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3D PRINTING IN PHARMACEUTICALS A COMPREHENSIVE REVIEW ON A NOVEL EMERGING TECHNOLOGY

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ABSTRACT: Three-dimensional printing (3DP) is an emerging technology that allows the fabrication of tailor-made drugs, devices, and organs that meet an individual patient's requirement. Thus, it has enormous potential to bring about a significant transformation in the pharmaceutical and healthcare sector. 3DP involves the production of structures with desired design by deposition of printing material in a layer-by-layer fashion. It permits on-demand fabrication of structures with high productivity economically. Currently, it is employed in a wide range of healthcare services such as drug formulations, medical devices, anatomical models, tissue engineering and regenerative medicine, engineered tissue models, and dentistry. The primary objective of this review to describe various approaches in personalized medicine, progress in dosage forms and devices, 3DP techniques, use of polymers in 3DP and adaptation of 3DP in pharmaceutical industries. We further describe recent approaches in the fabrication of conventional drug formulations and novel drug delivery systems and compare the 3DP with 3D bioprinting. Lastly, we discuss the limitations, regulatory aspects, and future trends of 3DP technology in the healthcare setup.

INTRODUCTION:

1. Overview and History of 3D printing Technology: The term three-dimensional printing (3DP) suggests various efficient technologies to create three-dimensional (3D) structures by laying consecutive layers of material. It is also termed as an additive manufacturing (AM) process that permits tailor-made production of 3D constructs according to the designs obtained from computer software or images gathered from magnetic resonance imaging (MRI) and/or computed tomography (CT) [1]. 3DP finds application in several sectors such as education, geoscience, aviation, clothing, healthcare, and pharmaceuticals [2].

The use of photopolymers to construct 3D structures began in the 1960s at Battelle Memorial Institute (Ohio). Subsequently, in 1971, Wyn Swainson applied for a patent based on dual laser beam technology known as photochemical machining [3]. Later in the 1970s, Dynell Electronics Corporation came up with solid photography [4]. In 1980, Hideo Kodama, a Japanese researcher, pioneered a rapid prototyping approach with the help of a solitary laser beam [5].

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A year later, he provided a detailed approach of solidifying thin successive layers of photopolymer [6]. It was Charles Hull, in 1984, who designed stereo lithography (SLG) and was awarded a patent two years later [7]. He then created 3D Systems, which eventually manufactured and sold SLG machines. In 1987, 3D Systems introduced the first commercial SLG printer in the world [4, 8]. In the initial part of the '90s, Sachs *et al.* introduced a patented 3DP technology in pharmaceutics by using inkjet printers. They used a binder solution on the powder bed to bind the particles together. This procedure was replicated several times till the intended structure was achieved [9]. In 2016, Aprecia Pharmaceuticals, using inkjet printing, introduced the first 3D printed tablet Spritam® (levetiracetam) that was approved by the Food and Drug Administration (FDA) [10]. With the swift progress in 3DP technology, the overall 3DP market stood at $9.9 billion in 2018 and is projected to attain a size of $34.8 billion by 2024 [11]. Following this trend, medical 3DP has been reported to sustain considerable progress because of enormous promising interest in tailor-made medical products. With the patents of several 3DP technologies expired, 3DP instruments and products have become economical and are readily available [12].

1.1. Approaches in Personalized Medicine: The term personalized medicine suggests tailored management that caters to the specific needs, characteristics, and desires of a particular patient [13]. The use of 3DP in healthcare has resulted in the manufacturing of tailor-made doses, formulations, implants, and other products, leading to increased patient compliance [14]. In various diseases, several treatment options are now available with the use of different 3DP approaches. In cancer patients, 3DP has resulted in developing *in-vitro* models that mimic and help better understand tumor pathogenesis and spread [15].

This helps to foretell the pattern in which the tumor cells proliferate and determine the exact location of the tumor, thus escalating the accuracy of treatment modalities [16]. In diabetic patients, insulin synthesis and response fluctuation have heightened the requirement of a tailored approach and personalized medicine [17]. Scientists at Boston University used stem cells and other related biomolecules and came up with an artificially manufactured functional pancreas [18]. Sabek *et al.* used 3DP technology and created nano-glands that encased islet cells like insulin synthesizing aggregates to supply fixed concentrations of insulin for a minimum of 28 days [19]. In those with cardiovascular diseases, traditionally, diagnosis and treatment rely on accurate 2D details of the diseased parts obtained from echocardiography, MRI, CT, and angiography. However, these are limited by their inability to depict the real size structure in 3D [20]. The models obtained through 3DP help understand the detailed anatomy of the heart and disease process and, thus, plan the management strategies with great accuracy [21]. With the help of MRI data and 3DP technology, Valverde *et al.* created a model of hypoplastic aortic arch and precisely planned the position, and size of stent placement [22]. Utilizing the human cells and other biomaterials involved in transplantation, 3DP can create the 3D bio-printed heart [23]. Similarly, in those with neurodegenerative diseases, 3DP can be used to evaluate the brain and other parts of the nervous system and create the strategies to manage several neurological diseases. Thus, they overcome the major limitations of *in-vitro* modelling techniques and conventional 2D imaging.

Ormabera *et al.* used plastic of acrylonitrile butadiene styrene and data of CT images to create 3D model of skull and planned surgical procedure [24]. Owens *et al.* used mouse Schwann cells and stem cells from bone marrow enclosed in cellular cylinders to create a multi-layered nerve graft. This graft was then transferred onto a support structure for managing sciatic nerve injury in rat model [25]. 3DP has been used in other disease conditions as well. Ackland *et al.* accessed the anatomy of temporomandibular joint through the data gathered from CT scan and created a tailor-made 3D prosthetic joint replacement [26].

In-vitro models of liver fibrosis, 3D hepatic cultures are being developed for creating effective antifibrotic therapies [27]. Using titanium, a C2 cervical vertebral bone was 3D printed and successfully placed to treat Ewing's sarcoma [28]. Thus, taking all the above details into account, 3DP permits the creation of a precise model of microstructures that result in improved surgical planning and practice to devise a better and more

efficient ways of treatment. Moreover, the use of a tailor-made dose of drug can lead to better patient management. Simultaneously, it improves efficacy with decreased adverse events to promote patient health.

1.2. Boon for the Research and Development of Printed Materials in Pharmaceuticals: The pharmaceutical application of 3DP has resulted in a profound transition in the development process of drug products. This has led to the conversion of non-digitalized formulations into 3D digital content [29–31]. Currently, 3DP is receiving immense attention due to its ability to decrease the wastage cost and simultaneously increase the preciseness, efficacy, and individualization. Moreover, it allows the development of innovative formulations and medical devices that have been challenging to produce with conventional technologies [1, 32, 33]. The principal properties of a 3D healthcare product, including drug load and rate of release, can be accurately altered by factors such as altering the counts of printed layers in a particular area or altering the complete area to be printed [34]. The use of 3DP allows the researchers to design and compose novel complex drug molecules and several active pharmaceutical ingredients (API) into a single formulation with the tailor-made release of drug and customized design that caters to the particular requirement. These tailor-made formulations can be readily made in a pharmacy using a locally available 3D printer or at their residence by the patient or their relatives. Thus, the primary benefit of the 3DP is its resilience to design and construct a variety of formulations [35–39].

