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Review Article

Printing Health: Revolutionizing Pharmaceuticals through 3D Innovation

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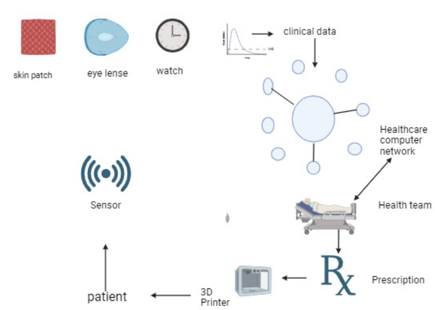
ABSTRACT

The influence of additive manufacturing has grown significantly in the last few years because of the rising awareness and need for customized pharmaceuticals, medical instruments, and equipment. With the innovation in three-dimensional printing (3D-Printing) technology providing a broad scope to explore the infinite dimensions in the pharmaceuticals field, 3D items of diverse geometries may be created. Cost-effectiveness and on-demand printing are two significant advantages of printed drugs over traditional drug production, as is the ability to create very complicated and sophisticated dose forms based on individual needs. This article discusses a few 3D printing processes useful for producing pharmaceuticals as well as how they may be applied to creating effective pharmacological and therapeutical dosage forms, demonstrating the viability of this printing technology for routine industrial production processes. The two main pharmaceutical application areas were covered in this article. First, drug delivery systems, including different medications like controlled release solid dosage form, more than one drug in the form of polypills, gastro-floating mechanism of the drug, in the form of oro-dispersible drug, and printed microneedles, are the subject that has received the most research. Second, 3D-Printing contributed to the creation of pharmaceutical tools, including drug-eluting devices and tools to help chemists dispense medication.

Graphical Abstract

Over the past 20 years, the additive manufacturing process has made remarkable progress. With the aid of 3D printing technology, we can easily print patient-specific medications in various geometries and enhance the medication's potency and dosage form.



Integrating technology with 3D printing

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Introduction

Three-dimensional printed drugs by additive manufacturing are creating an item by deposition method of material using a specific print head, nozzle, or different types of other printer technology, as defined by the International Standard Organization (ISO). Printing technology enables the creation of 3D objects with diverse basic and intricate geometries through a sequential layering procedure.[1] 3D printing technology encompasses a range of methods, such as fused deposition modeling (FDM), hot melt extrusion (HME), solid-state extrusion (SSE), stereolithography equipment (SLA), digital light processing (DLP), selective laser sintering (SLS), vat polymerization, and binder jetting.[2] By melting or depositing materials in consecutive layers through the 3D-printing (3D-Printing) technique, 3-dimensional things from digital design models. This methodology processes the layer-to-layer construction of object structures with a variety of geometrical properties. Other names for the technique include rapid prototyping, solid free-form fabrication, porous fabrication of solid dosage form, and additive manufacturing process.[3] 3D-printing technology has been more significant for the pharmaceutical field as well as helpful in engineering and many non-medical industrial sectors, including consumer products, automotive, and aerospace industries, since the late 1980s.[4] However, the development of adaptable biocompatible materials and recent fast advancements in 3D-printing processes have made it viable for 3D-printing technology to be used in the pharmaceutical business.

The pharmaceutical industry has moved one step closer to the age of personalized treatment through the adoption of additive manufacturing (AM).[5] Even when administered the same dose, in different patients this may be shown as inter-individual variations in medication reactions.[6] Due to these doses being beyond the therapeutic window, personalized medicine may reduce the likelihood of adverse effects or subtherapeutic benefits and promote patient satisfaction and adherence.[7,8] AM enables the production of intricate shapes for solid dosage forms and medical devices.[9] Although it has a comparatively slower manufacturing rate than traditional pharmaceutical mass production, this technique has some benefits over the traditional method, including potent drug individualization and comparatively inexpensive production costs for small batches.[10] Microneedles (MNs), which are drug delivery devices on a microscale, can be manufactured with AM technologies like DLP and SLA because of their ability to make extremely precise goods.[11] Furthermore, despite the fact that additive AM is a new technology in the market that facilitates quick prototyping, there are currently no set regulations governing it. However, it is very probable that challenges related to product quality, ownership, privacy protection, and intellectual property will emerge.[12] The economic benefits of 3D-printing pharmaceuticals over conventional manufacturing techniques focus on reducing production quantities, cutting waste, eliminating the use of complicated and expensive distribution networks between producers, treatment facilities, and pharmacy networks, and reducing paperwork.[13] 3D printing has shown to be beneficial not just in the pharmaceutical, medical-surgical, and healthcare industries but also in agriculture, education, robotics, food processing, electronics, construction, and jewelry creation.[13] Our current emphasis is on, the drug delivery system is the most extensively studied subject, encompassing microneedles, controlled release, gastro-floating, polypills, and orodispersibles. Furthermore, the utilization of 3D printing has played a significant role in the development of pharmaceutical equipment, including drug-eluting devices and pharmacy dispensing aids. The study conducted searches in the Medical Literature Analysis and Retrieval System Online (MEDLINE) and ExcerptaMedica Database (EMBASE) to find relevant research papers. For an article to be considered for inclusion, it must be published in the English language after 2018. Since several review articles describe the pharmacological usage of AM before 2018, only results from that year onwards were considered.[14] 3D-printing techniques need to be continuously refined and innovated to address the current challenges and eventually offer patient-specific healthcare with customized medications that can be ordered on demand.

History of 3D Printing

In the 1970s, Pierre A. L. Ciraud developed a method that included adding powdered material and then hardening each layer using a powerful laser concept of this technology is based on 3-dimensional printing. The commercialization of selective laser sintering (SLS) was the first successful use of Chunk Hull's invented technology. Ross Housholder obtained the initial patent and provided a description for the concept of combining sand with other substances in a patent titled "A modeling process forming a three-dimensional article in layers." Meanwhile, Carl Deckard pioneered a technique for hardening powdered beds using a laser beam. The photopolymerization of liquid resin produced by UV light is the mainstay of this strategy.

Scott Crump in the 1980s, submitted a patent application for fused deposition modeling (FDM), a technique that produces things by utilizing thermoplastic material.[15]

Demand for 3D Printing in the Current Scenario

In the present scenario healthcare sector is mainly based on a "one size fits all" paradigm. In this method, the same dose of the same drug applies to most of the patients and frequencies also.[17] Now it came to the focus that "one size fits all" is not appropriate for a wide range of therapies for every patient. The same drug at the same dose does not show the same responses in different

Table 1: The following lists a few 3D printing accomplishments in the biomedical and pharmaceutical fields[16]

Year	*Work on 3D-printing*
1980	The first patent filed on rapid prototyping technology by Dr. Hideo Kodama
1984	First Invented stereolithography apparatus by Charles Hull
1986	First producing apparatus using SLA technology by Carl Deckard
1989	Carl Deckard Granted a patent for SLA technology
	Scott Crump Filed a patent for FDM technology
1992	The first SLA technique introduced for 3D printing
1993	Emanuel Sachs take patent on 3D-printing technique
1996	Use biochemical ink for tissue generation
2000	Introduced SLM technique
2002	Fabricated functional kidney
2004	Dr. Bowyer Imaginate on RepRap concept for 3D-printing
2005	Z Corp First introduced the color 3D-Printing
2007	Selective layer customized for on-demand industrial part
2009	Release data on bioprinting blood vessels by Oranovo Inc.
2010	First in vivo introduced to use for bio-laser printing
2011	The first time 3D-Printing technology was used for silver and gold
	The first time 3D-printed based cars and robotics-based aircraft were introduced
2012	Artificial liver printed by
	First implant 3D printed prosthetics jaw
2013	3D-Printing metal gun produced by a solid concept
2014	integrated tissue creation using a multi-arm bioprinter.
2015	The first bio-printed kidney was Announced and released data by Organovo
	Spritam is first FDA approved 3D printed drug

individuals. Sometimes, these responses are modest, with less therapeutic response and unsatisfactory or less pharmacological effects, or they are exaggerated and linked to adverse drug reaction effects (ADRs). Both situations create complications for patient compliance.[18] Now, we focus on the initiation of customized and personalized drug delivery of medicines where drugs are adjusted or tailored according to the requirement of patients or tailored particularly according to individual patients who have similar types of genetic, pathological, or physiological characteristics. so for this approach, one size does not fit all, provides the required medicine with correct dose calculation, according to the exact condition of the patient, at a suitable time. Customized and personalized medicine aims to provide more precision medicines. It is safer for patients and most effective and improves patient compliance, with cost-effective.[19]

