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Review Article

EXPLORING THE POTENTIAL OF 3D PRINTING IN PHARMACEUTICAL DEVELOPMENT

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ABSTRACT

Pharmaceuticals have been transformed by additive manufacturing, often known as three-dimensional printing (3DP) a disruptive technology. The concept of additive manufacturing is examined, with a focus on its potential for quick prototyping, cost savings, and development of customized medicines. In the pharmaceutical industry 3DP is used to develop numerous dosage forms and drug delivery systems including oral films, controlled-release tablets and transdermal patches. It also makes it possible to produce specialized medical prosthetics, implants and gadgets. The applications of various 3DP types such as material extrusion, material jetting, binder jet printing and powder-based procedures like selective laser sintering, are thoroughly covered. This review assesses the compatibility of the common 3DP materials for pharmaceutical applications including hydroxypropyl methylcellulose, hydroxypropyl cellulose, Carbopol and Eudragit. This review article forecasts 3DP prospects and shortcomings. The technology's continued development and use in the pharmaceutical industry and other industries will depend on overcoming regulatory challenges, creating standardized procedures and optimizing material alternatives. By tackling these issues 3DP has a great deal of potential to revolutionize personalized medicine, medical device production and variety of other industries ultimately leading to better patient outcomes and healthcare solutions. Types and principles, materials, applications, scalability, regulatory compliance and potential future challenges are discussed in this review paper.

Keywords: Additive manufacturing, Personalized medicine, Fused deposition modeling, Polypills, Polymers, Dosage forms, Types of 3DP, Regulatory guidelines, Materials in 3DP

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INTRODUCTION

Three-dimensional printing (3DP) or additive manufacturing is a novel technique wherein the binding materials are deposited in layers to obtain 3D printed object [1]. 3D printers work like inkjet printers, where powder is slowly put on layer by layer to obtain a 3D printed image. Computer-aided design (CAD) software is employed in the fabrication of objects with various shapes and sizes. Signal is transferred to 3D printer by CAD software, which produces solid layers to build up objects [2]. Additive manufacturing helps in rapid prototyping, easily modifying product at design level, manufacturing small objects and cost reduction [3].

Producing personalized medicine has been gaining more relevance due to the development of 3DP. These are safe and efficacious, cost effective and improve patient compliance. Personalized medicines will provide aid to pediatric, geriatric and dysphagic patients [4]. Available dosage forms (oral liquids) of personalized medicine taken by dosing aids like calibrated spoons, droppers or syringes may not provide accurate dosing due to human errors. Additive manufacturing helps develop personalized medicines which avoid human errors [5].

Application of 3DP in pharmaceutical industry is growing, it is employed in fabrication of various pharmaceutical products like oro-dispersible films, controlled release tablets, polypills, gastro-floating tablets, self-emulsifying drug delivery systems, microneedles and transdermal patches [6]. Various medical prosthetics, implants and devices for individual patient needs are manufactured by 3D printing technology [7].

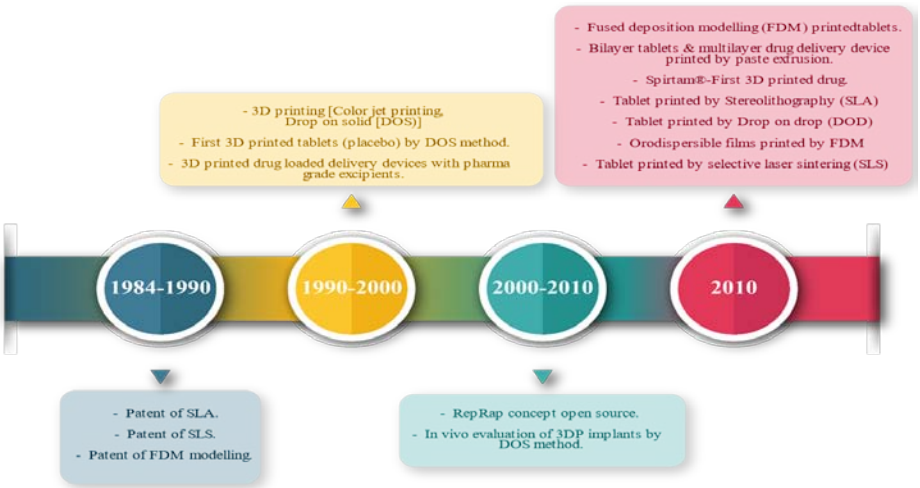

Fig. 1: Milestones in development of 3D technology

In mid 1980s, stereolithography apparatus was first invented and patented by Charles Hull. In this process UV light polymerizes the resins to obtain the desired object. In 1988, the first commercial SLA printer was produced by 3D systems [8]. In 1989 S. Scott and Lisa Crump patented fused deposition modelling (FDM), wherein a metal wire or plastic filament were heated in the nozzle and then extruded [9]. Later Carl Deckard, an undergraduate student at Texas University invented Selective Laser Sintering (SLS) technique. The first SLS printer was produced in the year 1992 [10]. Spritam® (levetiracetam) the first commercial 3D tablet was approved by the USFDA in August 2015 [11].

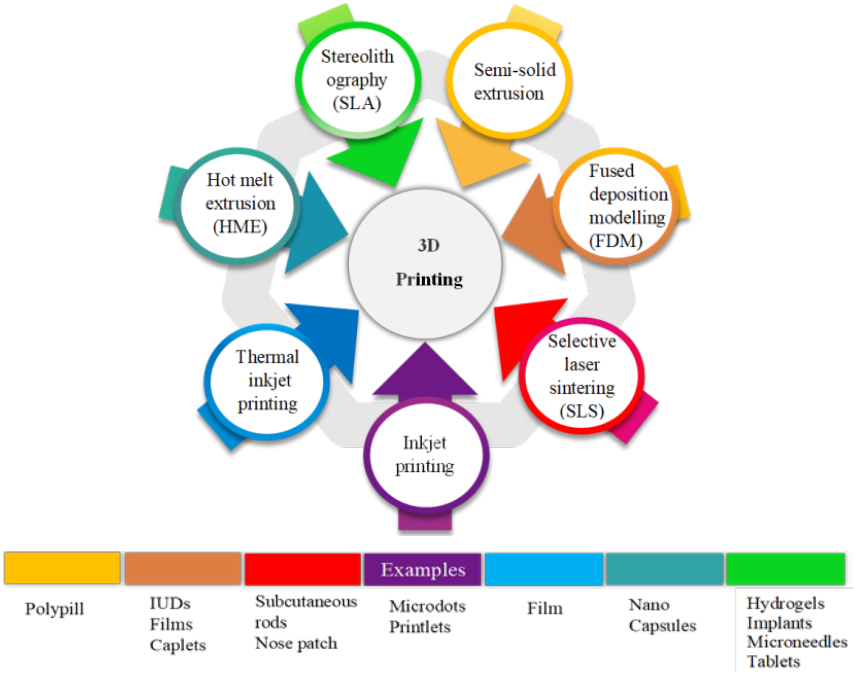

Fig. 2: Different dosage forms developed so far using available 3DP technologies

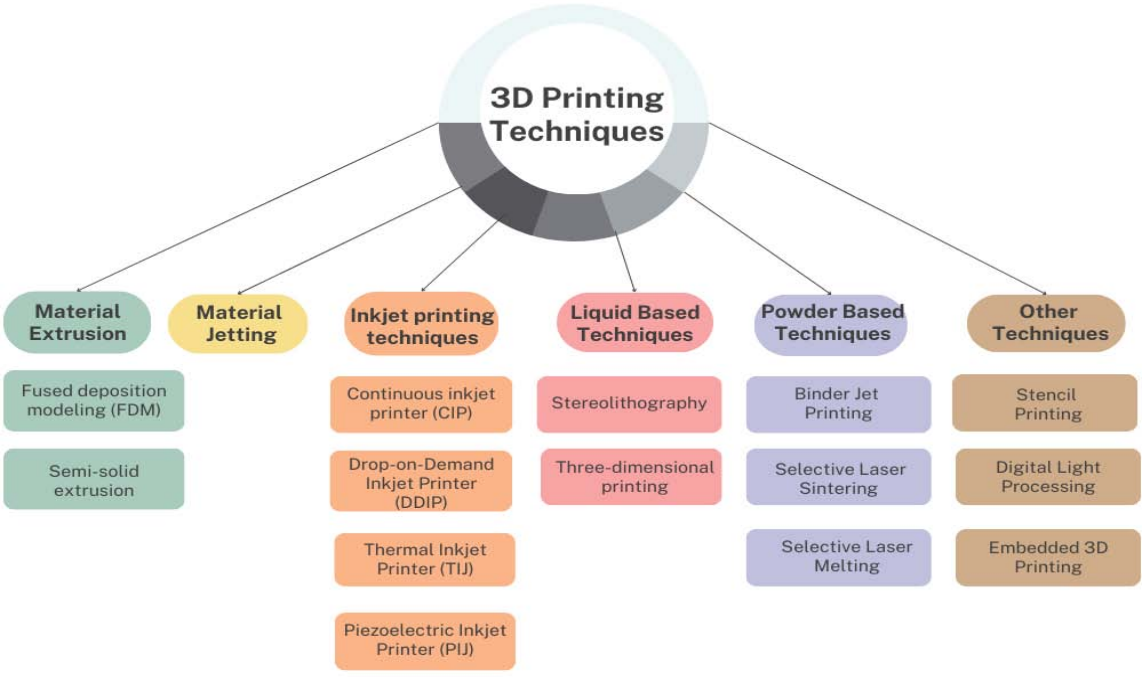

Fig. 3: Classification of techniques use in 3DP

Material extrusion

It is the least expensive and frequently used type of 3D printing. It is classified into two types: fused deposition modelling and semisolid extrusion [12, 13]. The pre-printing material is extruded in a continuous stream through a nozzle in both techniques. To obtain a particular geometry the nozzle or platform (or a combination of the two) is moved in the x, y, and z directions [14].