1.3. Boon for the Research and Development of Printed Materials in Medical Devices: The use of 3DP to develop implants and prostheses has transformed the field of manufacturing medical devices, thereby meeting the ever-rising need for tailor-made therapy. The 3DP permits the creation of customized products that fulfill individual requirements resulting from the specific anatomy and pathology of the patient. It further leads to the creation of structures with site-specific physical and mechanical characteristics and temporal and spatial oversight of bioactive ingredients. The tailor-made devices and prosthetics help re-establish movement, function, and appearance lost due to trauma or deformation.

Herbert *et al.* introduced a simple prosthetic foot [40]. They reported that 3DP is a simple and effective process of creating prosthetic sockets which the patients with amputation find convenient. Similarly, Zuniga *et al.* created economic 3D-printed hands for individuals with a reduction of upper-limbs [41]. It is reported that this prosthesis may have a definite influence on the quality of life (QoL) and can be used in various daily activities. 3DP finds a special mention in craniofacial reconstructive surgery. It helps accurately replicate facial features that greatly affect the physical image and result in aesthetic issues. Silicone prosthesis or patient's cartilage are frequently used to restore traumatic or congenital defects of ears [42].

Based on the 3D images, tissue casting molds can be created, polished chemically, and cast with medical-grade silicon. Unkovskiy *et al.* created nasal prostheses by printing dual prostheses of silicon that were subsequently sealed and coloured[43]. Both these prostheses matched well and filled the defects. Moreover, they demonstrated satisfactory acclimatization to the nearby skin. Apart from polymer-based implants, metals devices have also been reported to be successfully used. Ma et al. made a first attempt at creating tailor-made titanium plates that were implanted after resection of tumour around the knee joint [44]. Thus, the application of a 3D-printed plate was demonstrated as a considerable upgrade in the management of bone tumour. Another tailor-made titanium implant was introduced to reconstruct the chest wall defect after excision of the sternal tumour. It was reported to decrease the morbidity and was advantageous to the patient for restoring adequate function and structural chest reconstruction following resection [45].

2. 3DP Techniques:

2.1. Various 3DP Techniques, Advantages, and Disadvantages: Computer-aided designs are used to create 3D pharmaceutical products. Design is transformed to a machine-readable format that provides details of the external appearance of the 3D dosage form. The computer-aided program then slices this surface into various apparent printable layers and deports that layer-by-layer to the machine [14, 46]. The concept of 3DP utilizes sensor technology which requires the sensors to be located on patients.

These sensors produce clinical data that subsequently gathered in a designated network. Based on the physiological changes reflected in this data, the healthcare professional can devise the patient's next dose.

Thus, this dispensing system presents distinct merit of decreasing clinical response time to patient's requirements and improving compliance [47]. Following approaches are used in personalized medicine.

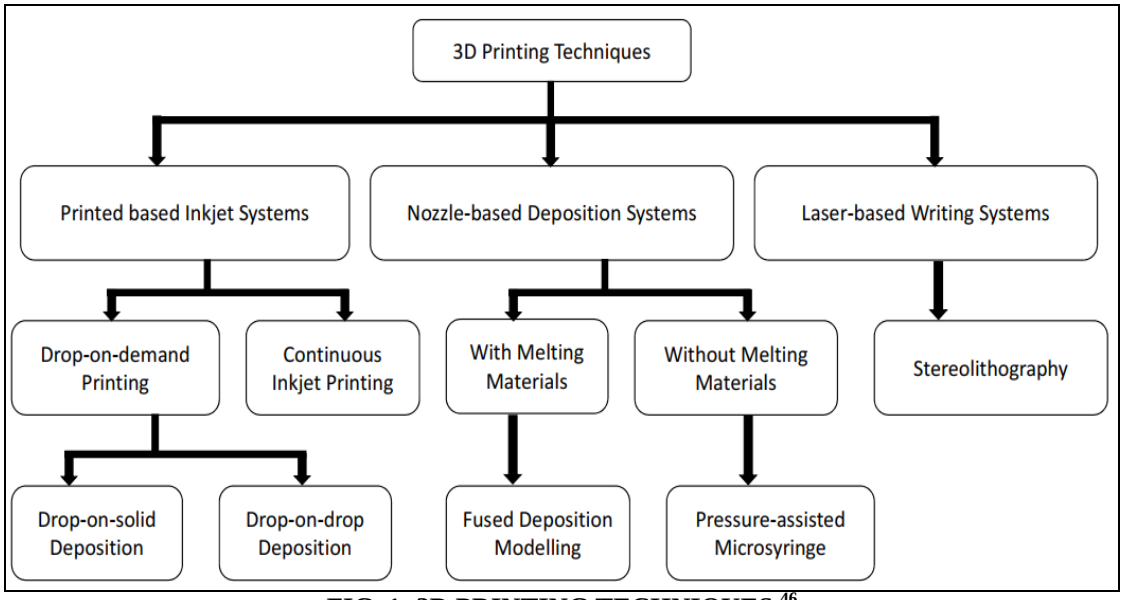

FIG. 1: 3D PRINTING TECHNIQUES [46]

2.1.1. Inkjet Printing: The technique originates from the approach used in computer-operated inkjet printing. It was used in the pharmaceutical industry by replacing ink and normal paper with pharmaceutical solutions comprising drugs and edible sheets known as substrates, respectively [48]. The dose can be altered by changing the number of layers to be printed in a defined area or altering the entire area to be printed. The drug and excipients are distributed in such a ratio that they can print as microdots on an edible substrate. Its advantages include precise control over the combination of dose and drug release pattern [47, 49]. The two chief varieties of printers used in this type of 3DP include piezoelectric and thermal inkjet printers [49]. Moreover, two characteristic printing classes include continuous inkjet printing (CIJ) and drop-on-demand (DOD) printing [34].

2.1.1.1. Continuous Inkjet (CIJ) Printing: In this technique, a persistent flow of ink is created by directing a liquid ink through an opening of 50-80 µm diameter. Using a piezoelectric crystal allows the liquid to flow and break into drops at continuous intervals with a particular velocity and size. These parameters are maintained by developing an electrostatic field.

Thus, the droplets are charged. A droplet guard is used to decrease the electrostatic repulsion between them. The electrostatic field makes the charged droplets move towards the substrate [47]. The advantages associated with CIJ printing include continuous generation of high-speed droplet resulting in less frequent clogging of the opening. While the disadvantages include costly maintenance and low-resolution [50].