Need for Personalized Medicines

- Disease symptoms may be same but the illness of patients may be different.
- The effectiveness of tailor therapy provides the best response.
- It improves medical healthcare approaches.
- Reduce types of adverse and allergic reactions.
- The drug's safety and effectiveness can be enhanced
- Personalizes medication ability to develop medicine by using advanced human genomics sequencing.
- It can reduce the steps of treatment and cost.
- Various types of 3-dimensional drug printing technologies help develop patient-centered (personalized) medicines. It also provides to comfortability for patients to adjust the dosage, frequency of dose, drug dissolution profile, and the physical description of a drug (e.g. size, shape, organoleptic property) for different types of drug delivery systems according to the requirements of the particular types of patients (Table 1).[20]
- 3D-printed chewable pharmaceuticals provide improved accuracy, precision, and adaptability in terms of dosage and organoleptic qualities such as color and flavor.[21] Various forms this technology can be created 'Polypills' means that it consist of different types of drugs or active pharmaceutical ingredients (APIs) with specified and distinct release pharmacokinetics for each API. This allows for the potential of physically separating the drugs in the event of incompatibility between two or more drugs in a single dose[22] make the possibility of developing various types of flavors of tablets, which could improve patient compliance.[23]
- Researchers are developing the technology, i.e., a combination of printers with software, use of suitable excipients with APIs to get the dose accuracy, release kinetics profile of APIs, stability of drug stability, safety, and efficacy for human beings.[24] While such kind of technical developments are important for drug safety, efficacy, and the use of technology, it is also important to understand and focus on social aspects and their overall impact
- Social factors play a crucial role in integrating new technology with current technologies in the pharmaceutical business, enabling its practical deployment in the real world. Nevertheless, it is crucial to consider the influence of various legal and regulatory factors, the ethical considerations surrounding its use, the organizational requirements, and make importance of social aspects when analyzing the possible future application of 3D-printing for personalized medicines. This analysis should also include determining the suitable locations for

Fig. 1: Conventional manufacturing

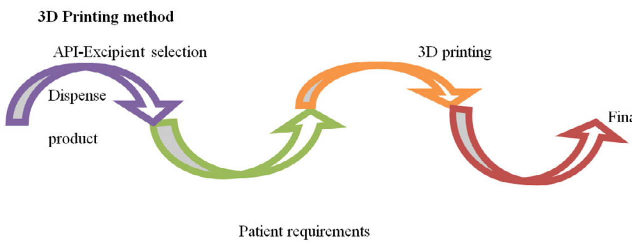

Fig. 2: Key difference between conventional and 3D printing methods

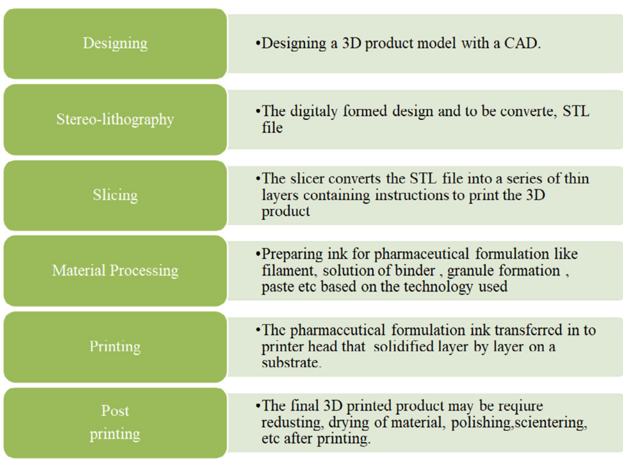

Fig. 3: General procedure for additive manufacturing

printing and evaluating the associated regulatory implications.[25]

Difference between Conventional and 3D-Printing Methods

Conventional manufacturing requires the optimization of several components for batch production or bulk production (Shown in Fig. 1),[22-25] but the 3D printing process does not need optimization for formulas or components (Shown in Fig. 2).[25,26] The conventional manufacturing process is time-consuming, requires more resources, and is effort-intensive, whereas 3D-printing is extremely efficient and very cost-effective regarding time, use of resources, and efforts. Furthermore, 3D technologies, are based on customized and personalized drug delivery systems that allow the fast design of drug profiles for specific patients. General important key points of additive manufacturing shown in Fig. 3.[26]

Types of 3D Printing Techniques

3D printing processes may be classified based on their energy sources, material sources, and mechanical features of the printers. The creation of medical equipment and

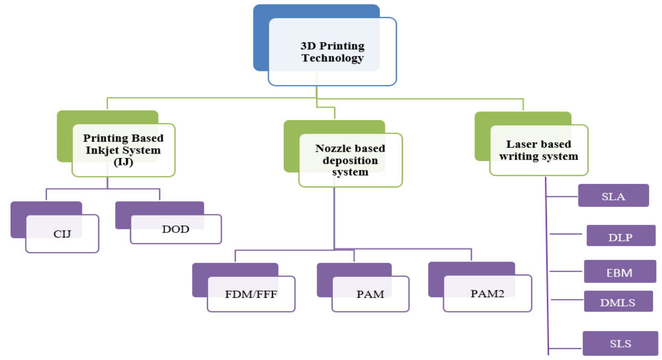

Fig. 4: various types of 3D-printing technologies

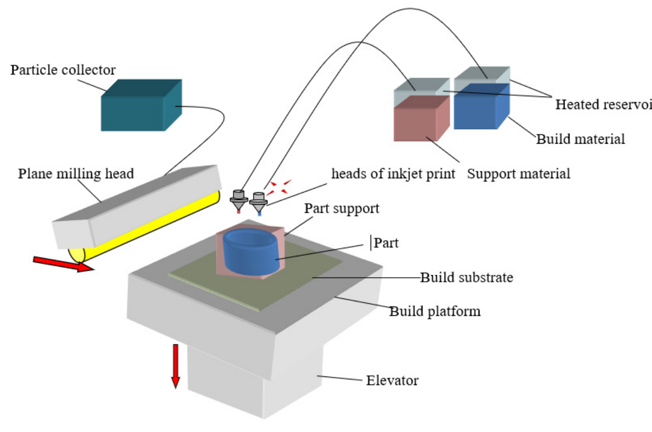

Fig. 5: Inkjet printing

pharmaceutical medications commonly involves three types of 3D printing technologies, as mentioned in Fig. 4 and Table 2 and 3[26] and some selected example shown in Table 4.

Inkjet System for 3D-printing (IJ)

Inkjet printing

The 3D printing process is injected based in which dropped ink is jetted out with the help of a nozzle and dispersed on top of a powder surface in the form of one by one to cobble together and create 3D objects. (Shown in Fig. 5A).[21-26]

Dose adjustments are achieved by modifying the number of layers printed in the designated region, while the medicine and excipients are formulated in a certain proportion that enables them to be printed as microdots onto an ingestible surface.

One notable benefit is accurately regulating the dosage mix and timing of medication delivery. Inkjet printing necessitates the use of starting materials with certain characteristics: -

- Particle size less than 1-µm to avoid clogging the printer head
- Viscosity less than 20 cP
- surface tension between 30 and 70 nm/m for efficient flow.

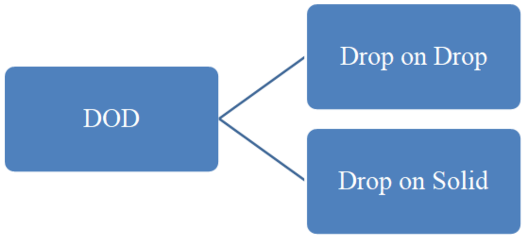

Fig. 5: Types of DOD

The inkjet system is divided into two subtypes of technology

Continuous inkjet printing (CIJ)

This printing method involves the continuous emission of inkjet through a specified number of apertures with a diameter (50–80 µm). This method employs a pump that operates at high pressure.

Drop on- demand printing (DOD)

This technology is based on producing droplets of size 10 to 50 µm with volume 1 to 7 pl. [26]
Drop-on-demand printing systems utilize two distinct types of printer heads.

- *Thermal head/bubble jet printing*

In this process, when heated ink creates bubbles and then ejects ink on the object. Thermal DOD This method is restricted to volatile liquids.[3] The main disadvantage of the thermal method sometimes temperature reaches up to 300°C, that's way possibly causes the degradation of the drug.

