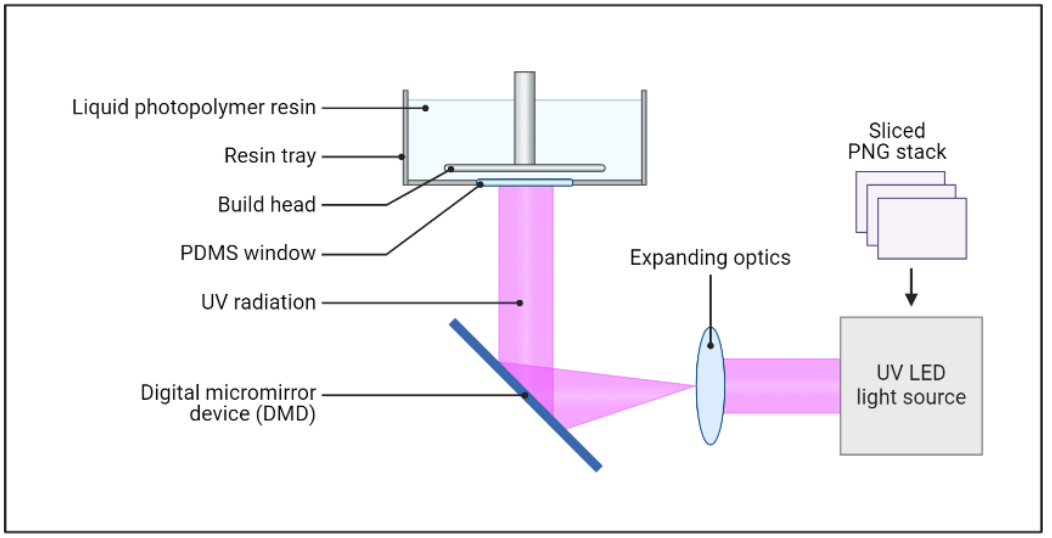

Figure 2 Diagram illustrating the process of DLP 3-D printing

There is currently relatively little research being done on DLP-based oral medication delivery. When Wang et al. created print-lets filled with paracetamol and 4-aminosalicylic acid, they observed there is no degradation of drugs throughout the process of 3D printing. A DLP printer utilising the photopolymerization method was used to produce print-lets, which are solid oral medication forms. While the SLA printers operate by printing each layer

sequentially in a linear pattern, the Digital Light Processing (DLP) printer it offers expeditious and effective print by illuminating a full layer all at once. DLP printer offers the advantage of having open software, allowing users can alter settings to achieve precise printing results for a given blend.

Printing process

Print-lets with an exposure period of 100 s were successfully created using screening formulations containing 5.0% water. The resins failed to form over shorter exposure durations. The duration of the process was extended due to the need for an exposure period of not less than 400 seconds in order to achieve a rise in water content of up to 10.1%. Nevertheless, due to the presence of 30.0% water in the formulation, printing could be achieved with an exposure length of 800 sec. The water content had an impact on how long the formulation was exposed to the light projector; as a result, a longer exposure time was needed when the water content increased. This was a requirement for choosing the printing parameters that were given. In order to minimise printing time, lidification was chosen. Due to the absence of standards for determining procedure variables for mixture containing photopolymers used in medicinal product manufacturing, it is necessary to find suitable printing settings for each formulation through a trial-and-error approach. Robles-Martinez et al. conducted a study that made a comparable observation.

By employing riboflavin as a photo-initiator in combination with PEG400, PEGDA, and water as the main components, it is possible to create extended-release ibuprofen printlets utilising Digital laser printing technology, which is a type of 3D printing method. Excipients have an impact on printing success, hence printing parameters must be adjusted for each composition [11]. The relationship between drug release and excipients in the investigated formulations is intricate and characterised by non-linearity. In order to achieve the desired drug release in printlets, artificially generated neural networks, known for their ability to generalise, can be a valuable tool for understanding the effects of the excipients on printlet characteristics.While there isn't a single programme or modelling approach that can handle "all" problems, applying a variety of programmes can aid with prediction and optimisation. It has been shown that a sufficient artificial neural network (ANN) can comprehend the input-output relationship in pharmaceutical DLP printing [12]