2.1.1.2. Drop-On-Demand (DOD) Printing: This technique involves several heads (around 100 to 1000) and can employ two kinds of translators *i.e.*, a thermal head or a piezoelectric crystal. The former is limited to volatile liquids, while the latter includes a wide spectrum of liquids [34]. Moreover, the thermal head attains a high temperature (~300 ºC), suggesting that employing solvents with high vapor pressure could degrade bioactive molecules, thus limiting its use. The piezoelectric crystal undergoes swift changes leading to abrupt alteration in volume [34, 46]. The capacity of piezoelectric printing to function at room temperature, with more biocompatible and less volatile liquids, makes it highly appropriate for creating drug delivery devices (DDDs) [46]. The DOD technique is comparatively simple,

economical, and provides high accuracy. It is associated with the ability to deposit small drops of controlled sizes and precise placement. Moreover, it limits the wastage of drugs. Thus, it is preferred over CIJ printing [51, 52]. Drop-on-powder (DOP) deposition is also termed as binder jet printing. It is classified as drop-on-drop (DOD) and drop-on-solid (DOS) deposition. The former technique involves layered deposition of the printed material on one another so as to create a hardened layer of material, while the latter technique involves deposition of droplets by printer head on solid material [53]. The inherent advantage of both these techniques is that different materials and colors can be used simultaneously to make multiple deposits which are formulated in a layer-by-layer fashion [34, 46, 54, 55].

2.1.2. Stereolithography (SLG): It is also termed as laser-based writing system. It uses the principle of photopolymerization which involves release of free radicals following interaction of ultraviolet (UV) rays with photo initiator [34]. A stereolithography apparatus (SLGA) is used, where particular surface area of photosensitive liquid resin is subjected to localized polymerization following exposure to a UV ray [56]. Here, UV rays traverse the surface of liquid resin resulting in exposure of *x/y* axis of each distinct layer, as the zaxis increasingly evolves during the building process [57]. When a particular layer hardens, new layers of liquid resin are laid over each other until a final product is developed. When a part is fabricated, they are washed to clear away the extra resin and the supporting structures are discarded manually [34]. Its advantages include high resolution, swift construction of models, and reduced thermal stress. Moreover, disadvantages are limited availability of compatible biomaterials, post-construction process, and long exposure to UV rays is potentially harmful to cells [58].

2.1.3. Fused Deposition Modelling (FDM) 3D Printing: This is a common and economical technique that uses a printhead identical to an inkjet printer. Here, a prototype is constructed in thin layers by the beads of molten plastic that are discharged from the printhead during its movement [59]. Thermoplastic polymers including polyvinyl alcohol (PVA), acrylonitrile butadiene styrene, or poly-lactic acid (PLA) are used [33, 60]. Molten polymers flow through the opening of the printhead and are laid in a layered manner, in the form of filaments, on a platform. After hardening, the filaments are fused, and thus, the process is also termed fused filament fabrication. Its ability to create multifaceted scaffolds with a precise dosing system makes it superior to powder-bed printing. By altering the proportion of infill, the surface area of the formulation, or 3D model design, FDM provides excellent physical strength with formulations of different kinetics. However, the limited availability of thermoplastic material and temperature-sensitive APIs decrease the use of this technique [10, 46].

2.1.4. Extrusion Based Bioprinting: Here, mechanical or pneumatic pressure is used to deliver bioink via an opening that replicates a computer-based theme [61]. Polymers or hydrogels are usually contained in plastic or metallic syringes and delivered through pneumatic, piston-based, or screw-based force. Systems using pneumatic forces are usually associated with delay in delivery as they employ compressed gas, but they function more effectively for highly viscous molten polymers. While systems using piston-based delivery usually bid greater explicit command over the hydrogel's release from the printhead's opening. However, systems using screw-based delivery results in better control and are useful in delivering extremely viscous hydrogels [62,63]. This technique in manufacturing living scaffolds has increased due to its greater process speed, accurate cell deposition, and command over the cell distribution rate. The maximum resolution obtained with this technology is relatively less than inkjet- or laser-based printing. However, its manufacturing speed is comparatively greater, and desired 3D models are easily attained [64]. Its chief advantage includes lack of high processing temperature and availability of a large spectrum of biomaterial. In contrast, disadvantages include the necessity of drying following fabrication and the use of organic solvents [65].

2.1.5. Selective Laser Sintering (SLS) 3DP: It uses laser energy to heat and fuse powder particles, which subsequently solidifies to create a 3D structure. Initially, the spreading system lays the powder uniformly on the platform, and a roller blade is employed to create an even surface. The laser is used to fuse the material by heating it to a

temperature below its melting point, and the height of the bed is adjusted to focus the laser on a freshly created surface. The loose powder on the platform helps by providing support during the process. A new layer is deposited and fused with an earlier layer by downward movement of the powder bed by one layer. The entire process occurs several times to create the final 3D printed object, which upon cooling separates from the loose powder [66]. The advantages of this process are a one-step fast manufacturing process, the absence of any solvent, and the creation of objects with high resolution [55]. However, its disadvantages include slow degradation and resorption of scaffolds, restriction to few materials that can be sintered, and cell-free manufacturing method [58].

2.1.6. powder Based 3DP: This method simultaneously utilizes powder jetting and inkjet printers to disperse thin layers of powder and apply liquid binder drops, respectively [67]. The ink is sprayed over a powder bed in 2D manner to create the end product in a layer-by-layer convention. Since powder and binder solutions are commonly employed in the pharmaceutical industry, this method can be easily adapted in pharmaceutical manufacturing.

However, it is associated with several disadvantages such as the requirement of extra drying to discard solvent residues, wastage resulting from the accumulation of excess powder, and poor mechanical strength of the drug delivery system (DDS) due to the porous nature of the powder [47, 67].

2.2. Adaptations of FDM 3D Printer for Pharmaceutical Production: Compared to the other 3DP techniques, FDM is the most frequently evaluated technique today. The FDM printers are economical, operator-friendly, and demonstrate high printing precision and reproducibility [68]. Despite of these advantages, none of the FDM printers are commercially accessible for pharmaceutical use. Recent studies have highlighted that commercial printers need to undergo several adaptations to fulfill pharmaceutical manufacturing requirements [69]. **Fig. 2** depicts the main parts of FDM printer that need adjustment. In numerous printers, the printing process exposes the filament coil in the spool **Fig. 2A** to humidity or particles resulting in contamination of the spool, thereby preventing it from being reused. This contamination can be prevented by connecting a closed compartment to the printer, thus enclosing the spool attachment. Similarly, the printer enclosure **Fig 2B** needs to be protected against contaminants, thus shielding the printed structures and excluding the requirement of strict particle control or laminar airflow in the manufacturing area [70]. The other sections of the printer that remain in continuous contact with the filaments **Fig 2C-A**, including extruder head, nozzle, and platform, should be manufactured from an inert material (such as stainless steel) that can be easily cleaned. Moreover, the mechanical sections of the printer **Fig 2F**, including the motors, should be fully covered to avoid lubricant oil from flowing over the product [70].