- *Electromagnetic head/piezoelectric crystal*

In this technique, a piezoelectric crystal undergoes fast deformation, resulting in a change in its volume and generating a powerful sonic pulse that is sufficient to expel the ink.[27] The piezoelectric drop-on-demand approach utilizes a different array of liquids. The piezoelectric drop-on-demand method is commonly used for more biocompatible and less volatile liquids at room temperature. For use of the piezoelectric method is more suitable than the thermal method in pharmaceutical applications.

Drop-on-demand printing (DOD)

This method is divided into two sub-types (Fig. 5B).[27]

- *Drop-on-drop deposition*

This technique is an Inkjet printing approach that is appropriate for producing minuscule drug delivery devices with diverse geometric configurations of medicines. In this approach, the droplet size has a diameter of 100 µm, and the thickness of a layer is less compared to the droplet size. The surface of wetting and solvent evaporation mostly causes this.[28] In the drop-on-drop deposition method, The formulation must be appropriate for jetting

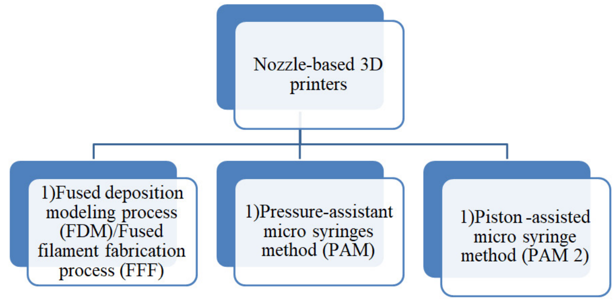

Fig. 6: Types of nozzle-based system

and quick material solidification during usage. [23,28] In these techniques, physical properties like viscosity, surface tension, and volatility should be suitable and optimized, reported between 8 to 14 cps[29] to prevent nozzle clogging, coffee ring effect, and fluid leakage problems.[23,29] The drug loading capacity and stability of the product are influenced by both its physicochemical and therapeutic qualities.[23.30]

- *Method of drop-on solid/drop-on powder bed deposition*[30]

A wide range of drugs are used in drop-on solid deposition method. In this method thickness of the powder bed is generally 200 µm and particle size generally ranges from 50 to 100 µm.[30] The spacing and thickness of the layers should be tuned to enhance adhesion. The topological properties and powder bed reactivity that contain binder ink are crucial, and represent significant elements that might impact the overall quality of the end product.[30]

Nozzle-based deposition system

The printing-based IJ method is the most general printing method but some drawbacks in this method, like insufficient hardness, rough surface, and low drug loading.[31] The addition of the drug through a binder solution and this solution dropped on a powder bed, but in a nozzle-based system, the addition of the drug in the solid powder earlier to the binder directly deposited mixed material through a nozzle and created a 3D object.[32] Nozzle-based 3D printers are divided into two subtypes, shown in (Fig. 6).[31-32]

- *FDM/FFF*

This method is used in various fields, including pharmaceutical, food, and bioengineering.[33] This approach involves utilizing thermoplastic material as a polymer and combining it with medicinal medications through an incubation process using certain solvents or

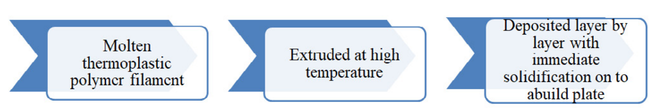

Fig. 7: Process of FDM technique

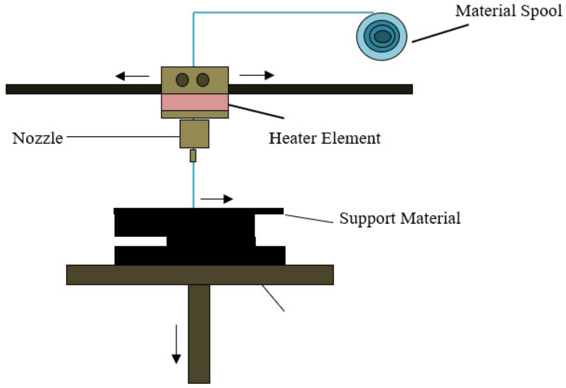

Fig. 8: Fused deposition modeling

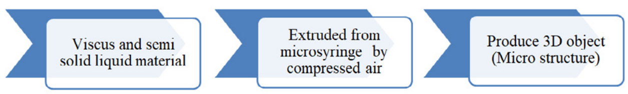

Fig. 9: Process of PAM technique

by melting the polymer and pharmaceuticals together at a precise temperature (Fig. 7).[34] The resulting mixture is then extruded in the filament process of FDM.[34]

The method of fused deposition modeling (FDM) is an affordable technology for producing intricate shapes and has excellent mechanical durability (Fig. 8).[34] As well as it allows adjustment of the drug releases.Some limitations of the FDM method for pharmaceutical applications such that it operates at high operating temperatures, the chances of degradation of drugs and very few options are provided regarding biodegradable thermoplastic polymers.

- *Pressure assistant micro-syringe (PAM)*

It is another method of the nozzle-based deposition system process of FDM (Fig. 9). [34]

In this technique (PAM) syringe can be moved like an Ink Jet printer head. Pam technology produces 5 to 10 µm or less microstructure.[35] PAM technology can help develop various types of complex types of drug delivery systems, and it can be easily operated at room temperature with a continuous flow, but limitations in this process like drug stability and safety issues for solvent during manufacturing and drying steps at room temperature.[30,36]

- *Piston-assisted micro syringe (PAM 2)*

In the PAM 2 method, a stepper motor is used rather than compressed air to release the printing material.[36] Process of PAM 2 shown in Fig. 10.[36]

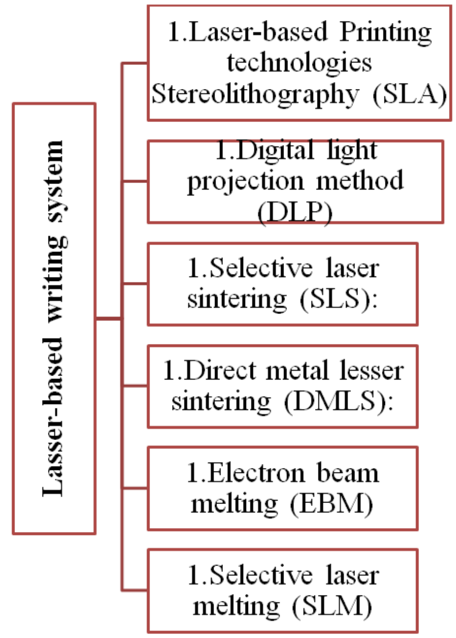

Fig. 11: Lasser-based 3D system

Process of PAM 2

Lasser-based writing system

The technique of direct laser writing is employed, utilizing two-photon polymerization of photopolymers. This method occurs when photosensitive materials are cured spatially using near-infrared (NIR) ultrashort laser pulses, reaching a certain threshold intensity. Laser-based writing systems are primarily categorized into six subcategories. (Fig. 11).[36]

Laser-based printing technologies stereolithography (SLA)

The fabrication of three-dimensional objects using the SLA technique relies on the precise solidification of liquid resin using photo-polymerization.[37] SLA process allows high resolution that is capable of the formation of complex structures and minimizing the heating during the printing procedure and this method applies to highly thermolabile drugs.[26,37] Process of SLA highlighted in Fig. 12.[37]

During operating SLA technology (Fig. 13)[38] selection of photopolymer is essential because liquids quickly solidify the liquid with UV light and for the safety of human use should be quality and safety approved as per regulatory guidelines. The FDA prohibits for SLA technique for pharmaceutical purposes. Nevertheless, it is widely employed in the realm of tissue engineering.[38]

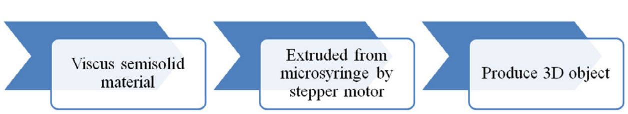

Fig. 10: Process of PAM-2 technique

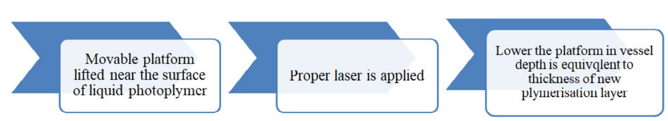

Fig. 12: Process of PAM-2 technique

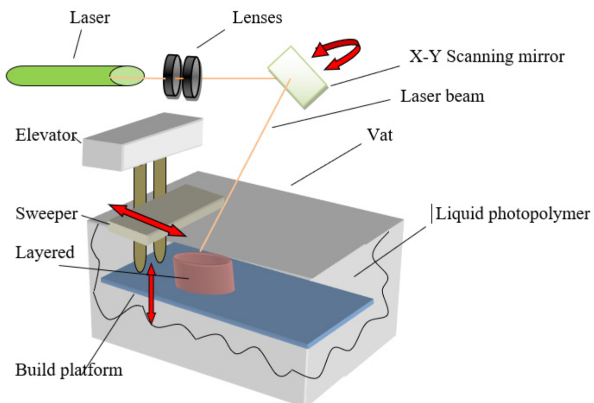

Fig. 13: In the SLA process vessel filled with liquid photopolymer with a movable platform