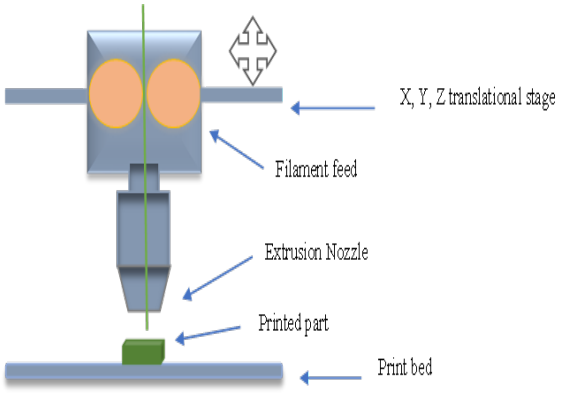

Fig. 4: Schematic of material extrusion [21]

Fused deposition modelling (FDM)

It is a widely employed additive manufacturing technique across various industries for producing three-dimensional prints involves the initial step of importing an STL (Standard Triangle Language, a file that stores information about 3D models generated through a stereolithography CAD program typically developed by 3D Systems into a preprocessing software. The key to enhancing the quality of manufactured objects lies in carefully controlling the four essential parameters of the FDM process, namely: a) Contour count b) Layer thickness c) Raster angle d) Road width [15]. Fused deposition modelling utilizes a heated extrusion nozzle [16]. In FDM, thermoplastic polymers in form of a filament are extruded through the printer head at a specific temperature at definite directions and the semi-molten material is deposited on the build plate to form the layers [17, 18]. The process of FDM can be divided into three stages: (i) molten material extrusion (ii) material layer deposition and (iii) layer solidification [19]. Generally, the initial printing step involves creating the outer layer and subsequently the internal structures are constructed layer by layer. To fill the internal space, an extruded polymer called "infill" is used with the extent of filling determined as needed [20, 21].

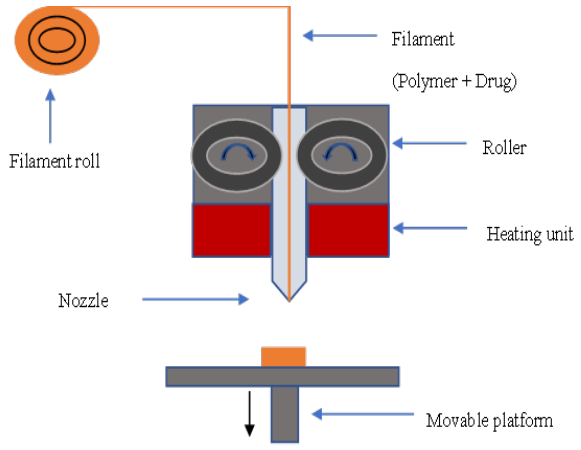

Fig. 5: Schematic of fused deposition modelling [22]

Semi-solid extrusion 3D printing

Extrusion-based semi-solid extrusion (SSE) printing is another important type of 3DP technique that could be very useful for soft materials [22]. Semisolid extrusion printers can print a range of materials using pneumatic or mechanical extrusion forces instead of relying solely on heat [23]. To create a three-dimensional object a syringe-based tool-head nozzle is used to extrude a combination of semi-solid materials [24]. These initial materials are typically pastes or gels those are created by carefully mixing solvents and components in specific quantities to achieve the desired viscosity for printing [25, 44]. The fluid must have the right viscosity to ensure a smooth extrusion.

Material jetting

The material jetting technique resembles to that of inkjet printers. The print head and platform are actuated to move in the x, y and z-axis. The material must be cross-linkable upon delivery for successful printing. Cross-linking processes not only includes semisolid extrusion but also involve photo, thermal, ionic and pH-dependent effects [26]. One of the most significant advantages of this approach is that it can print multiple materials at the same time, even materials with differing properties [27].

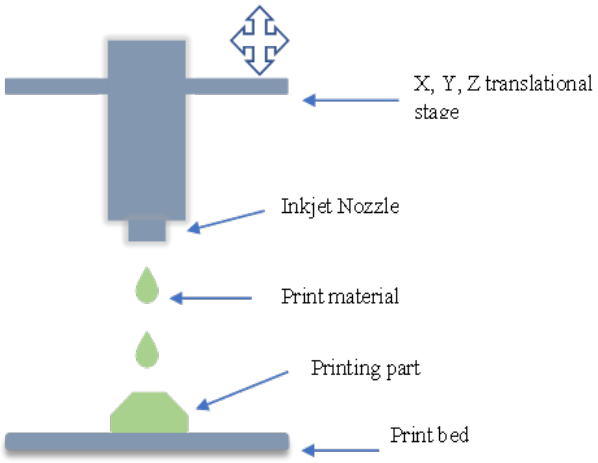

Fig. 6: Schematic of material jetting [21]

Inkjet printing method

Inkjet printing refers to the technique that use pattern generating devices to digitally control and place small liquid drops on a substrate [28]. In pharmaceuticals appropriate drug blends and excipients (known as ink) are deposited in small drops layer by layer on a suitable substrate [29]. Various types of inkjet printer are available, which are outlined below:

Continuous inkjet printer (CIP)

Continuous inkjet printers eject a stream of liquid droplets on a substrate continuously. Continuous inkjet printing involves the creation of a pressure wave within the ink flow. This wave disrupts the ink into consistently sized droplets through nozzle vibration, after which the droplets are expelled from the nozzle. This approach results in ink wastage due to the continuous expulsion of droplets. The benefits of this printing process include high-speed continuous droplet creation which prevents nozzle clogging [30].

Drop-on-demand inkjet printer

Drop on demand inject printing method is quite simple provides excellent precision in affordable cost. In continuous inkjet printer's droplets are expelled by external pressure, whereas in drop-on-demand inkjet printers droplets acquire their kinetic energy from nearby sources situated within the printhead [31]. Drop-on-demand inkjet printer further classified in thermal inkjet and piezoelectric printer based on printhead type [32].

Thermal inkjet printer (TIJ)

Thermal energy is used as the trigger mechanism to release droplets in TIJ, which then exit the nozzle. The print heads have resistors that are in direct contact with the fluid (ink) and produce heat when an electric current is applied to them. This heat causes a bubble to form within the volatile fluid, which then expands and ejects a small volume of fluid out of the nozzle, generating a droplet [29, 31].

Piezoelectric inkjet printer (PIJ)

This technology utilizes a piezoelectric element or actuator that undergoes a shape transformation when subjected to an electric voltage [33]. This creates pressure, which causes the fluid (ink) to be ejected from the nozzle. The nozzle is reloaded with fluid and ready to be activated once the element has returned to its original shape. The key benefits of this technology include its ability to operate at room temperature while using less volatile and more biocompatible fluids [34].

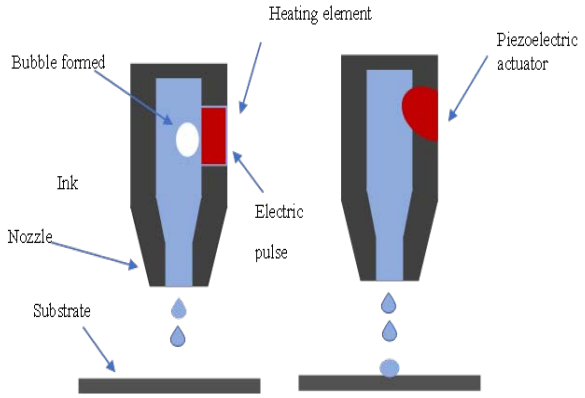

Fig. 7: Schematic for a) thermal inkjet printer b) piezoelectric inkjet printer [21]

Liquid-based techniques

Stereolithography

Stereolithography is based on the solidifying of liquid resins through photopolymerization by utilising ultraviolet light. First, a large vat is filled with resin and subjected to a radiation source from the top or the bottom in a desired geometric pattern. Stereolithographic techniques can attain reasonably high resolution by employing regular radiation sources to reach the diffraction limit of light. Continuous liquid interface processing (CLIP) and digital light processing (DLP) are other techniques related to stereolithography [34, 35].