Inkjet Printing

An essential auxiliary method utilised in numerous 3D printing methodologies in the field of pharmaceutics is the compaction of powders through the application of binder solutions employing inkjet printing. An example of such an application is Spritam (levetiracetam), which is the first pharmaceutical product approved by the FDA and made using 3D printing technology. It is specifically used for treating epilepsy. In nozzle-based inkjet printing, the production of micro-to pico-litre sized droplets often involves the utilisation of thermal or mechanical generated rushes to obtain very high shear rates in fluids. A study showed that mammalian nerve cells, which may have a tendency to be fragile, can endure significant degrees of stress during the printing process. The two types of inkjet printing technologies are DOD ink jet and continuous ink jet (CIJ). In a CIJ system, a charging electrode and an applied electric field cause a stream of droplets to be continually expelled. A catcher receives the uncharged raindrops. A voltage waveform in a DOD printing system can be used to expel

the droplet [13]. There were several techniques presented, including drop impact printing, surface acoustic waves (SAW) printing, acoustophoretic printing, aerosol jet printing (AJP), laser-based printing, electrohydrodynamic (EHD) jet printing, and needle-based printing. Continuous inkjet printing (CIJP) and drop-on-demand (DoD) printing technologies have been utilized in the pharmaceutical industry. These printing methods have found applications within the pharmaceutical field [14] Figure 5 shows the continuous mode and on- demand mode.

Continuous inkjet printing (CIJP)

Continuous Inkjet Printing (CIJP) use a pump with high pressure to propel the ink into the nozzle, thereby creating an uninterrupted flow of ink. The uninterrupted flow is then fragmented into discrete drops as a result of the surface tension forces.. The frequency at which the stream is broken into droplets can be adjusted to control the formation of the ink droplets. In order to create a particular printed design, the ink droplets are charged selectively as they pass between electrodes that apply an electric charge. The charged droplets subsequently pass through deflector plates, generating an electrostatic field. The electrified droplets are expelled onto the surface, while the non-electrified droplets are sent back into the system to be reused. The mechanism behind droplet formation and the incorporation of deflectors in continuous inkjet printing (CIJP) have been studied extensively. Figure 5 shows the continuous mode and on- demand mode.

Drop-on-demand (DoD)

Drop-on-demand (DoD) printing methods utilise electrical impulses to expel small quantities of liquid. DoD printheads can be classified into two main categories: thermal and piezoelectric. Thermal Drop-on-Demand (DoD) printheads utilise electrical signals to elevate the temperature of the liquid to a range of 200–300 °C, resulting in the formation of bubbles that enlarge and expel the fluid via the nozzle, thereby producing a droplet. Piezoelectric Drop-on-Demand (DoD) printheads utilise piezoelectric components that undergo deformation in response to an electric current, resulting in the ejection of a droplet. Due to its high precision and automation capabilities, DoD is widely used in pharmaceutical applications, enabling precise control over ink deposition [15]

Table 1. Three-dimensional printing technologies, mode of action, benefits and drawbacks

Three-dimensional printing technologies	Mode of action	Benefits	Drawbacks
Fused deposition modelling	3D objects are formed by depositing materials through a nozzle or aperture in a controlled manner, resulting in a layer-by-layer pattern.	Cost-effective, small-sized machinery, wide range of easily accessible, environmentally safe and non-polluting resources, capability to produce intricate, groundbreaking, and personalised medication formats	The need for a solvent, temperatures and crosslinking agents, challenges in recycling printing materials, potential risks of medication and excipient degradation, poor printing speed, and delamination are all factors to consider.
Selective laser sintering	The process involves the melting and fusing of thermoplastic polymers with high melting points, along with binding powder components that have lower melting points.	The porous structures may be fabricated with precision and high resolution (30 μm) , allowing for speedier production without the need for post curing.	Significant loss of powder material, inefficiency, high cost, a lack of suitable pharmaceutical ingredients and additives in the process.
Inkjet printing	Significant loss of powder material, inefficiency, high cost, a	Printing technology provides exceptional resolution and accuracy,	Issues such as low friability, nozzle clogging and hardness are present.