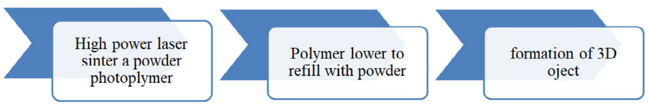

Fig. 14: Process of SLS technique

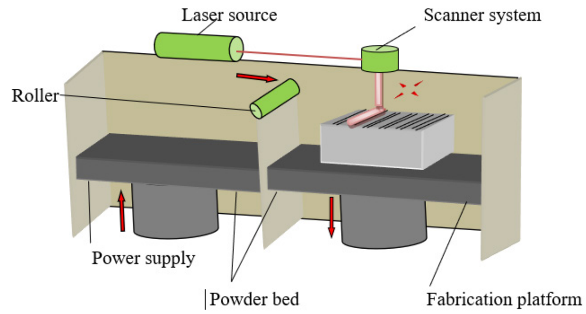

Fig. 15: Selective laser sintering

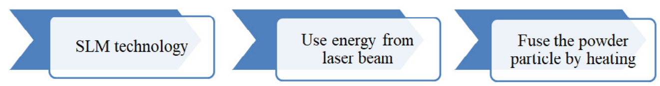

Fig. 16: Process of PAM-2 technique

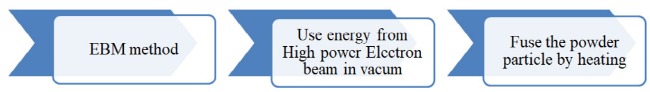

Fig. 17: Process of PAM-2 technique

Digital light projection technique (DLP)

his approach and the SLA approach are comparable. Using a laser beam and liquid photopolymer resins, this technique solidifies the liquid and produces a three-dimensional object.[39] The primary difference between DLP and SLA is that DLP allows for the simultaneous curing of a single layer by using a digital mirror device. By controlling millions of mirrors simultaneously, a complete layer may be cured all at once, significantly cutting down on the time needed to manufacture layers.[30.39] The DLP technique is faster than the SLA technique and makes it easy to adjust the layers' thickness.

Selective laser sintering (SLS)

This technology utilizes a source of high-energy laser to sinter a powder photopolymer. This technique involves selectively melting the powder of the photopolymer using a laser. Afterward, the platform that holds the polymer is lowered to be refilled with powder once more. Process of SLS technique shown in Fig. 14.[39]

The primary benefits of the SLS process are its ability to offer exceptional strength, resistance to chemicals, and rapid production speed. SLS technology diagrammatically shown in Fig. 15.[39]

Method of Direct Metal Lesser Sintering (DMLS)

This method is the same as the SLS process, but the DMLS technique is applied for metal alloy and the selective laser sintering (SLS) process is utilized for a diverse array of materials, encompassing various types of polymers, metals, and ceramics.[30,39,40]

SLM and EBM technique

The EBM and SLM techniques involve the full melting of metal powder and its subsequent deposition in a layer-by-layer fashion. SLM and EBM offer more consistent thermal field distribution in comparison to the SLS process, albeit they have lesser surface quality and precision.[40] SLM and EBM methods are mostly used in drug-loading implants.[41]

Method of Electron Beam Melting (EBM)

The first step in the EBM 3D printing process is to create or obtain a 3D model by using CAD software, scanning, or download. In this process utilizing metal powder, the 3D printer deposits it in thin, heated layers that are fused by an electron beam (Fig. 16).[40] This process is repeated until the part is finished. This processing takes place in a vacuum to minimize oxidation and leftover powder can be recycled.

Method of Selective Laser Melting (SLM)

Selective laser melting (SLM) technology, metallic particles are melted and fused together layer by layer using a powerful laser (Fig. 17).[40] This method creates products in a layered pattern, making it a form of additive manufacturing.

Drug loading mechanism

In the current scenario, many 3D printing technologies are available, but most things in pharmaceutical applications are loading mechanisms. Many drug-loading mechanisms have been implemented to achieve effective therapeutic doses.

Table 2: Summary of some selective 3D technologies

3D-printing	*Types of 3D printing technologies*	*Specific category*	*Types of mechanism of layering by 3D-printing*	*Advantages*	*Disadvantages*	*References*
Based on printing system (Inkjet)	Powder bed (inkjet printing)	Binder jetting	Selectively binding agent (liquid) deposited on powder materials	cost low with a faster rate of production cycle minimum processing steps possibility of on-demand individualized dosing possibility of precise dosing generation	a) Needs postprocessing (like Drying, powder removal b) Show low mechanical properties c) Need appropriate suitable viscosity of ink d) More powder wastage	[42-44]
	Poly-jet or thermo-jet (inkjet printing)	Material jetting	Droplets form-built material is selectively deposited			
Based on the deposition system through a nozzle	Method of fused deposition modeling (FDM) Method of pressure assistant micro-syringes (PAM) Piston assistant micro-syringe (PAM 2)	extrusion by melting Material	through a nozzle or an orifice, material is released	a) Economical 3D-printing that way acceptable for various applications b) Cheaper in cost because use of plastic material c) Physical parameter friability and uniformity of drug is high	a) In support requires leave marks removing sanding. b) Using thermoplastic material, limited testing agents available c) Because of using a high temperature of a process starting material chances of deteriorating e) In this process advanced filament	[36] [44] [36]
Based on the Laser writing system	Laser writing by stereolithography method (SLA) Method of laser digital light projection (DLP) Laser-based method of continuous layer interface production (CLIP)	Vat polymerization	Selectively light-activated polymerization in Liquid photopolymer through vat	a) The object's size is significantly smaller, with layers that are deci-micron and submicron in size. b) This is high accuracy and resolution 3D-printing process	a) Required post printing curing b) High cost of equipment c) More time-consuming process	[43] [46]
	Method of SLS (Selective laser sintering) Method of DLSM (Direct metal laser sintering) Method of SLM (Selective metal sintering) Method of EBM (Electron beam melting)	Fusion of Powder bed	Thermal energy selectively fuses a powder bed's region.	a) Posses' high porosity and internal microstructure b) Easy to maintain and reproducible	a) It needs a post-printing process as a finishing procedure b) Limited speed for sintering c) Chances of degradation of starting material due to use of high energy input	[47] [40]

Generally loading mechanism is divided into two parts:

- Adding pharmaceutical ingredients to the printing matrix either before or after the printing procedure
- Sometimes firstly without drug prepared implant, then drug loaded into implant by HME process:[41,47]

Procedure for 3D printing, the filament in the FDM can be filled with both the medication and the excipient. In the HME process, medications are either coated onto polymer pellets or combined with polymer beforehand.[48,53,54,59]. The drug dispersed in filament should be homogeneously and uniformly for the controlled form of drug loading into the implant because, during the printing process, no mixing effect occurs. If filaments have a less homogeneous drug distribution produced.[60] Where some part of the pure polymer is first melted by using an extruder then the remaining part of the polymer and calculated amount as per formulation is added gradually in the melted part. The homogeneity of medication mixing mostly relies on the type of extruder used, which can be either a single or twin-screw extruder.[45]The above drug loading processes indicate quality of filament is important for suitable feeding material and, thus for printed implants. Sometimes blending process of starting material also complies with the homogeneous mixing of drugs by another extrusion method of 3D-printing whether heat is supplied or not.[51,61,62]

Drug incorporation by immersing method: Drugs are introduced inside the filament by submerging the filament without the drug into a highly concentrated drug solution. The selection of solvent is important for dissolving enough medication and a choice of polymer material that should not be dissolved in the solvent because it helps to maintain the filament structure. In the diffusion-based technique, achievable drug loading is limited due to the characteristics of polymer, solvent, and drugs.