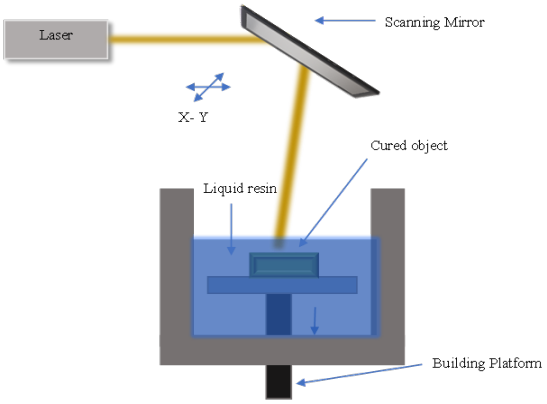

Fig. 8: Schematic of stereolithography [22]

Powder based techniques

Binder jet printing

It is also known as the drop-on-powder method which is an application of inkjet printing technology. A printer nozzle containing the binder fluid is designed to move along an x-y axis and jet the liquid onto the loose powder bed. Printhead of jet printer could be thermal or piezoelectric. The liquid drips moisten the powder, which causing the layer to harden and solidify [18]. Subsequently, the manufacturing platform moves downward along the z-axis while the powder supply platform rises. A roller is then used to transport a powder layer from the bed to the top of the previously bound layer. This method is performed several times until the 3D product is completed [18, 33].

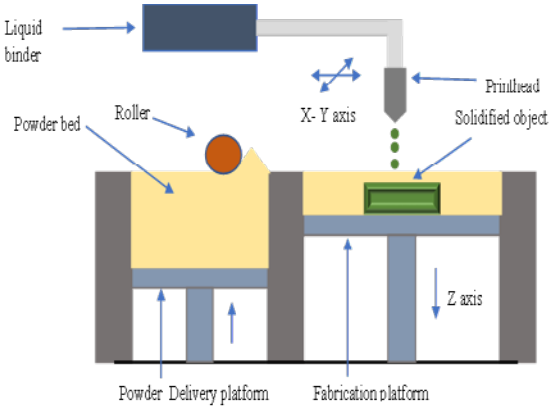

Fig. 9: Schematic of binder jet printing [22]

Selective laser sintering

Selective laser sintering works similarly to binder jetting however, instead of a binder, a laser is used to sinter powder particles together [36]. The spreading platform, powder bed and laser system are the three primary components of a SLS system [37]. This method is useful because it is a one-step rapid manufacturing procedure that does not require use of any solvent. Since is use laser precision, it also produces high-resolution objects [38].

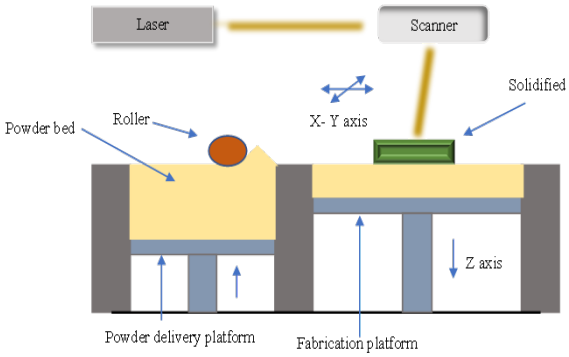

Fig. 10: Schematic of selective laser sintering [22]

Selective laser melting

A specific rapid prototyping, additive manufacturing (AM) or 3D printing process called selective laser melting (SLM) aims to melt and fuse metallic powders using a high power-density laser. SLM uses a powerful laser beam to create 3D parts, such as SLA, which uses a UV laser**.** The laser beam melts and combines different metallic particles together while printing [39]. A building platform is covered with metal powder which has been heated nearly to its melting point and spread using a roller. The cross-section of the 3D object is drawn into the powder material using a laser after which the chosen particles are fully combined to obtain 100% density. In this manner, the melting happens when the grain viscosity decreases with an interfacial connection between the grains but not when the temperature melts completely. Grain viscosity in 3D printing refers to the flow behavior and thickness of the material being used for printing, often associated with granular or particulate materials like powders. 2D cross-section made up of layers with thicknesses of 20

to 100 microns. An even layer of metallic powder is then applied using a recoater to construct the part and each layer is fused separately in a precisely regulated inert environment. Once the printing process is finished any leftover powder is cleared away. During the procedure laser is utilized to shape the powder layers and the object is created using with laser energy [40].

Other techniques

Stencil printing

Wickstrom and colleagues have introduced a novel printing technique that has not yet been employed in pharmaceutical manufacturing. The objective of their investigation was to determine whether drug-loaded polymer inks could be produced to develop pliable pharmaceutical products that have consistent content and mass. They used a prototype stencil printer and polyester as the stencil material to print discs containing Haloperidol (HAL) [41].

Digital light processing (DLP)

Digital light processing is a 3D printing technique that shares similarities with SLA, but instead of using a laser beam, it employs UV light from a projector to solidify each layer of a resin-based material. Madzarevic *et al.* utilized this technology to produce ibuprofen tablets through DLP 3D printing [42].

Embedded 3D printing

Embedded 3D printing (e-3DP) is a new type of additive manufacturing (AM) in which a viscoelastic ink is deposited into a reservoir that solidifies using a deposition nozzle that follows a predetermined path. Rycerz *et al.* demonstrated one of the initial applications of e-3DP in the pharmaceutical domain by producing dual drug-loaded chewable oral dosage forms. The team suspended paracetamol and ibuprofen in a locust gum solution and then embedded them in a gelatine-based matrix material to create the final product [43].

Table 1: Polymers used in 3DP

Polymers	Physicochemical properties	References
Hydroxypropyl methylcellulose (HPMC)	• Water soluble polymer. • Glass transition temperature from170 °C to 198 °C	[45, 46]
Hydroxypropyl cellulose (HPC)	• Water soluble polymer. • Glass transition temperature from-25 °C to 0 °C.	[47, 48]
Carbopol	• High molecular weight polymer. • Carbopol 971P and 974 P used in 3DP	[49, 50]
Eudragit	• Used in hot melt extrusion. • Glass transition temperature 9 °C to 150 °C. • Eudragit L and S series for delayed release, Eudragit E for immediate release, Eudragit RL and RS for controlled release.	[51, 52]
Polycaprolactone (PCL)	• It is partially crystalline and biocompatible. • M. P. range 55 °C to 60 °C, Glass transition temperature is 54 °C	[53, 54]
Polyvinyl alcohol (PVA)	• Water soluble synthetic polymer. • M. P. range180 °C to 228 °C, glass transition temperature is 85 °C	[55]
Ethyl cellulose (EC)	• Water-insoluble thermoplastic polymer	[56]
Soluplus®	• Amphiphilic nature. • Enhance solubility and dissolution of poorly soluble drugs.	[57]
Polyethylene glycol (PEG)	• PEG is a water-soluble, biocompatible, and amphiphilic polymer.	[58, 59]
Polylactic acid (PLA)	• Synthetic polymer that is insoluble and biodegradable	[60]
Polyvinylpyrrolidone (PVP)	• PVP dissolves in water and organic solvents.	[61]

Applications and scalability aspects

3DP is the process utilized to manufacture 3D products layers after layers using digital designs. The 3DP is regarded as a versatile tool for producing numerous products quickly. 3DP makes possible creation of custom drug dosages and formulations which makes personalized treatment of each patient possible [62]. The technology may also be used to fabricate customized medical devices such as prosthetics, hearing aids and orthotics, which can raise the standard of living and improve the quality of life for patients.

3DP, also known as additive manufacturing, has emerged as a promising technology in various fields, including pharmaceutics. Some of the applications of 3DP in pharmaceutical dosage form designing are as follows

Solid oral dosage forms (SODFs)

SODFs are the most suitable choice for drug administration due to their convenience in handling and manufacturing, as well as their high patient compliance [63]. The conventional manufacturing processes of SODFs are characterized by a multitude of steps, lengthy durations, high costs and a lack of customization to meet individual requirements. Furthermore, these methods are primarily focused on large-scale bulk production [64]. 3DP is a cutting-edge and emerging technology that has the potential to address these challenges. By utilizing three-dimensional printing, it becomes possible to create personalized shapes for SODFs, incorporate many drugs into a single dosage form and manufacture medication tailored to individual patients, resulting in improved safety, convenience and adherence [65].

Solid oral dosage forms manufactured using 3d printing

Tablets

The most prevalent SODFs produced by 3D printing are tablets. With the aid of 3DP, it is simple to create and modify tablets for various shapes, release profiles and special doses, including combinations of different medications [66].

Immediate-and modified-release tablets

3DP has made it possible to manufacture formulations that dissolve quickly in mouth [67, 68]. Modified-release tablets include delayed-release, controlled-release, sustained-release and targeted-release. The overall surface area of conventional modified tablets decreases during the gastrointestinal tract's absorption process, causing a non-constant drug release. 3DP may solve this problem with manufacturing tablets with complex geometries that provide the formation of both those with individualized release profiles and those with continuous sustained-release dissolving profiles [69].