	lack of suitable medicinal products and additives in the process.The sprayed formulations or binder selectively adhere a tiny amount of the medicinal ingredient and additives to a stable basis in the form of microdots.	together with efficient and cost-effective high-speed production. In addition, printing with a wide range of materials.	
Continuous inkjet	An electrostatically guided pressurised spray of droplets (50–80 μm) is utilised to solidify the material.	Increased drop velocity resulting in extended coverage, prevention of nozzle blockage, and accelerated output	There is a significant amount of ink that is wasted because of recirculation, and there is a limited supply of solvent-based inks.
Binder jetting	Polymeric powder or solid particles mixed with a liquid binder.	The capability to generate porous structures, utilise multi-material printing, and eliminate the requirement for support structures.	Restricted assortment of materials, inadequate structural integrity
Drop on demand	Multiple nozzles, either thermal or piezoelectric, are used to emit droplets with a size range of 10-50 μm.	Rapid solidification, cost-effective	Prone to nozzle obstruction, leading to imprecise jetting and droplet dispersion.
Selective laser sintering	The process involves the fusion and melting of polymers that are thermoplastic with high melting points, along with binding powder components that have lower melting points.	The porous structures may be fabricated with precision and high resolution (30μm), allowing for speedier production without the need for post curing.	The process is expensive, inefficient, and results in significant wastage of powder materials. Additionally, there is a scarcity of suitable medicinal products and excipients for the method.
Stereolithography	A laser beam is used in a computer mirroring device to trigger a photochemical process that converts a liquid monomer into a solid object.	Drug delivery systems offer exceptional accuracy and resolution, allowing for precise customisation of release patterns. They minimise drug breakdown and are designed to be small and efficient. These systems are ideal for developing personalised dosage forms in a clinical context and have minimal mechanical anisotropy.	The use of biocompatible photopolymerizable polymers is limited due to low drug loading capacity, potential toxicity, and the need for rinse and post-curing processes. Additionally, these polymers are not widely available.
Digital light processing	A beam of laser light is projected through a digital mirror device.	Manufacturing with both high speed capabilities and high resolution .	Requesting assistance with toxicity.

Techniques for 3D printing in delivery systems

Gastro Retentive Drug Delivery

Colon-Targeted Drug Delivery

Intrauterine Drug Delivery

Transdermal Drug Delivery

Gastro-retentive administration of drugs

Gastric floating tablet compositions provide numerous benefits, such as boosted drug bioavailability, delivery that is specific to a certain location or site, continuous medication delivery, enhanced absorption of the drug into the bloodstream, increased adherence to medication by patients. An innovative levitating drug delivery system has been reported that combines a tablet with air-filled chambers, fabricated using fused deposition modelling

(FDM) 3D printing technology and polylactic acid (PLA) filament. It contains a tablet core loaded with the model drug riboflavin. The tablet is encapsulated within air-filled chambers created through the 3D printing process. The use of FDM 3D printing with PLA allows for the customized design and construction of the floating device. This integrated tablet-in-device approach, enabled by 3D printing, aims to provide extended gastric residence time and controlled drug release from the floating delivery system. The ability to precisely engineer the geometry and composition using additive manufacturing techniques can lead to improved performance and personalization of gastric floating drug products [16]

Colon-Targeted Drug Delivery

Delivering drugs specifically to the colon offers several advantages, including minimizing systemic side effects, reducing the required drug dose, ensuring the medicine remains undamaged when it reaches the desired location. Traditional methods of delivering drugs to the colon utilize various approaches to achieve targeted release, such as The medication has a covalent relationship with an agent. Polymers that exhibit solubility, swelling, erosion, or enzymatic breakdown that is dependent on the pH. Bioadhesive polymers. Osmotic delivery systems for drugs. 3D printing has become an new and innovative way of delivering drugs to the colon. Studies have reported. The tablet shells were produced using FDM printing technology and PVA filament. They were designed to have empty interiors and were filled with different amounts of the medicine. This design allowed for controlled release of the drug specifically in the colon. The study achieved effective transportation of budesonide through the small intestine to the colon by utilising PVA filaments through 3D printing using FDM technology, in addition to hot-melt extrusion (HME) and a fluid-bed coating. Development of printed using 3D printer tablets incorporating various medicines with varying rates of release. These 3D printing approaches, often combined with other technologies like HME and coating, enable the development of customized colonic drug delivery systems with enhanced targeting and controlled release capabilities. The flexibility of 3D printing allows for the fabrication of complex geometries and incorporation of multiple drugs, advancing the field of site-specific and personalized colonic drug delivery[17]