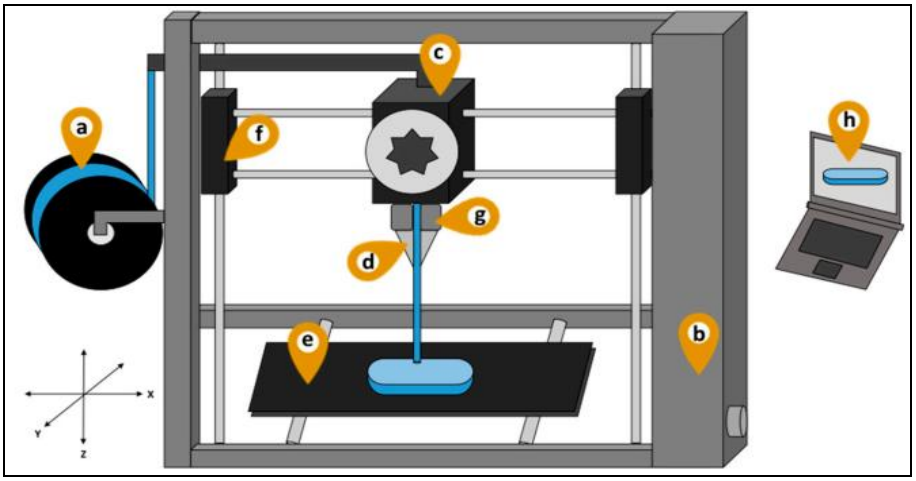

FIG. 2: SIMPLIFIED ILLUSTRATION OF A PHARMACEUTICAL FDM 3D PRINTER WITH VARIOUS SECTIONS THAT REQUIRE ADAPTATIONS. (A) SPOOL, (B) PRINTER ENCLOSURE, (C) EXTRUDER HEAD, (D) NOZZLE, (E) PLATFORM, (F) MOTOR, (G) HEATER, (H) 3D DESIGN SOFTWARE [69]

The temperature of heater **Fig. 2G** needs to be controlled precisely, as overheating of polymer could lead to variation in its viscoelasticity and compromise stability of the drug and control over drug release. The software **Fig. 2H** that controls the printer needs to accept electronic prescriptions directly from the clinics and simultaneously recommend the most suitable scenarios feasible for printing. The designs of 3D devices should preferably be pre-specified from the available database, thus cutting down the time required to define the shape of the device [71, 72].

2.3. Integrated Production Process: Globally, 3D FDM technology is used to fabricate several types of DDDs, and various measures are being taken to permit the commercial viability of this technology. One such measure is a complementary production chain through collaboration between online pharmacies and pharmaceutical industries **Fig. 3** [69].

2.3.1. Pharmaceutical Industry: Filament Production by Hot-Melt Extrusion: The use of FDM 3D printers for the fabrication of drug-loaded filaments involves 3 primary steps **Fig. 3**. In the first step, all the ingredients in a particular batch are blended (e.g., in an industrial V-blender).

In the second step, the blended components fabricate the drug-loaded filaments through the process of shear and heating in the hot-melt extruder. Terminally, the bulk of filament is loaded in smaller spools. This transitional pharmaceutical preparation should be placed in an air-tight manner to avoid degradation of the product till it arrives in the compounding pharmacies [69].

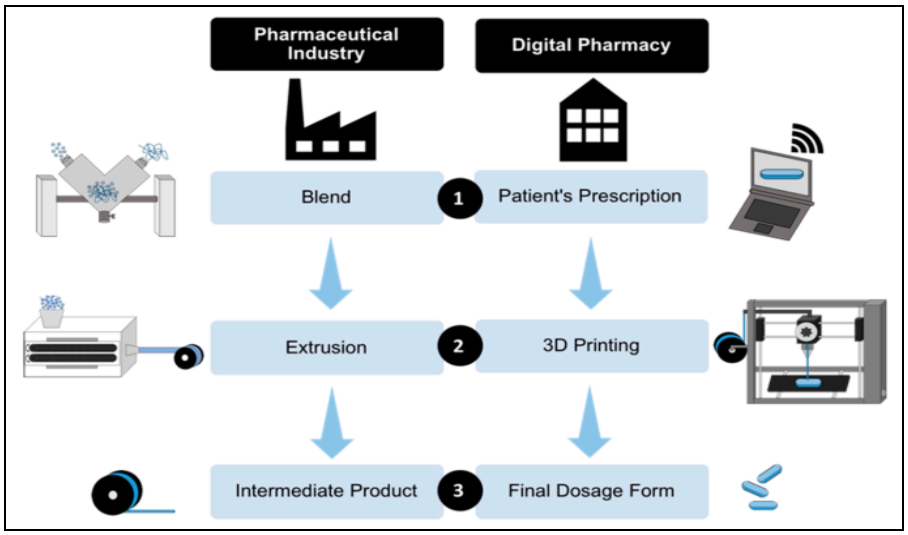

FIG. 3: DIAGRAMMATIC REPRESENTATION OF STEPS NEEDED FOR THE PHARMACEUTICAL FABRICATION OF FILAMENTS AND THE AMPLIFICATION OF TAILOR-MADE DDDS IN DIGITAL PHARMACIES [69]

2.3.2. Digital Pharmacy: 3D FDM Printing of Personalized Drug Products: The compounding pharmacies have the required setup to fabricate the 3D printed DDDs. The instruments can be placed over the currently available tables in the liquid and solid preparation rooms, thus needing only an additional power source to function [73, 74]. **Fig. 4** illustrates the design of a speculative compounding pharmacy using FDM 3D printers. The physician issues a prescription that reaches the pharmacy administrator and pharmacist for authorization, respectively. Following this, the prescription is dispatched for imprinting to one of the accessible printers. The printers are connected to one or more computers furnished with the required interfaces. Thus, at a fraction of the cost involved in the training of personnel and purchase of printers and software, it is feasible to convert a usual compounding pharmacy to a digital pharmacy [69]. The process of drug delivery is divided into 3 main stages **Fig. 3.** In the first stage, with the printer software, a trained technician sets the parameters of the 3D printer, including resolution, infill, velocity, temperature, and others [75]. Moreover, a required shape for the DDD is selected from database [76]. In the second stage, the printer is prepared, and the spool is attached. A modified pharmaceutical FDM printer produces tailor-made drugs for a particular

patient. Following the completion of the printing process, the product batch is removed and the third stage is initiated. In this stage, the fabricated DDD packing and labeling is performed according to current legislation and delivered to patient [77].