Orally disintegrating tablets (ODTs)

ODTs are oral delivery systems that can dissolve within seconds without the need for additional liquid. Patients with dysphagia and patients who have trouble swallowing may find ODTs especially beneficial. 3DP avoids the heavy compression pressures needed in the conventional manufacturing process, so the fabricated final structure is significantly more porous and disintegrates more quickly**.** Spritam is an example of an additive manufacturing (AM)

application in a pharmaceutical and fabricated using a technique called binder jetting, which dissolves within 2-27 seconds [74]. Another investigation by Tian *et al.* utilized the same technique to prepared oro-dispersible warfarin tablets [75].

Table 2: Applications of 3D printing on modified-release tablets

Release behavior	API(s)	Excipients	Techniques	Reference
Modified	Paracetamol	Polyvinyl alcohol	FDM/HME	[70]
	Acetaminophen	Methocel™E50, polyvinylpyrrolidone, ethyl cellulose, Eudragit® RS 100, stearic acid, SLS, fluorescein, colloidal silicon dioxide	Inkjet printing	[71]
	Rifampicin and Isoniazid	Polyethylene oxide, polylactic acid (PLA), polyvinyl alcohol (PVA)	FDM/HME	[72]
Immediate	Chlorpheniramine maleate	Microcrystalline cellulose powder, Eudragit® E 100, RLPO	Inkjet	[73]

Gastro floating tablets

With the use of 3DP, tablets with prolonged stomach retention (gastrofloating) were effectively produced. Traditional techniques to achieve gastrofloating systems in SODFs, CO2 effervescent systems were used to enable floating or non-effervescent systems that reduce perceived density are used to enable floating. By adjusting the infill density, 3DP makes it simple to modify tablet density [76]. Li *et al.* fabricated a number of lattice-filled dipyridamole tablets. This study showed that increasing lattice density resulted into sinking of tablet that increased drug release rate [77].

Polypills

The fabrication of multi-API tablets (polypills) is another advantage of 3DP. Patients with various illnesses who need to take a variety of medications throughout the day may gain benefit from it [78]. The first study on 3DP polypills to be published in the literature is that of Khaled *et al.* The team created polypills containing glipizide, captopril and nifedipine utilizing extrusion-based 3D printer. The polypill was developed to treat diabetics with hypertension [79].

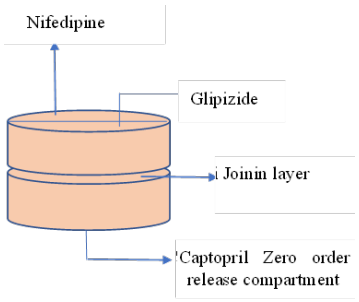

Fig. 11: Polypills with three APIs

Capsules

Capsules are dosage forms that contain shell around the medication. The cap and body of 3D printed capsules and capsule devices can be created separately and then filled and assembled or they can be produced and filled in one manufacturing process [80]. Melocchi *et al.* were the first to study the 3D printing potential for use in capsule production. The team utilized a swellable HPC-made capsular device prepared for oral pulsatile release via FDM printing [81].

Fig. 12: Capsules created using 3D printing

Orodispersible films

Orodispersible films (ODFs) are thin polymer films that stick to the tongue or palate before quickly dissolving or disintegrating. It is usually prepared by casting methods. Current investigations of their 3D printing preparation have also been made. Öblom *et al.* compared traditional oral powders in sachets (OPS) with Warfarin ODFs prepared by 3DP using semisolid extrusion and inkjet printing. In comparison to OPSs, the 3D-printed ODFs had higher drug concentration and more consistent unit doses [81].

Tablets for certain patient groups

The creation of tablets for certain patient groups, including pediatrics, dysphagic and blind patients is another important use of 3DP. Children's solid oral dose forms are often created by modifying adult formulas. But it could result in serious pharmaceutical errors. A method to prevent these possible errors may be 3DP [82]. Namely, Pediatrics patients get option to select the form and color of their choice. By using FDM Scouters *et al.* created candy-like SODFs that contained indomethacin. The formulations were successful in minimizing the bad taste of indomethacin and ensuring its rapid release [83].

Implants

An implant is a dosage type that helps patients who need long-term medication therapy and contains active components in a sustained-release matrix. 3D printed Implants include spine implants, shoulder joints (glenoid replacement, hip implants) and implants for the OMF area oral and maxillofacial surgery. Recently, A 3DP based multi-drug implant was developed by Wu *et al.* (2016). Tobramycin and Levofloxacin were implanted as APIs [84].

Transdermal microneedle (MN) patches

It is a type of transdermal drug delivery containing tiny needles on a matrix. By using 3DP technology, microneedles can be fabricated with more complex and advanced geometries as opposed to those that are limited to being made using traditional microfabrication processes. AM technologies, particularly SLA and DLP, offer alternative method for MN fabrication. To imitate a specific area of the human facial shape, Lim *et al.* created MN patches containing various curves with the help of DLP printer [85]. It was shown that curved MNs dispersed pressure uniformly which require for absorption that offered greater dermal absorption and delivered drug effectively.

Medical devices

Dose dispensing aids

Recently, AM has proven to be an effective technique for creating samples of pharmaceutical distributing equipment that is suitable for customized medication. Niese *et al.* created samples of pharmaceutical distributing equipment for a drug containing film which promotes variable dose with individualized treatment.

Drug eluting devices

Drug eluting dosage form enables the continuous release of a medicinal substances over a significantly long time. The shape, components and dose options for drug-eluting products are constrained. 3DP facilitate this by altering dose, dosage form shape and medication release profile.

Pharmaceutical models for drug testing

Acellular models

Models have long been used as a tool to improve learning. With the use of AM technology, we can go one step further and create

customized 3D printing models, enabling a more customized approach and more patient-centric treatment. For example, Spence *et al.* prepared various devices to transport large flow for nasal-cannula (HFNC) treatment.

Cellular models

3D printed cellular models are physiologically more relevant than conventionally manufactured cellular models. They more accurately represent tissue microenvironments, cell-to-cell communications and biological events which occur *in vivo*.

Opportunities

In the pharmaceutical industry, 3DP has several potential opportunities. Some of them are as follows:

Personalized medicine

3DP technology can be used to create customised dosage forms for each patient based on their specific physiological characteristics. This might result in more efficient medical interventions and better patient outcomes [86].

On-demand manufacturing

3DP makes it possible to quickly produce medications and medical equipment when needed, eliminating the need for mass production and storage facilities [87].

Improved drug delivery

By using 3DP it is possible to design medication delivery systems with accurate dosing and release characteristics. This aid in more effective drug release control, fewer side effects and higher patient compliance [88].

Production of complicated structures

Using conventional manufacturing methods it is difficult or impossible to build complicated structures such as scaffolds for tissue engineering or drug delivery systems [89].

Quicker drug development

3DP enables the quick creation of small batches of pharmaceuticals for testing and evaluation, which helps speed up the medication development process. New drug development and approval could proceed quickly as a result [90].

Rapid prototype development

3DP makes it possible to quickly and affordably prototype new medication formulations and medical devices, which makes the creation of pharmaceutical goods more effective [91].

Manufacturing effectiveness

Pharmaceutical businesses can streamline their processes by using 3DP to cut the time and costs involved with conventional drug manufacturing [92].

Challenges

The pharmaceutical sector has identified 3DP commonly referred to as additive manufacturing as a viable technology. It makes it possible to produce medical equipment, drug delivery systems, and personalised medications quickly, accurately and flexibly. However, there are a number of challenges that must be resolved.

Printing resolution

For 3DP, printing resolution is a key component. It is the measure of the layer thickness, typically expressed in microns, determining the level of detail and smoothness in the finished printed object. It establishes the degree of accuracy and precision. To achieve precise dosage and drug release in the pharmaceutical industry the printing resolution must be good enough [93].

Material choice

It is crucial to choose the right materials for 3D printing in the pharmaceutical industry. The materials should have appropriate mechanical qualities, be stable, and be biocompatible. There are few suitable materials readily available and creating new materials for 3DP is difficult [94].

Regulatory approval

A major obstacle to pharmaceutical 3DP is regulatory approval. To assure the safety and effectiveness of 3DP products the regulatory authorities need thorough testing and validation [95].

Quality control

It is necessary to guarantee product uniformity and safety. But because of the complexity of the production process, the unpredictability of the materials and the absence of standardized testing procedures, quality control for 3DP medications is difficult [96].

Intellectual property

Concerns about intellectual property rights are raised by the 3DP of medications. Legal problems may arise from the unlicensed printing of patented medicines or medical equipment [97].

Cost-effectiveness

Cost effectiveness is still an issue with 3DP in the pharmaceutical industry. Cost effectiveness of 3DP depends on factors like material costs, equipment, design complexity and production volume. Equipment and materials for 3DP are highly expensive and economies of scale have not yet been attained [98].

Sterilisation

To avoid contamination and guarantee the safety of the final product, sterilisation is an essential step in the manufacturing of pharmaceuticals. Specific sterilisation procedures can be necessary for 3DP items which could have an impact on their mechanical and structural qualities [99].