Intrauterine Drug Delivery

Vaginal rings are a type of gynaecological drug delivery device designed to release a consistent dose of medication. Researchers have developed a novel approach to create personalized vaginal rings using 3D printing technology. 3D-printed vaginal rings in various shapes (‘O’, ‘Y’, or ‘M’) using FDM printing. The printing filaments were created by combining and heating an unstructured solid combination that includes progestin with the polymer blend of PCL/PLA (8:2 ratio) and Tween 80. This innovative approach allows for the creation of customized vaginal rings tailored to individual needs, enhancing the efficacy and patient compliance of progesterone delivery. The use of 3D printing enables precise control over the ring's geometry and composition, ensuring optimal drug release profiles and minimizing side effects. The incorporation of amorphous solid dispersion and polymer blends helps maintain the stability and bioavailability of progesterone during delivery [18]

Transdermal Drug Delivery

Transdermal drug delivery systems offer several advantages, including enhanced therapeutic efficacy and improved patient compliance. Researchers have explored various 3D printing techniques to fabricate microneedle arrays for enhanced transdermal drug delivery. Polymer coating on metallic microneedles as a significant enhancement of transdermal permeation was observed when using polymer coatings containing antineoplastic drugs (5-fluorouracil, curcumin, cisplatin) on metallic microneedles in porcine skin models. Dissolvable microneedles fabricated using piezoelectric DoD inkjet printing. The adaptability of piezoelectric drop-on-demand (DoD) inkjet printing has been demonstrated for fabricating dissolvable microneedles. We can combine 3D printing techniques to create biodegradable microneedles. Micro-molding, Micro-stereolithography, and piezoelectric elements inkjet printers can be used together to create disposable microneedles that are wrapped in amphotericin B. These 3-D printing approaches enable the creation of customized microneedle arrays with enhanced drug loading, improved skin permeation, and controlled drug release. The flexibility of 3D printing allows for the incorporation of various drugs, including antineoplastic agents and antifungals, into the microneedle design. The use of dissolvable and biodegradable materials ensures the safe and effective delivery of drugs through the skin, while minimizing pain and improving patient acceptance.

Clinical Benefits of 3D Printed Prosthetics and Implants

The clinical advantages of three-dimensional printed objects have been proven in the creation of prosthetic devices as well as injectable medical items. The primary benefits of three-dimensional printing in this field are Prosthetic devices for the lower leg and wrist that are created using 3D printing technology have been developed after amputations, providing a personalized fit and functionality. 3D printed artificial ears have been fabricated using materials like polycaprolactone (PCL), polyethylene glycol, and cell-enriched hydrogels [19,20] A novel technique for producing affordable soft tissue prosthesis has been showcased, utilising a desktop 3D printing process that encompasses scanning, printing, polishing, and casting. These 3D printed prosthetic and implantable devices offer improved patient-specific fit, enhanced functionality, and reduced costs compared to traditional manufacturing methods. The ability to customize the design and composition of these medical products using additive manufacturing techniques has significant clinical benefits, leading to better patient outcomes and improved quality of life [19,20]

Table 2. Utilising 3D Printing Technology for Certain Drug Implants, Mouth Guards, and Nose Masks