For example, by impression method PVP, polymer filament loaded 5 ± 1% of ciprofloxacin drug amount in ethanolic solution, but aqueous solution of same drug 3 ± 1% loaded in PP polymer filament.[63] The main advantage of the immersion method, drugs do not come directly to high temperatures like the HME process. However, in the future, this method will not be very useful for the development of pharmaceuticals because using concentrated drug solutions is more costly as well as, the effect of heat exposure also, there are some more limitations on attainable drug loading by this technology. When using DLP process in which drugs are incorporated into the printed matrix in the form of suspended or dissolved in liquid photopolymer furthermore should be examined the impact of crosslinking behavior.[64,65] In the 3D inkjet process Drugs are added into the implant through a powder bed or binder solution of the printing process.[66–69]

By this process solubility and stability of the drug must be important within the appropriate concentration of binder solution, which typically contains acetone methanol or ethanol.[66–70]

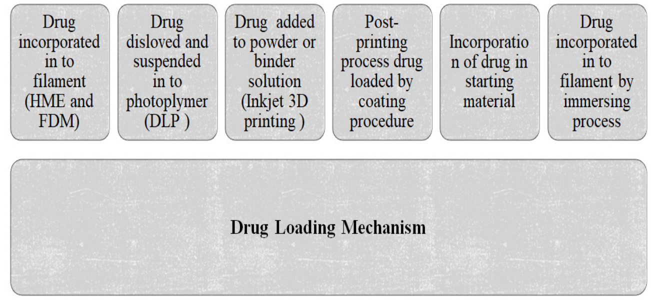

Fig. 18: Drug loading mechanism

Sometimes one or more drugs in to implanted by using multiple cartridges of printer that are independent of binder solution.[71,72]The aforementioned drug loading mechanisms exemplify the advancement of the printing process in comparison to drug inclusion by the manual approach employing the pipetting process, which was already employed in the first research.[73] post-printing procedure drug can be loaded in a drug-free 3D-printed implant by a coating process.[74,75] Sometimes, the solution of the drug may be added drop by drop to the object for the 3D-printing,[76,77] or in the drug solution whole implant can be immersed, often under this creating vacuum, to absorb the drug.[65,74–83] Post-printing process is more time-consuming and needs of the appropriate concentration of drug in the innermost part of the implant. Another, exceptional post-print drug-loading mechanism involves incubating the implant with sublimed iodine.[84] Mainly, drugs loaded with supercritical carbon dioxide or powder drugs are filled manually or sometimes drugs loaded in alginate gel that filled into hollow or reservoir structure of printed material. Some potent and sensitive drug materials were excluded before or during the printing process into printed implant matrix because of their degradation of drug properties. Like, heat-sensitive thermolabile drug material is not suitable for HME & FDM 3D-Printing processes because the polymers need to melt at high temperatures. Drug incorporation of starting materials, achieving homogeneous drug distribution but drug loading by immersion process is based on parameters like temperature and time. Accomplishing a long-term drug release profile depends on the distance of diffusion of drugs from the center of a matrix to the boundary of the neighboring tissues or body fluid, so it is vital for the long-term release of active ingredients depends on the fill quantity of the active ingredients in the entire matrix of implant because it is not easy to achieve by drug loading in post-printing process.

Based on the above points, we can use different drug loading mechanisms (Fig. 18)[41-83] as per the requirement of formulation but have some limitations due to different drug properties, use of types of printing ink material, as well as required properties, including dissolution profile of implants for the final product.

Application of Additive Manufacturing for Pharmaceutical Dosage Form

Different types of printing technologies are available at the present scenario, but 3 kinds of 3D printers like inkjet 3D printer (IJ), types of nozzle deposition, and types of laser-based 3D-printing, mainly accessible for manufacturing of pharmaceutical dosage basically in this review focuses on oral solid dosage and pharmaceutical devices that are under process and more fit for a wide range of application.

Solid oral dosage forms

The oral dosage form is one of the popular dosage forms in pharmaceutical drug delivery systems. Typical illustrations of the most used oral solid dosage forms include compressed as tablets and capsule forms of medications. The feasibility of 3D printing should be thoroughly designed for pharmaceutical manufacturing, particularly regarding tablets. 3D printing techniques for tablets can be divided into two categories: tablets with a single API and tablets with numerous APIs. [83,84]

Controlled release

A new technique for producing pharmaceutical tablets that can withstand regulatory testing and match the release of conventional commercial tablets was 3D printing. For a medicine to be absorbed and have a therapeutic effect, it must first be released from its dosage form. Mostly, oral dosage formulations are manufactured for immediate release (IR), which is necessary for the drug to be absorbed and show more therapeutic effects. Contrarily, prolonged or sustained release allows for the progressive release of medication, limiting variations in drug levels in systemic circulation caused by frequently ingesting a variety of IR dosage forms.[85] Traditional sustained-release tablets feature a non-constant drug release due to their total surface area decreasing as they undergo gastrointestinal tract absorption. This problem can be solved by AM by fabricating the tablets with different complex geometries, which enable both individualized release profiles and continuous sustained- release dissolution profiles.[85] A spherical shell was printed with an unfilled internal tetrahedron hollow using polyvinyl alcohol (PVP), then filled with a mixture of drug and PVA. Water caused the tablet to erode the four corners outward, revealing more and more of the tetrahedral-shaped core. Over time, this increased the drug solubility. Patients with hypertension, for example, may find the rapid drug release beneficial as they take this kind of pill at night and have the highest possible drug concentration in their blood by morning. Another illustration occurred when Kadry *et al.* fabricated tablets in different infill patterns by using an FDM printer.[86] By using the extrusion method, create the drug-impregnated filament of drug diltiazem and hydroxy propyl methyl cellulose powder, and as a result, show tablets quickly dissolved due to a hexagonal infill pattern. Yang *et al.* also reported tablet patterns affected the drug release rate. [87] A mixture of Ibuprofen and ethyl cellulose is use in filaments to develop the tablets with an FDM printer. Furthermore, it is known drug release rate depends on the surface area. Based on this, different release profiles of tablets can be designed by Khaled *et al*. for manufacturing tablets in various sizes and shapes by using an extrusion-based 3D technique.[88] The medication was released more quickly from the tablets with greater surface surfaces. To improve medication release, the idea of expanding the surface area has been applied. Isreb *et al.* suggested a unique radiator-like construction with a surface area-to-mass ratio that was 7 to 8 times greater than that of conventional tablets.[89]

Polypills

A single tablet known as a polypill can have numerous APIs loaded into it to integrate complex treatments into one regimen. Recently, many polypills have been prepared with regulated release characteristics using 3D-printing technologies.[89] A polypill with six active ingredients was developed by Wald and Law in 2003 as a preventative measure for lowering cardiovascular illnesses by more than 80%. The fact that it failed to take into account the various dosage or combination requirements of various persons, or how such needs can change over time, as well as worries regarding chemical incompatibility between components, led to harsh criticism at the time.[90] For the treatment of diabetes and hypertension, polypills with controlled release characteristics using 3D-printing technology, 3D extrusion-based printing was first used to create a polypill containing captopril, nifedipine, and glipizide (Fig. 19A).[89] A drug captopril osmotic pump compartment, connecting layer, and sustained release of drug nifedipine and glipizide compartments made up this polypill. Following ingestion, the connecting layer immediately breaks down, resulting in the polypill separating into two compartments, one captopril and the other for sustained release compartment. The drug nifedipine and glipizide (sustained release compartment) are released by diffusion through the gel layer and the compartment of captopril drug is osmotically released in zero order through a controlled porosity shell.[91] Also, they created a polypill containing five APIs using 3D-printing technology.[91] This polypill has two compartments,

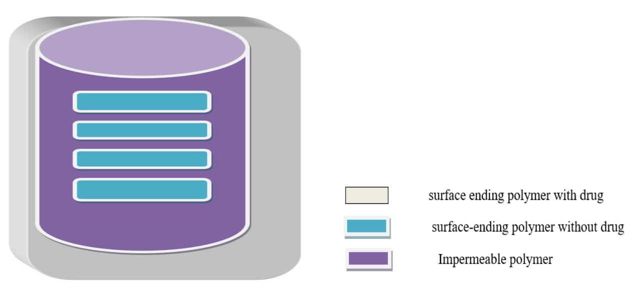

Fig. 19: A) The polypill illustrating the usage of various polymers

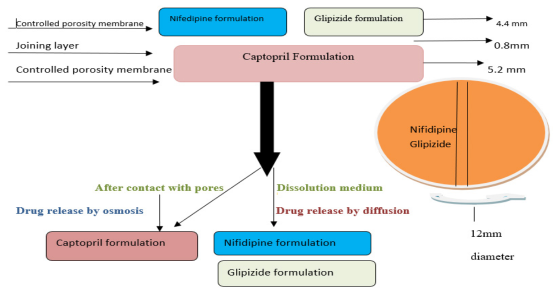

Fig. 19 B): Diagram representing multi-drug and multifunctional polypill (The Polypill contains three drugs in one tablet)