Scalability

Because 3DP in the pharmaceutical industry is still in its infancy, it may be difficult to scale up manufacturing to fulfil the demand for personalised medications at a large scale [100].

Printing software

Modelling, slicing, printing and post processing are the four basic processes in 3DP. In printing process, the computer is first used to create a printing model and slice it to specify the printing route of each layer and then the formulation with a complicated structure is manufactured in accordance with the prefabricated model. The modelling and slicing software must thus be continuously upgraded to match higher printing requirements as the complexity of the desired structure rises [94].

Printability

A material's ability to be printed using a particular 3DP process is known as printability. It may be difficult to create the intended product since some pharmaceutical materials may not be compatible with specific 3DP procedures [101].

Post-processing

In order to give 3DP objects the desired qualities, post-processing may be necessary such as cleaning, polishing or coating. The choice of appropriate post-processing processes is crucial for maintaining product quality although post-processing can be time-consuming [102].

Design optimisation

In 3DP design optimisation is essential to ensuring the usefulness, safety and effectiveness of the final product. However, it could be challenging to produce pharmaceutical items for 3DP with optimized features due to the complexity of the production process and the nature of the material [103].

Uniformity

To achieve consistent dosing and efficacy 3D-printed items must be uniform. Due to variances in the printing process, it might be difficult to produce medications using 3D printing with consistency [103].

Regulatory aspects

As 3DP technology has developed, it has given the pharmaceutical sector new opportunities. However, when using 3DP technology in pharmaceuticals there are a number of regulatory aspects that must be taken into account due to the complexity of pharmaceutical products.

Adherence to GMPs

Good Manufacturing Practices (GMPs) are a set of rules that guarantee pharmaceutical products are consistently created and monitored in accordance with quality standards. GMP compliance must be achieved while using 3DP in the pharmaceutical industry to maintain the product's quality and safety [104].

Validation

To ensure that the finished product complies with the necessary requirements, 3D printing procedures must be validated. This includes verifying the raw components, the printing technique and the final product.

Intellectual property

There are questions about intellectual property rights raised by the use of 3DP technology in pharmaceuticals [105]. As a result, regulatory authorities demand that patent rules and regulations be strictly followed.

Material safety

It is important to determine the safety and compatibility of 3D printing materials with pharmaceutical items. This includes figuring out how the substance and the active pharmaceutical ingredients (APIs) might interact.

Labelling and packaging

The labelling and packaging specifications for pharmaceutical products made using 3DP are the same as those for goods made using more traditional manufacturing methods. This includes the demand for accurate dosage, strength and expiration date labelling.

Currently, there are no specific global guidelines governing 3D printing in pharmaceuticals [106]. However, many regulatory bodies have issued guidance on using 3D printing in medical devices and drugs. In addition to regulatory organizations, many nations also have their own laws governing the usage of 3D printing in the pharmaceutical industry. Depending on the nation these laws may have standards for GMP compliance, validation, material safety and packaging. A few examples are given below:

United States

In 2015, Spritam (levetiracetam), a medication used to treat epilepsy received Food and Drug Administration (FDA) approval. [107] Since then, several other 3D-printed medications have received approval, including medication for Parkinson's disease produced by GlaxoSmithKline. The FDA released guidelines for the 3D printing of medical devices in 2017, offers suggestions for design, production and testing. This draft guidance is broadly organized into two topic areas such as Design and Manufacturing Considerations and Device Testing Considerations [117]. The FDA released drafted guidance also offers suggestions for labelling and premarket filings [107].

European Union

The European Medicines Agency (EMA) has published a reflection paper on the applications of 3DP in the pharmaceutical sector in 2020, with recommendations on issues related to quality, safety and efficacy [108]. Medical devices made using 3DP are likewise subject to the *In vitro* Diagnostic Regulation (IVDR) and Medical Device Regulation (MDR) of the European Union [109].

International standards organization

The Additive Manufacturing Technologies was established by American society for Testing and Materials (ASTM) Committee F42 in 2009. With over 150 members attending two days of technical sessions F42 assembles biannually often in the spring and autumn (in the US and abroad respectively). The committee which now has over 725 members, comprises of eight technical subcommittees. All of the standards established by F42 are published in the Annual Book of ASTM Standards, vol. 10.04. These norms concentrate on a number of distinct areas, including general norms (such as nomenclature, test techniques, safety), feedstock material norms, application-specific norms (including medicinal uses), process and equipment norms and completed part norms. The standards for 3DP are to the extent feasible based on current standards and where needed updated for 3DP.

International organisation for standardisation

Several standards for 3DP in healthcare have been produced by the International Organisation for Standardisation (ISO), including ISO 13485 for quality management systems and ISO/ASTM 52900 for additive manufacturing terminology. ISO 10993 developed by the International Organisation for Standardisation (ISO), offers instructions for the biological assessment of medical devices, including those made via 3DP [110].

Australia

Guidelines on the regulation of medical equipment made via 3DP have been published by the Australian Therapeutic Goods Administration (TGA) [109].

Canada

Health Canada Guidelines on Acceptance of Medical Devices Manufactured through Additive Manufacturing or 3D Printing document provides instructions on the manufacture and sale of medical devices made through additive manufacturing or 3DP [109].

Japan

Guidelines on the use of 3DP in pharmaceutical manufacture have been released by the Pharmaceutical and Medical Devices Agency (PMDA) in Japan. These guidelines include suggestions for quality control, safety and efficacy testing and regulatory criteria [110].

India

In India, 3D printing is still a relatively new technology in the pharmaceutical industry, and there are currently no established regulatory standards. The Central Drugs Standard Control Organisation (CDSCO), a division of the Indian Ministry of Health and Family Welfare, is in charge of overseeing 3DP in medical devices. With respect to the registration of medical devices, the CDSCO has published guidelines that provides the specifications for quality management systems and conformity evaluations. Additionally, the CDSCO has developed a legal process for authorising 3DP medical devices. These devices must register with the CDSCO and pass a conformity assessment procedure to validate their safety and efficacy before being supplied in India [111].

Additionally, the Bureau of Indian Standards (BIS) has produced guidelines for material qualities, dimensional accuracy and mechanical features for 3DP in general [112]. These rules may be relevant to 3DP in the pharmaceutical business even if they are not particular to the industry.

The regulatory framework for medical devices may apply to 3DP medical devices, including those used for drug delivery, even if there are no regulatory compliances for 3DP in pharmaceuticals in India. Companies who are interested in designing and producing 3DP medications in India should coordinate closely with the relevant regulatory bodies to make sure that all laws and rules are followed.

CONCLUSION

The potential of Additive manufacturing is tremendous. It has ability to bring revolution in pharmaceutical industry, especially in personalized medicine which will improve patient compliance, reduce side effects, resolve issues related to shelf life. This technology offers flexibility in the development of formulation which is difficult through conventional process. Dosage forms with complex shapes and release profiles can be manufactured. Spritam the first FDA approved commercial tablet has been an aspiration to healthcare industry.

As of now 3DP cannot compete with the conventional drug manufacturing, advancement in future in the printing speed and resolution must be altered which will reduce the energy consumption and the cost of production. For the approval of 3DP dosage forms defining appropriate regulatory guidelines is required. Overcoming these challenges in 3DP technology will help boost the manufacturing of personalized medicines.

ABBREVIATIONS

3DP-3D Printing, CAD-Computer aided design, FDM-Fused deposition modelling FDM, SLS-Selective laser sintering, TIJ-Thermal inkjet printer, SODFs-solid oral dosage forms, ODTs-Orally disintegrating tablets, API-Active pharmaceutical ingredients, AM-Additive manufacturing, ODFs-Orodispersible films, GMP-Good manufacturing practises, FDA-Food and drug administration, CDSCO-Central drugs standard control organisation