AIM	DRUG	POLYMER	3D PRINTING TECHNOLOGY	KEY POINT
The T-shaped uterine gadget and injectable needles.	Indomethacin	Ethylene vinyl acetate	The processes of hot- melt fused deposition modelling and fused deposition modelling are utilised using the Makerbot Replicator 2X, a product of Makerbot Inc. based in NY, USA.	Ethylene vinyl acetate can serve as a raw material for 3D printing in order to create prototypes of implantable devices that are loaded with drugs.
Treatment of osteosarcoma	Ifosfamide, methotrexate, doxorubicin	Poly L-lactic acid	Stereolithography 3D printer Zcorp Zprinter 650	Treatment of osteosarcoma using regionally administered, multi-drug chemotherapeutic and non-reoperation techniques for durable results.
Controlled release	Ethinyl estradiol	Poly(ε-caprolactone), poly	Theriform™ is a three-dimensional printing technology developed by	Implantation resulted in the suppression of the follicle-

		(lactideco-glycolide)	Therics Inc. in Princeton University, NJ.	stimulating and the production of lute hormones. The blood profile can be forecasted based on the in- vitro release.
Constant slow release	Isonicotinic acid hydrazide	Poly L-lactic acid	Fochif Mechatronics Technology Co. Ltd., Shanghai, China	The multifunctional doughnut-shaped tablets demonstrated a consistent and gradual release pattern in a laboratory setting over a period of thirty days.
Patient-specific wound dressing	Silver nitrate, copper sulphate, zinc oxide	Polycaprolactone	The three-dimensional scanning device being referred to is the Sense™ three-dimensional scanner, manufactured by 3D Systems Inc., a company based in the United States. FDM and HME are two additive manufacturing techniques employed by the Makerbot Replicator 2X, a three-dimensional printer developed by Makerbot Inc. in New York, the United States.	The integration of three-dimensional imaging and three-dimensional printing enables the creation of customised dressings for injuries specifically designed for the nasal cavity and hearing.
Wearable personalized oral delivery mouth guard	Clobetasol propionate	Polyvinyl acetate with Poly L-lactic acid	A dental scanning model and CAD system that is freely available.	Drug-eluting systems produced using three-dimensional printing have the capability to be tailored with regard to of their dimensions, form, and rate of drug release.
Personalised nose mask	Beta hydroxy acid	Polyurethane, Polycaprolactone, and Poly L-lactic acid	The three-dimensional scanning device being referred to is sense™ 3D scanner, manufactured by three-dimensional systems Inc. in the United States. FDM and HME are two techniques used in three-dimensional printing. The specific 3D printer model mentioned is the Makerbot Replicator 2X, manufactured by Makerbot Inc. in New York, the United States. The Stereolithography 3D printer from Formlabs, UK, utilises the technique of stereolithography.	The combination of three-dimensional scanning and SLA printing has the capacity to create personalised drug-loaded devices that are tailored in terms of their dimensions and form.
Complex release profile	Levofloxacin	Poly L-lactic acid B	Fochif Mechatronics Technology Company Limited., located in Shanghai, China, specialises in printing using inkjet technology	The release profile displays two distinct modes, characterised by alternating pulsatile and steady state patterns.

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References

1. Hsiao W-K, Lorber B, Reitsamer H, Khinast J: 3D printing of oral drugs: a new reality or hype? Expert Opin Drug Deliv. 2018, 15:1–4. 10.1080/17425247.2017.1371698
2. Al-Dulimi Z, Wallis M, Tan DK, Maniruzzaman M, Nokhodchi A: 3D printing technology as innovative solutions for biomedical applications. Drug Discov Today. 2021, 26:360–83. 10.1016/j.drudis.2020.11.013
3. Thakkar R, Pillai AR, Zhang J, Zhang Y, Kulkarni V, Maniruzzaman M: Novel On-Demand 3-