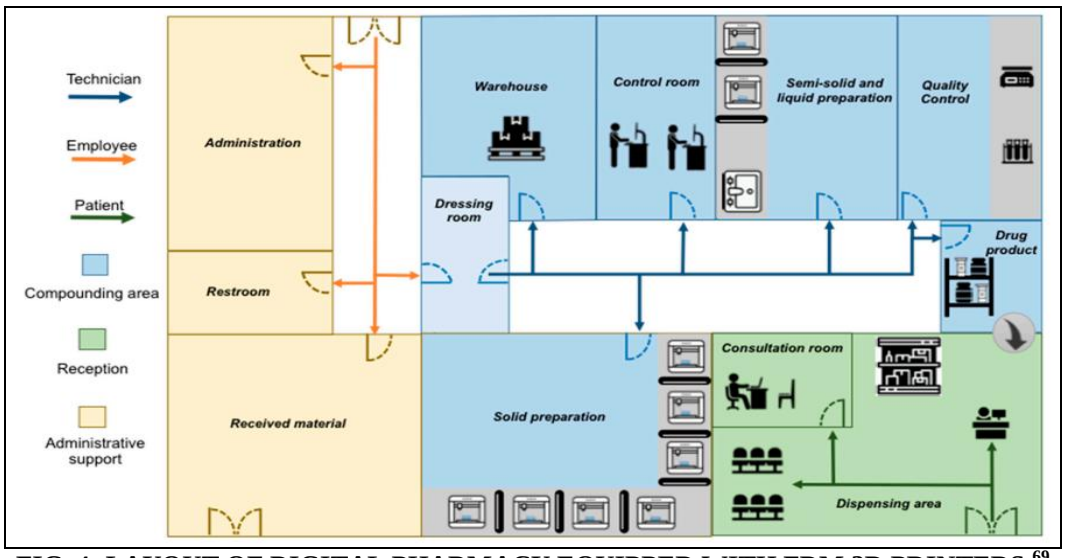

FIG. 4: LAYOUT OF DIGITAL PHARMACY EQUIPPED WITH FDM 3D PRINTERS [69]

2.3. Comparison of 3D Printing and 3D Bioprinting: 3DP is further categorized into bioprinting. The term bioprinting suggest printing of structures with the help of viable cells, biological molecules and biomaterials [78, 79]. It aims to provide a substitute for autologous and allogeneic tissue implants and replace animal testing for drug discovery and studying the disease pathology [80]. The differences between 3DP and 3D bioprinting are listed in **Table 1**.

TABLE 1: DIFFERENCES BETWEEN 3D PRINTING AND 3D BIOPRINTING [81]

Characteristics	3D Printing	3D Bioprinting
Techniques	Fused deposition modeling (FDM) Stereolithography (SLGA) Selective laser sintering (SLS) Electron beam melting (EBM) Direct energy deposition (DED)	Inkjet bioprinting Laser-assisted bioprinting (LAB) Extrusion bioprinting
Benefits	Economical, swift, and simple Exceedingly high resolution Excellent for formulations with complex structures Superior mechanical properties Bulk metal repair and retrofit	Economical Widely accessible Fast printing Non-contact, high cell viability Deposition of high-density cells
Limitations	High processing temperature Cytotoxicity Limited material selection Low resolution Fragile physical properties	Nozzle clogging Complex operation Time consuming preparation Low cell viability
Salient features	Thermoplastic material is continuously heated into a semi-liquid state for extrusion Electron beams or UV light requiredto begin polymerization reactions,nozzle-free Powder bed fusion process, high energy input, nozzle-free	Conventional inkjet printing based technique Ribbon structure preparation required for fabricating material, nozzle-free Continuous filaments of bioink extruded by various driving forces
Applications	Fabrication of oral dosage forms, surgical instruments, implants, and prosthesis	Fabrication of organs and tissues, drug screening and development

2.4. Polymers as Raw Materials in 3DP: Bio-fabrication is a new technique and involves the use of polymers in 3DP, which could modify the release rate of drug and provide superior stability for incorporated APIs [82]. Polymers of natural and synthetic sources are distinctly used to embellish

the 3DP dosage form [83]. Natural polymers include chitosan, alginate, and gelatin; however, these polymers often decide the cross-linkers, which may be cytotoxic [84]. Thus, synthetic polymers such as Polyurethane (PU), Polyvinylpyrrolidone (PVP), Hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), Poly (methacrylates) (Eudragit) and Polylactic acid (PLA) have received tremendous attention to avoid the disadvantages associated with natural polymers [85]. Some of the essential polymers employed in 3DP formulations are:

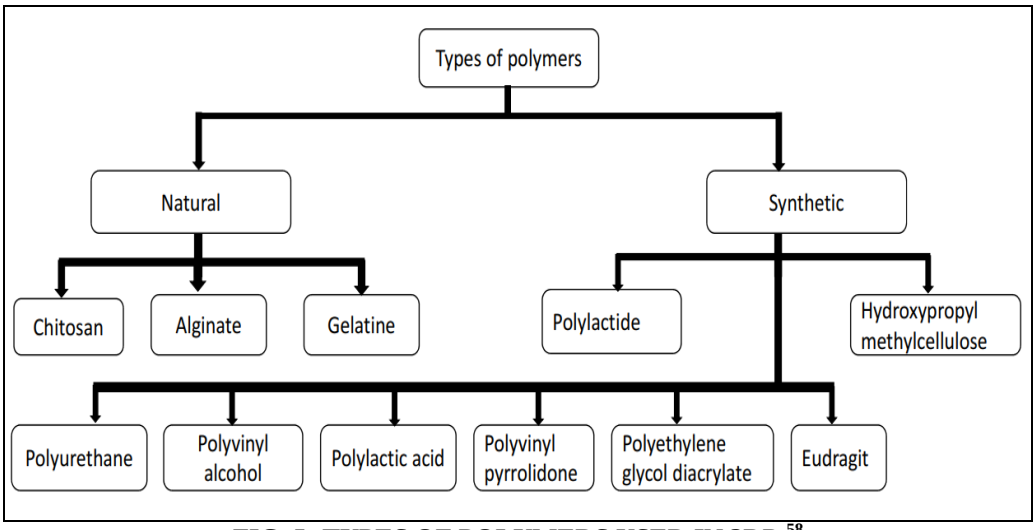

FIG. 5: TYPES OF POLYMERS USED IN 3DP [58]

2.4.1. Polyvinyl Alcohol (PVA): PVA has higher water-soluble and thermoplastic characteristics responsible for its mechanical strength and reabsorption qualities [86]. The leading reason for choosing PVA as 3DP material is its gas transmission temperature of about 84-86 °C [87]. However, at a higher temperature of around 340-450 °C, PVA starts degrading, making it more ambient for 3DP [88]. Currently, various research studies are ongoing to include PVA in 3DP formulations [89]. One of such programs involves ethanolic solution 2% w/v fluorescein loaded PVA filament. Marker Blot Replicator 2 × 3D printer was used to include this PVA filament in tablets [90]. Strikingly, ethanol increases the drug encasing proprieties of PVA. For thermolabile drugs, PVA is limited by its higher melting point. Conventionally, researchers are combining PVA and PLA to create 3D-printed formulations. Use of 3DP technology has enabled inclusion of two incompatible drugs together in a single dosage form (such as rifampicin and isoniazid) [91].