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CONFLICT OF INTERESTS

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REFERENCES

1. Prasad LK, Smyth H. 3D Printing technologies for drug delivery: a review. Drug Dev Ind Pharm. 2016 Jul 2;42(7):1019-31. doi: 10.3109/03639045.2015.1120743, PMID 26625986.
2. Berman B. 3-D printing: the new industrial revolution. Bus Horiz. 2012 Mar;55(2):155-62. doi: 10.1016/j.bushor.2011.11.003.
3. Jamroz W, Szafraniec J, Kurek M, Jachowicz R. 3D printing in pharmaceutical and medical applications-recent achievements and challenges. Pharm Res. 2018;35(9). doi: 10.1007/s11095-018-2454-x.
4. Chen G, Xu Y, Chi Lip Kwok P, Kang L. Pharmaceutical applications of 3D printing. Addit Manuf. 2020 Aug;34:101209. doi: 10.1016/j.addma.2020.101209.
5. Okwuosa TC, Soares C, Gollwitzer V, Habashy R, Timmins P, Alhnan MA. On demand manufacturing of patient-specific liquid capsules via co-ordinated 3D printing and liquid dispensing. Eur J Pharm Sci. 2018 Jun;118:134-43. doi: 10.1016/j.ejps.2018.03.010, PMID 29540300.
6. Park BJ, Choi HJ, Moon SJ, Kim SJ, Bajracharya R, Min JY. Pharmaceutical applications of 3D printing technology: current understanding and future perspectives. J Pharm Investig. 2018 Oct 29. doi: 10.1007/s40005-018-00414-y.
7. Trenfield SJ, Awad A, Madla CM, Hatton GB, Firth J, Goyanes A. Shaping the future: recent advances of 3D printing in drug delivery and healthcare. Expert Opin Drug Deliv. 2019 Oct 3;16(10):1081-94. doi: 10.1080/17425247.2019.1660318, PMID 31478752.
8. Vaz VM, Kumar L. 3D printing as a promising tool in personalized medicine. AAPS PharmSciTech. 2021;22(1):49. doi: 10.1208/s12249-020-01905-8, PMID 33458797.
9. Al Su A, Aref SJ. History of 3D printing. In: Elsevier. 3D printing applications in cardiovascular medicine; 2018. p. 1-10. Available from: https://linkinghub.elsevier.com/retrieve/pii/B9780128039175000018. [Last accessed on 08 May 2023]
10. Carl Deckard selected for AMUG innovators award; 2016. Available from: https://additivemanufacturing.com/2016/11/03/carl-deckard-selected-for-amug-innovators-award.
11. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207958Orig1s000TOC.cfm.
12. Mwema FM, Akinlabi ET. Basics of fused deposition modelling (FDM); 2020. p. 1-15.
13. Yap CY, Chua CK, Dong ZL, Liu ZH, Zhang DQ, Loh LE. Review of selective laser melting: materials and applications. Appl Phys Rev. 2015 Dec;2(4):041101. doi: 10.1063/1.4935926.
14. Shakor P, Sanjayan J, Nazari A, Nejadi S. Modified 3D printed powder to cement-based material and mechanical properties of cement scaffold used in 3D printing. Construction and Building Materials. 2017 May;138:398-409. doi: 10.1016/j.conbuildmat.2017.02.037.
15. Yasa E. Selective laser melting. In: Additive manufacturing. Elsevier; 2021. p. 77-120.
16. Gu P, Zhang X, Zeng Y, Ferguson B. Quality analysis and optimization of solid ground curing process. J Manuf Syst. 2001 Jan;20(4):250-63. doi: 10.1016/S0278-6125(01)80045-5.
17. Galati M. Electron beam melting process. In: Additive manufacturing. Elsevier; 2021. p. 277-301.
18. Prince JD. 3D printing: an industrial revolution. J Electron Resour Med Libr. 2014 Jan 11;11(1):39-45. doi: 10.1080/15424065.2014.877247.
19. Gurr M, Mülhaupt R. Rapid prototyping. In: Polymer science: a comprehensive reference. Elsevier; 2012. p. 77-99.
20. He Y, Zhong FJ, Feng GW, Wei LZ. Optimization of tool-path generation for material extrusion-based additive manufacturing technology. Jin Yan Addit Manuf. 2014;1:32-47.
21. Kjar A, Huang Y. Application of micro-scale 3D printing in pharmaceutics. Pharmaceutics. 2019;11(8):390. doi: 10.3390/pharmaceutics11080390, PMID 31382565.
22. Vaz VM, Kumar L. 3D printing as a promising tool in personalized medicine. AAPS PharmSciTech. 2021;22(1):49. doi: 10.1208/s12249-020-01905-8, PMID 33458797.
23. Murphy SV, Atala A. 3D bioprinting of tissues and organs. Nat Biotechnol. 2014;32(8):773-85. doi: 10.1038/nbt.2958, PMID 25093879.
24. Ahn SH, Lee HJ, Lee JS, Yoon H, Chun W, Kim GH. A novel cell-printing method and its application to hepatogenic differentiation of human adipose stem cell-embedded mesh structures. Sci Rep. 2015;5(1):13427. doi: 10.1038/srep13427, PMID 26293341.
25. Hospodiuk M, Dey M, Sosnoski D, Ozbolat IT. The bioink: a comprehensive review on bioprintable materials. Biotechnol Adv. 2017;35(2):217-39. doi: 10.1016/j.biotechadv.2016.12.006, PMID 28057483.
26. Bhattacharjee N, Urrios A, Kang S, Folch A. The upcoming 3D-printing revolution in microfluidics. Lab Chip. 2016;16(10):1720-42. doi: 10.1039/c6lc00163g, PMID 27101171.
27. Goole J, Amighi K. 3D printing in pharmaceutics: A new tool for designing customized drug delivery systems. Int J Pharm. 2016;499(1-2):376-94. doi: 10.1016/j.ijpharm.2015.12.071, PMID 26757150.
28. Kotta S, Nair A, Alsabeelah N. 3D printing technology in drug delivery: recent progress and application. Curr Pharm Des. 2018;24(42):5039-48. doi: 10.2174/1381612825666181206123828, PMID 30520368.
29. Azizi Machekposhti S, Mohaved S, Narayan RJ. Inkjet dispensing technologies: recent advances for novel drug discovery. Expert Opin Drug Discov. 2019;14(2):101-13. doi: 10.1080/17460441.2019.1567489, PMID 30676831.
30. Içten E, Giridhar A, Taylor LS, Nagy ZK, Reklaitis GV. Dropwise additive manufacturing of pharmaceutical products for melt-based dosage forms. J Pharm Sci. 2015;104(5):1641-9. doi: 10.1002/jps.24367, PMID 25639605.
31. Acosta Velez GF, Wu BM. 3D pharming: direct printing of personalized pharmaceutical tablets. Polym Sci. 2016;2(1):11.
32. Vadodaria S, Mills T. Jetting-based 3D printing of edible materials. Food Hydrocoll. 2020;106:105857. doi: 10.1016/j.foodhyd.2020.105857.
33. Trenfield SJ, Madla CM, Basit AW, Gaisford S. Binder jet printing in pharmaceutical manufacturing. 3D Printing of Pharmaceuticals; 2018. p. 41-54.
34. Lee KJ, Kang A, Delfino JJ, West TG, Chetty D, Monkhouse DC. Evaluation of critical formulation factors in the development of a rapidly dispersing captopril oral dosage form. Drug Dev Ind Pharm. 2003;29(9):967-79. doi: 10.1081/ddc-120025454, PMID 14606661.
35. Hwang HH, Zhu W, Victorine G, Lawrence N, Chen S. 3D-printing of functional biomedical microdevices via light-and extrusion-based approaches. Small Methods. 2018;2(2):1700277. doi: 10.1002/smtd.201700277, PMID 30090851.