Dimensional (3-D) Printed Tablets Using Fill Density as an Effective Release-Controlling Tool. Polymers (Basel). 2020, 12:1872. 10.3390/polym12091872
4. Fina F, Goyanes A, Rowland M, Gaisford S, Basit AW: 3D Printing of Tunable Zero-Order Release Printlets. Polymers (Basel). 2020, 12:1769. 10.3390/polym12081769
5. Elkasabgy NA, Mahmoud AA, Maged A: 3D printing: An appealing route for customized drug delivery systems. Int J Pharm. 2020, 588:119732. 10.1016/j.ijpharm.2020.119732
6. Kantaros A: 3D Printing in Regenerative Medicine: Technologies and Resources Utilized. Int J Mol Sci. 2022, 23:14621. 10.3390/ijms232314621
7. Chen H, Zheng K, Bu T, Li X, Wang X, Pan H: Fabrication of 3D-Printed Hydrocortisone Triple Pulsatile Tablet Using Fused Deposition Modelling Technology. AAPS PharmSciTech. 2024, 25:58. 10.1208/s12249-024-02757-2
8. Mathew E, Pitzanti G, Larrañeta E, Lamprou DA: 3D Printing of Pharmaceuticals and Drug Delivery Devices. Pharmaceutics. 2020, 12:266. 10.3390/pharmaceutics12030266
9. Healy A V., Fuenmayor E, Doran P, Geever LM, Higginbotham CL, Lyons JG: Additive Manufacturing of Personalized Pharmaceutical Dosage Forms via Stereolithography. Pharmaceutics. 2019, 11:645. 10.3390/pharmaceutics11120645
10. Awad A, Fina F, Trenfield SJ, Patel P, Goyanes A, Gaisford S, Basit AW: 3D Printed Pellets (Miniprintlets): A Novel, Multi-Drug, Controlled Release Platform Technology. Pharmaceutics. 2019, 11:148. 10.3390/pharmaceutics11040148
11. Madzarevic M, Medarevic D, Vulovic A, Sustersic T, Djuris J, Filipovic N, Ibric S: Optimization and Prediction of Ibuprofen Release from 3D DLP Printlets Using Artificial Neural Networks. Pharmaceutics. 2019, 11:544. 10.3390/pharmaceutics11100544
12. Robles-Martinez P, Xu X, Trenfield SJ, et al.: 3D Printing of a Multi-Layered Polypill Containing Six Drugs Using a Novel Stereolithographic Method. Pharmaceutics. 2019, 11:274. 10.3390/pharmaceutics11060274
13. Alva C, Vidakovic I, Lorber B, et al.: Can Liposomes Survive Inkjet Printing? The Effect of Jetting on Key Liposome Attributes for Drug Delivery Applications. J Pharm Innov. 2023, 18:497–505. 10.1007/s12247-022-09643-z
14. Shah MA, Lee D-G, Lee B-Y, Hur S: Classifications and Applications of Inkjet Printing Technology: A Review. IEEE Access. 2021, 9:140079–102. 10.1109/ACCESS.2021.3119219
15. Carou-Senra P, Rodríguez-Pombo L, Awad A, Basit AW, Alvarez-Lorenzo C, Goyanes A: Inkjet Printing of Pharmaceuticals. Advanced Materials. 2024, 36:. 10.1002/adma.202309164
16. Fu J, Yin H, Yu X, Xie C, Jiang H, Jin Y, Sheng F: Combination of 3D printing technologies and compressed tablets for preparation of riboflavin floating tablet-in-device (TiD) systems. Int J Pharm. 2018, 549:370–9. 10.1016/j.ijpharm.2018.08.011
17. Charbe N, McCarron P, Lane M, Tambuwala M: Application of three-dimensional printing for colon targeted drug delivery systems. Int J Pharm Investig. 2017, 7:47. 10.4103/jphi.JPHI_32_17
18. Fu J, Yu X, Jin Y: 3D printing of vaginal rings with personalized shapes for controlled release of progesterone. Int J Pharm. 2018, 539:75–82. 10.1016/j.ijpharm.2018.01.036
19. Boehm RD, Miller PR, Schell WA, Perfect JR, Narayan RJ: Inkjet Printing of Amphotericin B onto Biodegradable Microneedles Using Piezoelectric Inkjet Printing. JOM. 2013, 65:525–33. 10.1007/s11837-013-0574-7
20. Ross S, Scoutaris N, Lamprou D, Mallinson D, Douroumis D: Inkjet printing of insulin microneedles for transdermal delivery. Drug Deliv Transl Res. 2015, 5:451–61. 10.1007/s13346-015-0251-1