2.4.2. Polyurethane (PU): PU, a biocompatible thermoplastic polymer, could act like a human tissue due to soft oligodiol and diisocyanate [92]. Its advantages include flexibility to be used in biomedical wound and surgical dressings and drug carriers [93]. FDM technique was used to prepare 3D printed formulation of theophylline and metformin by employing PU [94]. Use of PU leads to increased porosity on the surface of the tablets; thus, it indirectly results in improved sustained release property of the formulation [95].

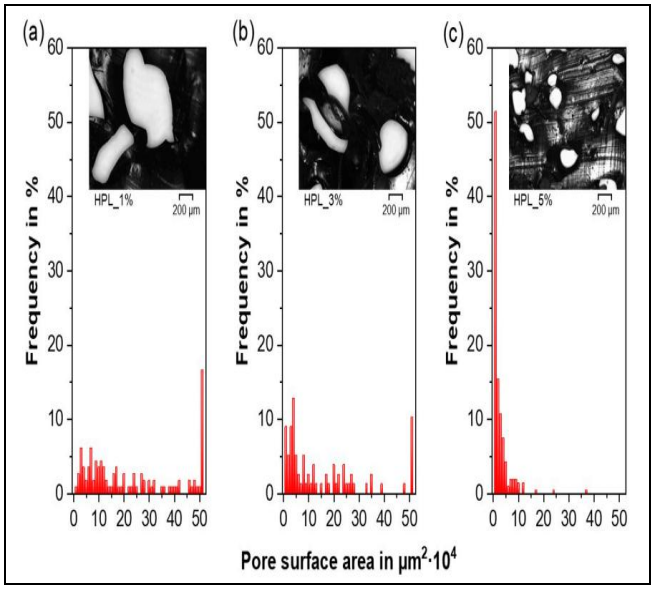

FIG. 6: PORE SURFACE AREA DISTRIBUTION AND A CHARACTERISTIC MICROGRAPH FOR THE PREPARATION CONSTITUTING HYDROPHILIC THERMOPLASTIC POLYURETHANE (HPL) AND NAHCO3 1% (A), 3% (B), AND 5% (C) [96]

PU has been used with polycaprolactone (PCL) to create characteristics of sol-gel transition in human skin contact, however, at room temperature, it remained less viscous. In the coming years, PU could be employed in the preparation of hydrogel injections and injectable formulations [97].

2.4.3. Polylactide (PLA) and Poly (lactide-co-glycolide) PLGA: The characteristic properties of PLA are its easy fabrication quality and less toxicity [98]. Although the nature of PLA is hydrophobic and partially crystalline, it can be readily hydrolyzed and excreted during normal body clearance [99]. PLA is very specific and results in levorotatory (L) and dextrorotatory (D) configuration, leading to stereo-complexes of L-PLA and D-PLA. Currently, PLA is combined with Polyethylene oxide (PEO) in a variety of 3D printed preparation. This is due to the excellent biodegradability, hydrophilicity, and biocompatibility of PLA and PEO, respectively [100]. Lately, colorectal cancer has been treated with PLGA-PCL coated 5-flourouracil (5-FU) sustained-release formulation through the creation of a multi-head dispersion system (MHDS) [101].

2.4.4. Poly (Ɛ-caprolactone) PCL: The outstanding advantages of PCL are its elasticity, biocompatibility, semi-crystalline nature with limited water absorbability, and less toxicity [102]. Researchers fabricated indomethacin containing a 3D printed T-shaped archetype intrauterine system (IUS) with FDM method [103]. Other researchers fabricated salicylic acid-containing 3D printed preparation for treating acne with FDM and SLGA [104]. PLA and PCL scaffolds have been embedded with the modified silica-based stabilized nanoparticles [105].

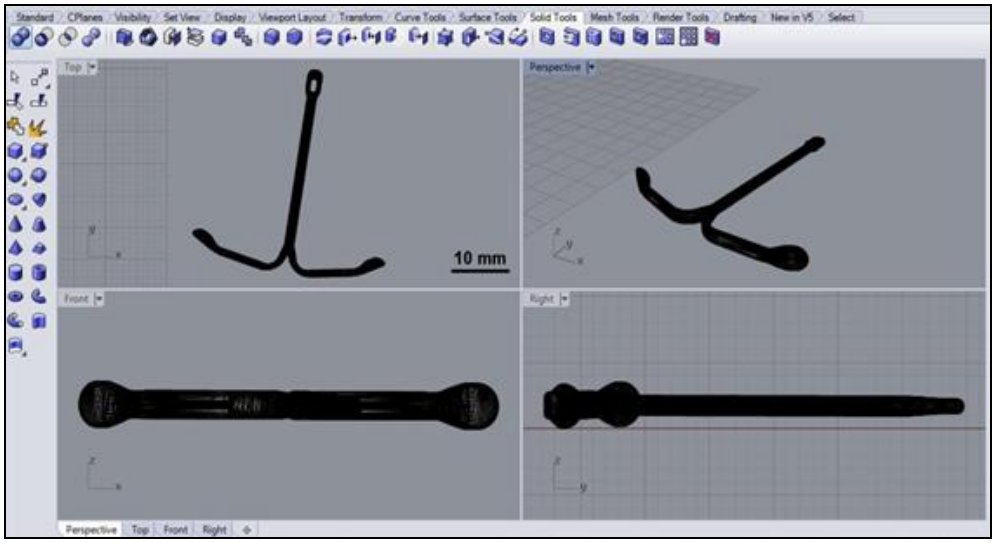

FIG. 7: THE SCREENSHOT OF THE IUS PROTOTYPE IN RHINOCEROS 5.0 SOFTWARE [103]

2.4.5. Hydroxypropyl Methylcellulose (HPMC): HPMC has been extensively used for better fabrication of printable drug-polymer filament [106]. Zhang et al. fabricated 3D printed tablets with the zero-order release of API [107]. Similarly, Kadry *et al*. created 3D printed Diltiazem and HPMC containing multi-purpose filaments [108]. Recently, Fina *et al*. reported the chances of employing SLS to develop a novel solid dosage form for accelerated release of drug to fabricate a qualitative orally disintegrating preparation [109]. In this novel preparation, a combination of HPMCE-5 and vinylpyrrolidone-vinyl acetate copolymers was used [110]. These polymers were mixed individually with 5% acetaminophen and 3% Candurin® Gold Sheen colorant to initiate SLS printing, resulting in 3DP tablets [55].

2.4.6. Eudragit (Methyl prop-2-enoate;2-methylprop-2-enoic acid): The Poly (meth) acrylates are usually known by the term Eudragit [111]. Combination of alkaline and neutral group with RS and RL polymers of Eudragit results in pH-dependent and controlled drug release [112]. With the help of FDM and hot-melt extrusion (HME) 3DP methods, drugs such as captopril, 5-ASA, prednisolone, and theophylline have been incorporated in customized immediate-release tablets. Implementation of such unique ideas can lead to customize medicine and economic

production. Alhijjaj et al. used FDM 3DP methods for manufacturing customized medicine [113]. They successfully fabricated felodipine tablets by employing Eudragit E PO, PEG, tween 80, and PEO [114]. The polymer obtained demonstrated excellent printability and was perfectly adapted for the commercially available FDM 3D printers [115].