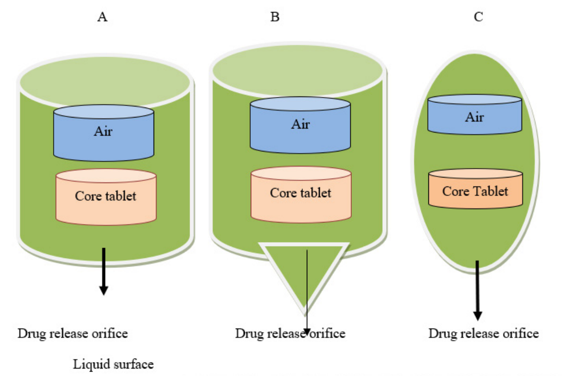

Fig. 20: Housing design of the 3D printed floating tablet, A) cylinder B) top, and C) Sphere

one for immediate release and the other for prolonged release, each with its own controlled release profile. In the compartment of immediate release, present aspirin and hydrochlorothiazide drugs, whereas drugs ramipril, atenolol, and pravastatin were in the sustained release compartment.

Use of 3D printed polypills to regulate more intricate release profiles to develop a multi-action release profile, many types of drug carrier molds or templates are made. This allows for the acquisition of a more complex release profile rather than only zero or first-order releases.

Specifically, the drug-containing surface eroding polymer (Fig. 19B)[89-91] fabricated with a particularly complex shape that allows the desired dissolution of the drug release profile. By altering the form and design of the surface-eroding polymer that contains a pharmaceutical medication, many drug release profiles can be achieved, including steady release, increasing or decreasing release, and pulse release (drug release synchronised with the patient's biological cycle).

Gastro floating tablet

Orally administered drugs show better absorption in different parts of the gastrointestinal tract depending on their physiochemical properties. One such medication, dipyridamole, was designed for gastrofloating tablets through an extrusion-based 3D printing method that enhances the gastric retention period and also enhances the bioavailability and therapeutic effect. To extend the gastric retention period of drugs, there are designed primarily two types of gastric floating devices (Fig. 20.)[92] One type uses CO2 gas to sustain buoyancy, whereas the other type uses non-effervescent systems that are designed to reduce bulk density to float gastro-floating tablets. A technique created by Huanbutta and Sangnim where a 3D-printed container consisting body and cap that carries drug loaded tablet core. Drug release is done by pore in the container. [92] The printing ink is made of a mixture of microcrystalline cellulose as the extrusion molding agent and HPMCs for its hydrophilic properties. It is printed using an extrusion-based printer at room temperature.

Various infill rates were employed to investigate buoyancy and drug release rate features.[93] The tablet descended as lattice density rose, and by the rise in weight, the faster rate of drug release. A hot melt extruder was used to incorporate the medication, domperidone, into HPC filaments. The low density and stiff shells caused the observed prolonged floating and release. Another study created tablets with various interior architectures using a novel AM technology called pressure-aided micro-syringe (PAM).[94] A range of typical pharmaceutical excipients, including lactose, microcrystalline cellulose, PVP, and HPMC, can be printed using PAM. As these excipients must adhere to laws for pharmaceutical applications, it is advantageous to utilize them as printing inks.

Oro-dispersible

Patients tend to use oral forms of medication since they find them to be the most convenient.[93,94] Oro-dispersible tablets can be taken without the use of water as they are made to dissolve in the mouth. Oro-dispersible tablets often have a kind of special porous structure, which enhances the drug release dissolution profile. The traditional manufacturing process needs particular compaction forces for punching tablets, but in the additive manufacturing process, no need for any compaction for that's why the 3D-printing tablet's final structure is significantly more porous and disintegrates more quickly. Spritam™ (FDA-approved drug) was printed via a 3D printing binder jetting method that dissolves in 2 to 27 seconds and it is the first 3D-Printing medicine approved by the US Food and Drug Administration (FDA).[30,43,93,94,] preparation of oro-dispersible warfarin tablets with the same method; the tablets were dissolved in one minute.[95] Additionally, it proved that SLS could make oro-dispersible paracetamol tablets with various dissolution rates[43,95]

Pediatrics preparations

Due to changes in physical features and pharmacokinetics, dosage requirements for young individuals can be noticeably different from those for other patients.[96] As a result, doses for such a group must be carefully tailored to minimize toxic consequences. Although syrups can be used as pediatric formulations and are dose-adjustable, they are prone to dosage errors.[10,90,93,96] A 3D-printed miniature tablet is a creative solution to this issue. A micro tablet may be simpler to administer than syrups because of its smaller size and milder flavor. Additionally, AM can be utilized to change doses by regulating the amount of material employed.[97] Scoutaris *et al.* suggested a different dose form for young children, which included chewable tablets with amusing shapes and flavor masking. This study used drug-polymer H-bonding interactions, which were made possible by hot melt extrusion, to conceal the disagreeable taste of indomethacin. To appeal to younger children, the drug-loaded filament was then put into a 3D printer and created into a playful shape second.[10,98]

Implant

An implant is a sustained-release drug delivery matrix containing active drugs. For long-term treatment of patients, this technique become helpful. Traditional approaches for implants only focus on prolonged and extended drug delivery systems, but recent use of new advanced technologies of 3D printing-based implants, printed to complex forms of macro and micro structures implants in single one device that are useful to achieving multi-drug loading and sophisticated drug release characteristics. Such as fabricated levofloxacin implants with a predetermined microstructure, that release profile exhibits in a single implant.[66,96,97]

Recent studies have proved that multiple API-loaded 3D-printed implants helped to increase the additional therapeutic properties of drugs.[98] 3D-printed scaffolds having the combination of calcium phosphate cement along with vascular endothelial growth factor (VEGF) loaded hydrogel strands helped in bone defect recovery.[99,67] 3D-printed implants that are designed with multiple drugs used in the treatment of tuberculosis disease transdermal microneedle (MN) patches.

Microneedles have an array of micro-sized needles that are used for transdermal drug delivery systems to increase penetration of biologically active chemicals in the skin. Because of its microstructure, microneedles may deliver the macromolecules of substances via the skin more effectively than conventional patches. Recent advancements in 3D printing techniques with high resolution are beneficial in the manufacturing of microneedles. To achieve this, AM technologies, particularly SLA and DLP, offer microneedle manufacturing alternatives. The biocompatible liquid resin was printed using an SLA printer onto microneedle patches, which were subsequently cleaned by using alcohol to get rid of any leftovers.[100] After that, place tiny layers of insulin sugar onto the MN surface by inkjet printing. Similar to this, Uddin *et al.*, using an SLA printer, created polymeric MNs and then coated the MN with formulations containing cisplatin.[101] It has been demonstrated that crucial factors to take into account when printing MNs using SLA 3D printers are that MNs have mechanical strength, buckling load, and the force necessary to puncture human skin.[102]

Pharmaceutical devices

Different kinds of 3D-printed devices used in the pharmaceutical field are given below:

Aids for dose dispensing

The creation of prototypes is one of the primary uses of AM outside the pharmaceutical business. In the past use of customized dies or molds was called prototyping, which was time-consuming and expensive to acquire. We can quickly and easily create and reprint customized and personalized models with AM. Printing of drugs is a comparatively cost-effective procedure that does not require various types of specialized equipment.[118] Additionally, a variety of biodegradable and ecologically friendly materials are readily accessible on the market today, reducing the environmental effect. Recently, additive manufacturing has verified a powerful printing technology for pharmacy dispensing equipment that is suitable for personalized and customized medicines. Niese *et al.*, formed the pharmacy dispensing device for active ingredients- containing continuous film to provide customized medicine and adjustable dosage. [119]