36. Bártolo PJ. Stereolithography: materials, processes and applications. Springer Science+Business Media; 2011.
37. Mazzoli A. Selective laser sintering in biomedical engineering. Med Biol Eng Comput. 2013;51(3):245-56. doi: 10.1007/s11517-012-1001-x, PMID 23250790.
38. Fina F, Madla CM, Goyanes A, Zhang J, Gaisford S, Basit AW. Fabricating 3D printed orally disintegrating printlets using selective laser sintering. Int J Pharm. 2018;541(1-2):101-7. doi: 10.1016/j.ijpharm.2018.02.015, PMID 29454028.
39. Regenfuss P, Streek A, Hartwig L, Klötzer S, Brabant T, Horn M. Principles of laser micro sintering. Rapid Prototyp J. 2007;13(4):204-12. doi: 10.1108/13552540710776151.
40. Balasubramanian KR, Senthilkumar V. Additive manufacturing applications for metals and composites. IGI Global; 2020.
41. Wang D, Yang Y, Liu R, Xiao D, Sun J. Study on the designing rules and processability of porous structure based on selective laser melting (SLM). J Mater Process Technol. 2013;213(10):1734-42. doi: 10.1016/j.jmatprotec.2013.05.001.
42. Wickstrom H, Koppolu R, Makila E, Toivakka M, Sandler N. Stencil printing-a novel manufacturing platform for orodispersible discs. Pharmaceutics. 2020;12(1):33. doi: 10.3390/pharmaceutics12010033, PMID 31906316.
43. Madzarevic M, Medarevic D, Vulovic A, Sustersic T, Djuris J, Filipovic N. Optimization and prediction of ibuprofen release from 3D DLP printlets using artificial neural networks. Pharmaceutics. 2019;11(10):544. doi: 10.3390/pharmaceutics11100544, PMID 31635414.
44. Rycerz K, Stepien KA, Czapiewska M, Arafat BT, Habashy R, Isreb A. Embedded 3D printing of novel bespoke soft dosage form concept for pediatrics. Pharmaceutics. 2019;11(12):630. doi: 10.3390/pharmaceutics11120630, PMID 31779123.
45. Oblom H, Sjoholm E, Rautamo M, Sandler N. Towards printed pediatric medicines in hospital pharmacies: comparison of 2d and 3d-printed orodispersible warfarin films with conventional oral powders in unit dose sachets. Pharmaceutics. 2019;11(7):334. doi: 10.3390/pharmaceutics11070334, PMID 31337146.
46. Li CL, Martini LG, Ford JL, Roberts M. The use of hypromellose in oral drug delivery. J Pharm Pharmacol. 2005;57(5):533-46. doi: 10.1211/0022357055957, PMID 15901342.
47. Siepmann J, Peppas NA. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Adv Drug Deliv Rev. 2001;48(2-3):139-57. doi: 10.1016/s0169-409x(01)00112-0, PMID 11369079.
48. Picker Freyer KM, Durig T. Physical mechanical and tablet formation properties of hydroxypropylcellulose: in pure form and in mixtures. AAPS PharmSciTech. 2007;8(4):E92. doi: 10.1208/pt0804092, PMID 18181552.
49. Guirguis OW, Moselhey MTH. Thermal and structural studies of poly (vinyl alcohol) and hydroxypropyl cellulose blends. NS. 2012;04(1):57-67. doi: 10.4236/ns.2012.41009.
50. Panzade P, Puranik PK. Carbopol polymers: a versatile polymer for pharmaceutical applications. Res J Pharm Technol. 2010;3(3):672-5.
51. Azad MA, Olawuni D, Kimbell G, Badruddoza AZM, Hossain MS, Sultana T. Polymers for extrusion-based 3D printing of pharmaceuticals: a holistic materials–process perspective. Pharmaceutics. 2020;12(2):124. doi: 10.3390/pharmaceutics12020124, PMID 32028732.
52. Prasad LK, Smyth H. 3D Printing technologies for drug delivery: a review. Drug Dev Ind Pharm. 2016;42(7):1019-31. doi: 10.3109/03639045.2015.1120743, PMID 26625986.
53. Dos Santos J, da Silva GS, Velho MC, Beck RCR. Eudragit®: a versatile family of polymers for hot melt extrusion and 3D printing processes in pharmaceutics. Pharmaceutics. 2021;13(9):1424. doi: 10.3390/pharmaceutics13091424, PMID 34575500.
54. Patlolla A, Collins G, Arinzeh TL. Solvent-dependent properties of electrospun fibrous composites for bone tissue regeneration. Acta Biomater. 2010;6(1):90-101. doi: 10.1016/j.actbio.2009.07.028, PMID 19631769.
55. Goyanes A, Det-Amornrat U, Wang J, Basit AW, Gaisford S. 3D scanning and 3D printing as innovative technologies for fabricating personalized topical drug delivery systems. J Control Release. 2016;234:41-8. doi: 10.1016/j.jconrel.2016.05.034, PMID 27189134.
56. Matijasic G, Gretic M, Vincic J, Poropat A, Cuculic L, Rahelic T. Design and 3D printing of multi-compartmental PVA capsules for drug delivery. J Drug Deliv Sci Technol. 2019;52:677-86. doi: 10.1016/j.jddst.2019.05.037.
57. Goyanes A, Kobayashi M, Martínez Pacheco R, Gaisford S, Basit AW. Fused-filament 3D printing of drug products: microstructure analysis and drug release characteristics of PVA-based caplets. Int J Pharm. 2016;514(1):290-5. doi: 10.1016/j.ijpharm.2016.06.021, PMID 27863674.
58. Kempin W, Franz C, Koster LC, Schneider F, Bogdahn M, Weitschies W. Assessment of different polymers and drug loads for fused deposition modeling of drug loaded implants. Eur J Pharm Biopharm. 2017;115:84-93. doi: 10.1016/j.ejpb.2017.02.014, PMID 28232106.
59. Hardung H, Djuric D, Ali S. Combining HME and solubilization: soluplus®-the solid solution. Drug Deliv Technol. 2010;10(3):20-7.
60. Pelras T, Glass S, Scherzer T, Elsner C, Schulze A, Abel B. Transparent low molecular weight poly(ethylene glycol) diacrylate-based hydrogels as film media for photoswitchable drugs. Polymers. 2017;9(12):639. doi: 10.3390/polym9120639, PMID 30965940.
61. Ulery BD, Nair LS, Laurencin CT. Biomedical applications of biodegradable polymers. J Polym Sci B Polym Phys. 2011;49(12):832-64. doi: 10.1002/polb.22259, PMID 21769165.
62. Farah S, Anderson DG, Langer R. Physical and mechanical properties of PLA, and their functions in widespread applications-a comprehensive review. Adv Drug Deliv Rev. 2016;107:367-92. doi: 10.1016/j.addr.2016.06.012, PMID 27356150.
63. Fu J, Yin H, Yu X, Xie C, Jiang H, Jin Y. Combination of 3D printing technologies and compressed tablets for preparation of riboflavin floating tablet-in-device (TiD) systems. Int J Pharm. 2018;549(1-2):370-9. doi: 10.1016/j.ijpharm.2018.08.011, PMID 30107218.
64. Yu DG, Zhu LM, Branford White CJ, Yang XL. Three-dimensional printing in pharmaceutics: promises and problems. J Pharm Sci. 2008;97(9):3666-90. doi: 10.1002/jps.21284, PMID 18257041.
65. Seoane Viano I, Trenfield SJ, Basit AW, Goyanes A. Translating 3D printed pharmaceuticals: from hype to real-world clinical applications. Adv Drug Deliv Rev. 2021;174:553-75. doi: 10.1016/j.addr.2021.05.003, PMID 33965461.
66. Solanki NG, Tahsin M, Shah AV, Serajuddin ATM. Formulation of 3D printed tablet for rapid drug release by fused deposition modeling: screening polymers for drug release, drug-polymer miscibility and printability. J Pharm Sci. 2018;107(1):390-401. doi: 10.1016/j.xphs.2017.10.021, PMID 29066279.
67. Siamidi A, Tsintavi ME, Rekkas D, Vlachou M. 3D-printed modified-release tablets: a review of the recent advances. Mol Pharmacol. 2020:1-13.
68. Chen G, Xu Y, Chi Lip Kwok PCL, Kang L. Pharmaceutical applications of 3D printing. Addit Manuf. 2020;34:101209. doi: 10.1016/j.addma.2020.101209.
69. Goyanes A, Robles Martinez PR, Buanz A, Basit AW, Gaisford S. Effect of geometry on drug release from 3D printed tablets. Int J Pharm. 2015;494(2):657-63. doi: 10.1016/j.ijpharm.2015.04.069, PMID 25934428.
70. Yu DG, Yang XL, Huang WD, Liu J, Wang YG, Xu H. Tablets with material gradients fabricated by three-dimensional printing. J Pharm Sci. 2007;96(9):2446-56. doi: 10.1002/jps.20864, PMID 17497729.
71. Genina N, Boetker JP, Colombo S, Harmankaya N, Rantanen J, Bohr A. Anti-tuberculosis drug combination for controlled oral delivery using 3D printed compartmental dosage forms: from drug product design to *in vivo* testing. J Control Release. 2017;268:40-8. doi: 10.1016/j.jconrel.2017.10.003, PMID 28993169.
72. Rowe CW, Katstra WE, Palazzolo RD, Giritlioglu B, Teung P, Cima MJ. Multimechanism oral dosage forms fabricated by three dimensional printing™. J Control Release. 2000;66(1):11-7. doi: 10.1016/s0168-3659(99)00224-2, PMID 10708874.