2.4.7. Polyvinyl Pyrrolidone (PVP): PVP is a unique and best-suited polymer for DDS due to characteristics such as affinity to complex with hydrophobic and hydrophilic substances broad-spectrum solubility in different organic and non-organic solvents. Moreover, it has excellent stability, non-significant toxicity, and bio-compatibility [116]. It has multiple uses in a gastroprotective dosage form. In their study, Ng et al. concluded that PVP could improvise both homogeneity and viability of cells during the process of DOD 3D bioprinting [117]. Similarly, by using PVP as primary polymer, Tochukwu *et al.* came up with immediate-release tablets through lower temperature FDM method [118]. In the shape of caplet, the 3D printed 10% theophylline loaded filaments were created through HME method [119]. It was concluded that theophylline's integrity and crystalline properties remained untouched, and the tablets had outstanding mechanical properties with superior immediate *in vitro* release qualities due to the use of PVP as an integral polymer [120].

2.4.8. Polyethylene Glycol Diacrylate (PEGDA): PEGDA is a hydrophilic ethylene oxide unit with low toxicity and a polymerizable ending [121]. It acts as a cross linking monomer which is useful in preparing 3D printed hydrogels [122]. Highly concentrated pH sensitive PEGDA is used to prepare delayed drug release formulation [123]. A combination of PEG and PEGDA are used to prepare 3DP hydrogels through SLGA technique [124]. Joas *et al.* used PEGDA, 2-(acryloyloxy) ethyl trimethylammonium chloride and 3-sulfopropyl acrylate to fabricate 3D printed hydrogel for tissue engineering use [125]. PEGDA is commonly used to prepare stable superparamagnetic iron oxide nanoparticles.

2.4.9. Other Polymers in Use in 3DP Technology: Other polymers such as ethyl cellulose (EC) and ethyl vinyl acetate (EVA) are generally used. Last few years have witnessed the use of EC in the preparation of novel multilayer drug delivery technology of 3D printed acetaminophen, in varying concentrations [75]. These acetaminophen multilayer preparations have been demonstrated to undergo simultaneous surface erosion, leading to a desired drug release system [38]. Similarly, EVA has been used to prepare subcutaneous rods (SR) and T-shaped IUS with the help of the FDM method [126]. The majority of the 3D printed prototype has been reported to be amorphous in nature [127]. Moreover, use of polymers, including Kollidon VA64 or amalgamation with Kollidon 12PF help to eradicate the issue of drug degradation in FDM technology [128].

3. Recent Approaches Use of 3DP in Design of Conventional Dosage forms: Several researchers have manufactured different dosage forms and have achieved a breakthrough. However, many dosage forms are still in the nascent stage of development. 3DP has successfully resulted in the development of the following dosage forms:

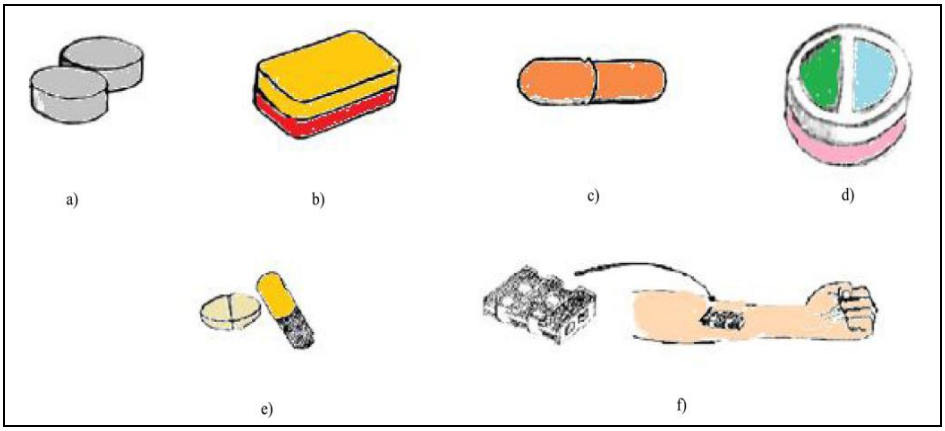

FIG. 8: VARIOUS DOSAGE FORMS: A) IMMEDIATE RELEASE TABLET, B) BILAYER TABLET, C) CAPSULE, D) POLYPILL, E) SEDDS (AS CAPSULE AND TABLET), AND F) IMPLANT [12]

3.1. Immediate Release Tablet (IRT): This form of tablet rapidly disintegrates and dissolves to release the drug [130]. Goyanes *et al.* fabricated paracetamol IRT formulation through SLS technique in 3DP. Three distinct proportions of Paracetamol (5%, 20% and 35% of drug loadings) were developed and the ultimate preparation did not suggest any chances of degradation. It demonstrated a release profile that was pH-independent, and the rate of drug release varied according to the content [55]. Okwuosa *et al.* introduced IRT of theophylline by employing PVP polymer as excipient by 3DP (HME followed by FDM) in a tablet shaped-like caplet [119].

3.2. Bilayer Tablets (Immediate and Sustained-Release Layers of Tablet): It is a biphasic delivery system that releases a drug at two distinct rates of release of two distinct drugs at the same time. Benefits associated with such dosage form is the distribution of one drug with varying release profiles fabricated on different layers or two separate drugs with same or distinct release profiles, enhanced effectiveness of treatment due to synergistic properties, decrease in number of tablets ingested, decreased cost, and easy manufacturing process [131]. Khaled *et al.* successfully fabricated a bilayer tablet of guaifenesin with immediate and sustained release layers for quick relief of symptoms and to provide sustained therapeutic levels for a prolonged duration, respectively [132].

3.3. Capsule: It is a formulation that encapsulates a drug in a soft or hard soluble shell [133]. These are marketed in a variety of sizes to contain the desired quantity of drugs in the form of granules, powder, emulsion, solution, and other formulations. 3DP technique has been used successfully to develop erodible capsules of varying size and thickness with hydroxypropyl cellulose (HPC) to allow pulsatile delivery of several formulations. It can enclose a variety of solid and liquid dosage forms, including pellets, powders, dispersions, solutions, and other formulations [134, 135].

3.4. Polypill: A DDS contains various drugs in distinct doses in terms of fixed-dose combination (FDC). It can be used for the usual requirement of several groups of individuals or tailor-made to meet the specific requirement of a particular individual with the help of 3DP method. An example of such a polypill with different controlled release profiles is a combination of nifedipine, captopril, and glipizide. It has been conveniently manufactured at room temperature through extrusion-based 3DP technique for management of hypertension in diabetics [136]. Another example is a polypill containing a combination of hydrochlorothiazide and aspirin and atenolol, pravastatin, and ramipril for immediate and sustained release in the management of the cardiovascular disorder, respectively [137].