Drug-eluting devices

Drug-eluting dosage forms reduce the patient's requirement for frequent dosing by providing the sustained release of therapeutic substances for a considerably prolonged time than oral dosage forms. This considerably reduces issues with non-adherence, whether deliberate or accidental.[120] Using the local method can decrease the exposure limit of healthy tissues and reduce the side effects compared to the systemic distribution of drugs.[121] When compared to other delivery methods, using an implanted device might sometimes offer extra benefits. Particularly, sustained-release devices do not have the same risks related to increased eye pressure as intraocular injections do.[59] Drug-eluting implants are available in different varieties of their use, including opioid addiction, cardiovascular illness, ocular delivery, and contraception.[59] By adjusting various dosage, geometry, and dissolution release profiles of the dosage forms, AM can be employed to get around this. The most recent advancements in this field include drug-eluting catheters, implants for cancer therapy, and hormone-containing dosage forms for gynecological uses. FDM has been utilized to create constructions that elute hormones. Utilizing biodegradable polymers of polycaprolactone (PCL), Tappa *et al*. created adaptable devices.[122] The medications, which included progesterone and estrogen, were forced into the filaments. In this investigation, three different dosage forms like, implants (subcutaneous), devices (intrauterine), and vaginal

Table 3: Representing some pharmaceutical Dosage forms that are fabricated by a 3D-printer

Dosage form	*3D technologies*	*API*	*Polymer*	*References*
Single API oral dosage form				
Tablet	FDM	API (Drug)	Thermoplastic polyurethane	[103]
IR tablets	Extrusion based 3D-printing	Paracetamol	excipients	[104]
Extended-release tablet (release up to 24 hours)	FDM	Prednisolone	Polyvinyl alcohol filament	[105]
ER tablets	FDM	API (Drug)	Use of Tween 80, polyethylene glycol (PEG), Polyethylene oxide with either Eudragit (EPO) or POLYOX ™	[33,105]
Approximate near zero-order controlled release developed	3D printer technology	Pseudoephedrine--hydrochloride	Hydroxypropyl methylcellulose (HPMC)	[106]
Linear release profile (Tablet Doughnut shape)	3D printing technology	multilayered acetaminophen	Excipients	[107]
Enteric tablets	FDM	API (Drug)	Hypromellose acetate succinate	[108]
Gastro-floating tablet	Extrusion based printing	API (Drug)	Excipients	[109]
ER tablets	SLA and ink-jet 3D printer	APIs Paracetamol (PCM) or 4-aminosalicylic acid	At various compositions 2,4,6-trimethyl benzoyl, polyethylene glycol and phosphine oxide	[110,111]
Tablets	IJ with UV photo-initiation	Ropinirole hydrochloride	Excipients	[112]
Complex geometry solid dosage form (honeycomb architecture	Hot melt 3D ink-jet printer	AIPS	Excipients	[110,111,112]
Polypills	3D-printing based on extrusion	Immediate release (captopril) and sustained release nifedipine and glipizide	Not available	[22]
Polypills (5 APIS)	3D-printing	Ramipril, atenolol, pravastatin (sustained release Aspirin, hydrochlorothiazide (IR)	Not available	[104]
Sustained release tablets	Extrusion based 3D-printing	API +HPMC Aspirin and hydrochlorothiazide	Cellulose acetate shell formation for API filling	[104]
Multiple drug-containing devices (Duo caplet design)	Multi-nozzle 3D printer	Acetaminophen and caffeine	Excipients	[108]
Modified release drug oral dosage form (caplet)	FDM method fluid bed coating with hot melt extrusion)	Budesonide	Excipients	[34]
Modified release	SLA	4 -Amino-salicylic acid (Thermolabile +paracetamol)	NA	[111]
Implant	3D-printing	Levofloxacin	NA	[66]
Scaffolds for bone defect	3D-printing	endothelial growth factor loaded hydrogel strands (VEGF) and calcium phosphate cement	NA	[99]
preparing implant (for chronic osteomyelitis)	3D-printing	Combination of levofloxacin (LVFX) and tobramycin	NA	[68]

Patch-like implant (extended-release for chronic disease)	3D-printing	Polylactic-glycolic acid, polycaprolactone and 5-fluorouracil	NA	[62]
Microneedles				
Microneedle	3D-printing	Dacarbazine	NA	[116]
Microneedle	3D-printing	Diclofenac	NA	[117]
Microneedle	3D-printing	Insulin	NA	[98]

pessaries, were created. To melt the filaments during the printing process a high temperature is required. The FDM method can be utilized to print drug-filled filaments. In a different investigation, Fu *et al.* developed various type of controlled-release progesterone vaginal rings in various doses and types of shapes using FDM.[122]

Challenges of 3D Printing

The adoption of personalized medicines by healthcare system stakeholders, including patients, is one of the major concerns. It is quite difficult to train and educate the personnel in the practices of personalized medicine. This is because personalized medicine differs from standard practice in that physicians must further assess each patient's unique characteristics based on biomedical, genetic, and behavioral aspects, among other genomic, before deciding which medicine is best for them. Sometimes chances of personal data may be used for fraudulent purposes, which raises privacy and legal issues; however millions of variants need to be identified before the use of personalized therapy. Consequently, it may be costly and time-consuming to search patients' problems on the basis of genetic profiles and their mapping. Pharmacogenomics is still difficult in routine medical practices to improve healthcare. Furthermore, there are still problems with how test results should be understood and shared despite ongoing improvements in the validity and accuracy of genomic testing.[135-137]

The development and administration of customized medicine dosages need regulatory agency approval, which is another major barrier to the successful use of personalized medication.

These concerns need significant proof that makes printed medication superior to conventional medicine strategies, which is also important to consider the possibility of the higher cost associated with customized therapies. Furthermore, suitable strategies should be developed to meet the specific parameters for specific patients as practices progress. The adaptation of health insurance plans with regard to regulatory and legal manufacturing of personalized medication presents another hurdle to the realization of personalized medication for healthcare professionals, hospital management, and health plan sponsors. Due to the above issues need to rethink the current healthcare structures and insurance policies to accommodate personalized medicine practices, especially to genetic testing and customized therapies.[44,138]

3D printing challenges for industries

The following are some common obstacles (Fig. 21).[138,139] those various industries face when establishing additive manufacturing:

Regulatory aspects for 3D-printing in the present scenario

In the present scenario use of various 3D-printing technologies is a rapidly prototyping novel technology in the healthcare field. The first approved 3D-printed tablet spritam (Fast disintegrating tablet) was made by Aprecia Pharmaceutical and it is the only one 3D printed drug to date approved by the Food and Drug Administration (FDA) in the year 2015.[139] Only Spritam 3D printed drug are accessible as the marketed product.[139] Due to some drawbacks like complexity, small manufacturing, and unfeasible standardization, 3D-printed tablets are not feasible if personalization is attempted.[140,141]Numerous problems with 3D printed tablets lead to regulatory challenges. These have been addressed in reviews of the literature Food and Drug Administration.[139–143] Although 3D-printed technology has advanced quickly in recent years, 3D-printed medications do not yet comply with current regulatory standards. As a result, future regulatory changes will be necessary for 3D-printed medications because of the combined nature of the product. 3D-printed drug-eluting implants have certain challenges, such as being assigned to the appropriate product category (medical *vs* medical products).[143] Establishing a regulatory framework and manufacturing standards for 3D printed and non-additive products is crucial for the advancement of 3D technology, as it ensures product efficacy and safety.[140]

In 2017, the FDA released a guideline letter in which it acknowledged the paucity of prior research and clinical expertise in the area. They talked about the material, printing the validation design, and the post-printing procedure. The factors and features of printing are the evaluation of the finished product's mechanical and physical quantities as well as biological factors like biocompatibility, sterility, and cleanliness.[142] For instance, the quality of a printed object may be affected by its orientation, position, or removal of support structure or leftover material during the printing process. It is also impractical to mechanically test a product for a single patient.[142] The primary regulatory obstacles facing 3D printing dosage forms and medical devices are those