73. Rahman Z, Barakh Ali SF, Ozkan T, Charoo NA, Reddy IK, Khan MA. Additive manufacturing with 3D printing: progress from bench to bedside. AAPS J. 2018;20(6):101. doi: 10.1208/s12248-018-0225-6, PMID 30209693.
74. Tian P, Yang F, Xu Y, Lin MM, Yu LP, Lin W. Oral disintegrating patient-tailored tablets of warfarin sodium produced by 3D printing. Drug Dev Ind Pharm. 2018;44(12):1918-23. doi: 10.1080/03639045.2018.1503291, PMID 30027774.
75. Fina F, Madla CM, Goyanes A, Zhang J, Gaisford S, Basit AW. Fabricating 3D printed orally disintegrating printlets using selective laser sintering. Int J Pharm. 2018;541(1-2):101-7. doi: 10.1016/j.ijpharm.2018.02.015, PMID 29454028.
76. Chen G, Xu Y, Chi Lip Kwok PCL, Kang L. Pharmaceutical applications of 3D printing. Addit Manuf. 2020;34:101209. doi: 10.1016/j.addma.2020.101209.
77. Li Q, Guan X, Cui M, Zhu Z, Chen K, Wen H. Preparation and investigation of novel gastro-floating tablets with 3D extrusion-based printing. Int J Pharm. 2018;535(1-2):325-32. doi: 10.1016/j.ijpharm.2017.10.037, PMID 29051121.
78. Chai X, Chai H, Wang X, Yang J, Li J, Zhao Y. Fused deposition modeling (FDM) 3D printed tablets for intragastric floating delivery of domperidone. Sci Rep. 2017;7(1):2829. doi: 10.1038/s41598-017-03097-x, PMID 28588251.
79. Maroni A, Melocchi A, Parietti F, Foppoli A, Zema L, Gazzaniga A. 3D printed multi-compartment capsular devices for two-pulse oral drug delivery. J Control Release. 2017;268:10-8. doi: 10.1016/j.jconrel.2017.10.008, PMID 29030223.
80. Pereira BC, Isreb A, Forbes RT, Dores F, Habashy R, Petit JB. 'Temporary Plasticiser': a novel solution to fabricate 3D printed patient-centred cardiovascular 'Polypill' architectures. Eur J Pharm Biopharm. 2019;135:94-103. doi: 10.1016/j.ejpb.2018.12.009.
81. Melocchi A, Parietti F, Loreti G, Maroni A, Gazzaniga A, Zema L. 3D printing by fused deposition modeling (FDM) of a swellable/erodible capsular device for oral pulsatile release of drugs. J Drug Deliv Sci Technol. 2015;30:360-7. doi: 10.1016/j.jddst.2015.07.016.
82. Charoenying T, Patrojanasophon P, Ngawhirunpat T, Rojanarata T, Akkaramongkolporn P, Opanasopit P. Fabrication of floating capsule-in- 3D-printed devices as gastro-retentive delivery systems of amoxicillin. J Drug Deliv Sci Technol. 2020;55:101393. doi: 10.1016/j.jddst.2019.101393.
83. Elkasabgy NA, Mahmoud AA, Maged A. 3D printing: an appealing route for customized drug delivery systems. Int J Pharm. 2020;588:119732. doi: 10.1016/j.ijpharm.2020.119732, PMID 32768528.
84. Lim SH, Tiew WJ, Zhang J, Ho PCL, Kachouie NN, Kang L. Geometrical optimisation of a personalised microneedle eye patch for transdermal delivery of anti-wrinkle small peptide. Biofabrication. 2020;12(3):035003. doi: 10.1088/1758-5090/ab6d37, PMID 31952064.
85. Vaz VM, Kumar L. 3D printing as a promising tool in personalized medicine. AAPS PharmSciTech. 2021;22(1):49. doi: 10.1208/s12249-020-01905-8, PMID 33458797.
86. El Aita I, Breitkreutz J, Quodbach J. On-demand manufacturing of immediate release levetiracetam tablets using pressure-assisted microsyringe printing. Eur J Pharm Biopharm. 2019;134:29-36. doi: 10.1016/j.ejpb.2018.11.008. PMID 30439504.
87. Sandler N, Preis M. Printed drug-delivery systems for improved patient treatment. Trends Pharmacol Sci. 2016;37(12):1070-80. doi: 10.1016/j.tips.2016.10.002, PMID 27992318.
88. Chung JJ, Im H, Kim SH, Park JW, Jung Y. Toward biomimetic scaffolds for tissue engineering: 3D printing techniques in regenerative medicine. Front Bioeng Biotechnol. 2020;8:1-12.
89. Awad A, Trenfield SJ, Goyanes A, Gaisford S, Basit AW. Reshaping drug development using 3D printing. Drug Discov Today. 2018;23(8):1547-55. doi: 10.1016/j.drudis.2018.05.025, PMID 29803932.
90. Lemu HG, Kurtovic S. {3D} Printing for rapid manufacturing; 2012. p. 470–9.
91. Ventola CL. Medical applications for 3D printing: current and projected uses. P T. 2014;39(10):704-11, PMID 25336867.
92. Science PS, Fusion C, Mohiuddin TMG, Lombardo A, Nair RR, Bonetti A. 3D printing PLGA-a quantitative examination of the effects of polymer composition and. Mater Des. 2021;11(20):5035-40. doi: 10.1016/j.matdes.2020.109338.
93. Cui M, Pan H, Su Y, Fang D, Qiao S, Ding P. Opportunities and challenges of three-dimensional printing technology in pharmaceutical formulation development. Acta Pharm Sin B. 2021;11(8):2488-504. doi: 10.1016/j.apsb.2021.03.015, PMID 34567958.
94. Paxton NC. Navigating the intersection of 3D printing, software regulation and quality control for point-of-care manufacturing of personalized anatomical models. 3D Print Med. 2023;9(1):9. doi: 10.1186/s41205-023-00175-x, PMID 37024730.
95. Wu HC, TCTC. Article information: about emerald www.emeraldinsight.com Quality control problems in 3D printing manufacturing: a review. Qual Control. 2017.
96. Ballardini RM, Lindman J, Ituarte IF. Co-creation, commercialization and intellectual property-challenges with 3D printing. Eur J Law Technol. 2016;7(3):1-39.
97. Choonara YE, Du Toit LC, Kumar P, Kondiah PPD, Pillay V. 3D-printing and the effect on medical costs: a new era? Expert Rev Pharmacoecon Outcomes Res. 2016;16(1):23-32. doi: 10.1586/14737167.2016.1138860, PMID 26817398.
98. Amza CG, Zapciu A, Baciu F, Vasile MI, Popescu D. Aging of 3d printed polymers under sterilizing UV-C radiation. Polymers (Basel). 2021;13(24):1-16. doi: 10.3390/polym13244467, PMID 34961017.
99. Khan FA, Narasimhan K, Swathi CSV, Mustak S, Mustafa G, Ahmad MZ. 3D printing technology in customized drug delivery system: current state of the art, prospective and the challenges. Curr Pharm Des. 2018;24(42):5049-61. doi: 10.2174/1381612825666190110153742, PMID 30636582.
100. Kissi EO, Nilsson R, Nogueira LP, Larsson A, Tho I. Influence of drug load on the printability and solid-state properties of 3D-printed naproxen-based amorphous solid dispersion. Molecules. 2021;26(15). doi: 10.3390/molecules26154492, PMID 34361646.
101. Dizon JRC, Gache CCL, Cascolan HMS, Cancino LT, Advincula RC. Post-processing of 3D-printed polymers. Technologies. 2021;9(3). doi: 10.3390/technologies9030061.
102. Vithani K, Goyanes A, Jannin V, Basit AW, Gaisford S, Boyd BJ. An overview of 3D printing technologies for soft materials and potential opportunities for lipid-based drug delivery systems. Pharm Res. 2018;36(1):4. doi: 10.1007/s11095-018-2531-1, PMID 30406349.
103. Varghese R, Sood P, Salvi S, Karsiya J, Kumar D. 3D printing in the pharmaceutical sector: advances and evidences. Sensors International. 2022;3. doi: 10.1016/j.sintl.2022.100177.
104. Ballardini RM, Mimler M, Minssen T, Salmi M. 3D printing, intellectual property rights and medical emergencies: In Search of New Flexibilities. IIC Int Rev Ind Prop Copyr Law. 2022;53(8):1149-73. doi: 10.1007/s40319-022-01235-1, PMID 36065358.
105. Khairuzzaman A. Regulatory perspectives on 3D printing in pharmaceuticals. AAPS Adv Pharm Sci Ser. 2018;31:215-36. doi: 10.1007/978-3-319-90755-0_11.
106. Prasanthi Nori L, Manikiran SS. An outlook on regulatory aspects of 3D printing in pharmaceutical and medical sectors. CTPPC. 2022;4(3):98-108. doi: 10.18231/j.ctppc.2022.017.
107. van Riet Nales DA, van den Bemt B, van Bodegom D, Cerreta F, Dooley B, Eggenschwyler D. Commentary on the EMA reflection paper on the pharmaceutical development of medicines for use in the older population. Br J Clin Pharmacol. 2022;88(4):1500-14. doi: 10.1111/bcp.15207, PMID 35141926.
108. Biglino G, Hopfner C, Lindhardt J, Moscato F, Munuera J, Oberoi G. Perspectives on medical 3D printing at the point-of-care from the new European 3D printing special interest group. 3D Print Med. 2023;9(1):14. doi: 10.1186/s41205-022-00167-3, PMID 37142797.
109. Longhitano GA, Nunes GB, Candido G, da Silva JVL. The role of 3D printing during COVID-19 pandemic: a review. Prog Addit Manuf. 2021;6(1):19-37. doi: 10.1007/s40964-020-00159-x.
110. Schuh JCL, Funk KA. Compilation of international standards and regulatory guidance documents for evaluation of biomaterials, medical devices, and 3-D printed and regenerative medicine products. Toxicol Pathol. 2019;47(3):344-57. doi: 10.1177/0192623318804121, PMID 30392453.

111. Bhat S, Venkatesh MP, Balamuralidhara V, Kumar TMP. Comparison of 3D printing in USA, Europe and Australia and IPR. J Pharm Sci Res. 2019;11(7):2515-20.
112. Beg S, Almalki WH, Malik A, Farhan M, Aatif M, Rahman Z. 3D printing for drug delivery and biomedical applications. Drug Discov Today. 2020;25(9):1668-81. doi: 10.1016/j.drudis.2020.07.007, PMID 32687871.
113. Tevetia N, Bhatt S, Pathak A, Prakash S, Bhardwaj A, Tyagi M. Global prospective of medical devices and their regulations. Int J Health Sci. 2022;6:2764-78. doi: 10.53730/ijhs.v6nS6.9957.
114. https://www.manufacturingtodayindia.com/people/9363-regulations-for-3d-printing.
115. https://www.oandp.com/articles/news_2016-05-13_01.asp?cv=1andmf=0.