Table 4: Representing some selective drug eluting devices

Drug eluting devices	*Objectives*	*Printer type*	*Implant shape*	*Drug loading*	*Drug*	*Polymer material*	*References*
Gynaecological devices	Preparing vaginal ring in different shape for release profile of drug like personalized and controlled release	FDM	Particular in shape of O/Y/M vaginal ring and Pessaries	Perfused HME	Progesterone	PLA PCL PEG PCL	[54]
	Biodegradable long-lasting implant with various drug load for sustained release profile	FDM	T-shaped IUS	HME	Indomethacin	PCL	[60]
	Antibacterial vaginal mesh with suitable mechanical properties	FDM	Vaginal mesh	HME	Levofloxacin	TPU	[58]
	Implant of different grades of EVA	FDM	T-Shaped IUD S.C rod	HME	Indomethacin	EVA	[123]
Stunts and catheters	Bioactive laden bioabsorbable catheter	FDM	Catheter	HME	Gentamycin sulfate, methotrexate	PLA	[124]
	Preparing 3D-Printing Catheter for incorporation of anti-infective catheters	FDM	Catheter	HME	Tetracycline hydrochloride	TPU	[125]
	For antimicrobial and increased visibility of CT images	FDM	Mesh Y- stent	Post-print (gaseous incubation	Iodine	PVP	[74]
	For specific nasal support with bioactive agents	FDM	Nasal stent	Post printing (Dip coating)	Penicillin	PLA PVP	[74]
	3D model printed for antibiotic and chemotherapeutic -eluting filament	FDM	Disc, bead, catheter	HME	Gentamycin sulphate, methotrexate	PLA	[53]
	Preparing 3D Model and incorporate antimicrobial to inhibit biofilms	FDM	Disc	HME	Nitrofurantoin	PLA	[126]
Antitumoral devices	Multilayer drug implant for osteosarcoma treatment that tested *in-vitro* and *in-vivo*	INK	Sphere shaped	embedding	Cisplatin, ifosfamide, Methotrexate, durorubicin	PLA	[81]
	Bullet shaped hollow implant with modified release properties	FDM	Bullet shaped	Post print immersion	Cytoxan	PLA	[127]
	Biodegradable patch, with high concentration anticancer drug with modified release	Heat EXT	patch	Melt mixing	5-fluorouracil	PLGA, PCL	[62]
	Enhance bone osseointegration by 3D printed alloy implant with rough surface	SLM	Wafer	Post print droplet	Doxorubicin	Titanium	[76]

surgical meshes geometry	Surgical meshes imprengement with contrast agent and characterization of tomography properties	Heat EXT	Mesh	Embedding	Iodine. Gadolinium, Bariba	PCL	[128]
	Surgical meshes with antibiotic encapsulated in alginate	FDM	Mesh	Post print droplets	Gentamycin	PCL	[78]
	Meshes loaded with antibiotic with various pore size, shape & thread thickness between two different materials	FDM	mesh	Preprint filament soaking	Ciprofloxacin hydrochloride	PP, PVA	[63]
	3D-Printing at room temperature and UV crosslinking of silicon in to different structure and drug loads resultant in different release profile	Semi-solid (EXT+UV)	Mesh	Embedding	Prednisolone	Silicon	[129]
	3D-Printing antibacterial surgical mesh and potential as on-demand manufacturing	FDM	Mesh	HME	Gentamycin	PLA	[51]
implant with simple geometry	Preparing scaffold by leaching method Combination of 3D-Printing and salt	Heat EXT	Scaffold	Post-print coating	Cefazolin	PCL	[130]
	DLP 3D printed construct Influences relatively increased drug loading on printability & mechanical properties of drug	DLP	Disc cylinder	embedding	Dexamethasone	PEGDA	[64]
	Implantable 3D printed drug carriers, In-vitro testing		Cylinder	Powder filling during printing	Diclofenac sodium	PLA PETG	[131]
Complex geometry	Different implant design of biodegradable material for sustained drug release	FDM	Window implant	Post-print powder filling	Methylene blue, Ibuprofen sodium	PLA. PVP, PEG, PCL	[132]
	By DLP Method improves the additives, printing parameters and internal and external structured 3D printed model design	DLP	Multiple shape	Embedding	Diclofenac sodium, ibuprofen	PEGDA DPPO PEG	[65]
	Design implant with gel core that coaxial coextrusion of drug	EXT	Rod, scaffold, spiral	Embedding, injected	Bevacizumab, dexamethasone	PCL Poloxamer alginate	[39]

Implant for bone treatment and surgical screws	3D-Printing of antibacterial scaffold for osteomyelitis treatment	INK	Scaffold	Powder mixture	Rifampicin, sitafloxacin	Ceramic, PLGA-Coating	[133]
	3D-Printing of scaffold with antibiofilm and osteogenic properties	FDM	Scaffold	Post-print immersion	Minocycline	PLA	[50]
	Patient specific fixation implants for localized drug delivery	FDM	Screw, Pin, Plate	HME	Gentamycin sulphate	PLA	[50]
	At low temperature create scaffold for 3D printed antimicrobial drug	Heat EXT	Disc	embedding	Rifampicin	PCL	[134]
	3D printed stainless steel implant coated to create a mechanism of the slow-release drug profile	SLM	Cuboid	Post print airbrush coating	Dexamethasone	Stainless steel	[75]
	With the help of solution technique influence the drug eluting printing parameter	EXT	screw	embedding	Vancomycin, ceftazidime	PCL, Nha	[61]

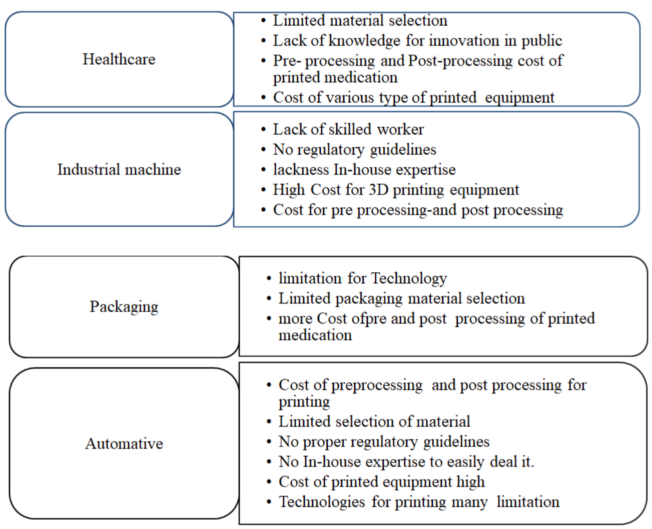

Fig. 21: Industrial challenges

related to process validation, which includes patient-specific acceptance criteria implementation, parameter testing, and printing parameter monitoring.[141] An FDA investigational new drug (IND) approval was recently granted to TRIASTEK for their chronotherapeutic drug delivery system T19, which is made using a melt extrusion-based 3D printing method and has an internal geometric structure to govern drug release.[137,140,142] A year after the spiritam approval, this highlights the continuous process of developing 3D-printed human pharmaceutical products that meet approved regulatory standards. Expecting positive results from the clinical trials. Soon, T19 might be the second authorized 3D-printed medication, and there might be more.[144]

Future Prospective for 3D-Printing Technologies

Research employing various forms of 3D-printing is growing. Nonetheless, the capacity to develop personalized medication is a primary benefit of all forms of 3D-printing currently in use.[144] Because additive manufacturing is quick, simple and accessible, it encourages the manufacturing of pharmaceutical and medical devices based on patient requirements in a clinical setting.[137] In the medical field versatility in 3D-Printing is demonstrated by altering the release profile and amount of dose of tablets with the help of CAD, which changes their geometry, as well as by using HME to insert medication into FDM manufactured injectable devices or mesh implants.[145] Before the manufacturing of personalized and customized 3D printed products must be understood in a clinical context, further research is important to understand which process parameters effect on print quality and how to improve repeatability in 3D printing.[145] The quantity of medications that may be placed into filaments using FDM is likewise restricted because these substances must be able to endure high temperatures during the procedure. However, if research in 3D printing keeps going up, make it past the proof-of-concept stage due to the diversity in 3D printed products and the numerous benefits offered for manufacturing.[145] guidelines released by the US FDA for producing medical devices using 3D-Printing technology to increase the adaptation of this technology. Therefore, in the upcoming year, we expect to witness a rise in the quantity of 3D-printed pharmaceutical and medical products available for purchase.[56]

Conclusion

To create personalized pharmaceutical solutions, 3D-printing of medical equipment & drug delivery systems is a potent tool. Studies on oral, oro mucosal, and topical dose forms developed quite quickly after the first medicine made using 3D printing technology received FDA approval. By their underlying operating principles, many 3D printing methodologies have been created and divided into subgroups. Pharmaceutical application of 3D-printing technology is very intricate and complicated the flexibility to adjust the shape and microstructures of pharmacological dosage forms has increased. In contrast to traditional pharmaceutical manufacture, With the help of additional manufacturing, a wide variety of dosage forms can be prepared with high accuracy regarding the ratio of API to excipients. Regulations and standards must be created in advance of AM being the new standard to address concerns that are certain to arise.

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