3.5. Implants: Implants are devices situated inside or on the body surface and release drugs at a pre-desired rate. Several polymers can be selected for must-have manufacturing characteristics needed to release drugs and be safe. Such polymers can be biodegradable or non-biodegradable. The former include polymers such as PLA, polyglycolic acid (PGA), and others, while the latter includes ethylene-vinyl acetate, PU, and silicone rubber [126, 138, 139].

Water *et al.* fabricated a nitrofurantoin implant with PLA that was able to release the drug at a controlled rate for 45 days [140]. Wu *et al.* fabricated a multilayer implant containing isoniazid and rifampicin in distinct layers to treat bone tuberculosis [141]. Similarly, Gbureck *et al.* prepared an antibiotic implant including vancomycin, tetracycline, and ofloxacin. They used hydroxyapatite, brushite, and others as substrates, on which antibiotic solution was adsorbed and released at a sustained rate [142].

4. Recent Approaches for 3DP in Design of Novel Drug Delivery Systems: 3DP conforms to unique and novel architectural properties and simultaneously facilitates designing and manufacturing of oral formulations with distinct shapes and sizes; intricate characteristics including tablets with porosity gradients, torture channels, and designed internal structure and multicompartment systems including polypills constituting multiple APIs in a single formulation. These characteristics may allow the regulation of drug release rate by fabricating particular complex release patterns according to the patient's requirement, thus increasing the effectiveness of drug [143]. In pharmaceutical research and

manufacturing, contemporary investigations into 3DP techniques have remained concentrated on limited production to allow individualization and enhance adherence.

4.1. Tablets of Several Geometries: Goyanes *et al.* assessed the practicability of employing a FDM technique to produce tablets of various geometries. They used filaments of PVA to fabricate acetaminophen tablets. They observed that alteration in the geometries of tablets led to different rates of drug release, thereby permitting a superior grade of customization.

The surface area to volume ratio has been demonstrated to determine the rate of drug release. The acetaminophen tablets shaped like a pyramid had the largest ratio, and those cylinder-shaped had the smallest ratio and resulted in the fastest and slowest release rate, respectively. Moreover, this study demonstrated that tablet shape significantly affects the *in-vivo* transit time and could be exploited to develop a DDS for a particular gastro-intestine site [76].

4.2. Tablets with Honeycomb Architecture: Kyobulaa *et al.* used molten beeswax as a hydrophobic drug carrier with 3D injecting printing method and fabricated a fenofibrate tablet with the modified release. The advantages associated with these tablets are their ability to provide tailored loading of drug and their distribution, resulting in an enhanced drug release rate. The use of middle-sized honeycomb channels demonstrated that increase in diameter and surface of honeycomb results in an increased amount of drug release. The advantages of such dosage form are adaptability for manipulating distinct shapes and sizes for tailor-made formulation without changing the composition of primary preparation, manufacturing instruments, and processing parameters. Moreover, this dosage form can conceal the obnoxious taste [144].

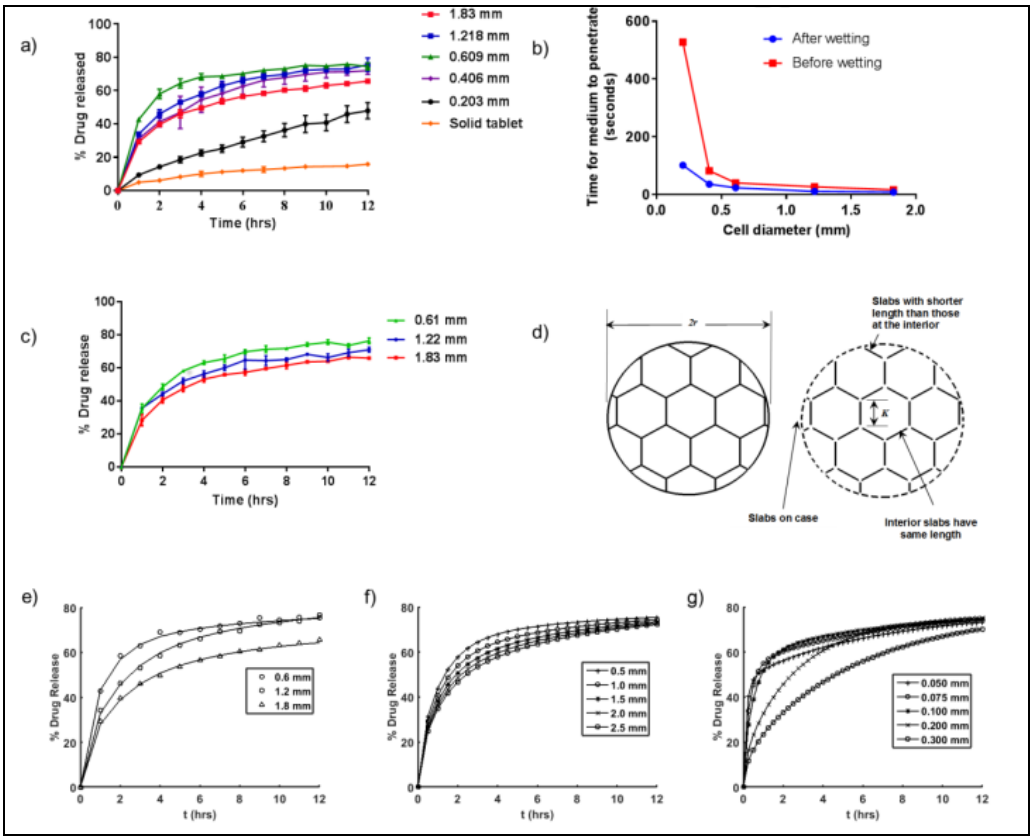

FIG. 9: *IN-VITRO* STUDIES AND FORECASTING OF DRUG RELEASE. a) Dissolution profiles of the printed solid and honeycomb-like tablets of fixed constant weight; b) A plot illustrating the mean time required for the solution to pass through the honeycomb-like tablet as a measure of cell diameter; c) Ratio of surface area to volume and their effect on the release of drug; d) Use of honeycomb geometry to foretell the release profiles; e) A numerical model to study the experimental dissolution profiles for tablets with varying cell diameters (0.6, 1.2, and 1.8 mm); f) Dissolution profiles obtained due to varying cell diameter between 0.5 and 2.5 mm in the enhancement of 0.5 mm; and g) Dissolution profiles obtained due to varying thicknesses of honeycomb wall (0.05, 0.075, 0.1, 0.2, 0.3 mm) [144]

4.3. Tablets with a Quick Onset of Action: Aprecia Pharmaceuticals was the first company to develop a commercial 3D tablet Spirtam® (levetiracetam). It is a pyramid-shaped, complex IRT manufactured through powder bed binding technology that was devoid of compression. The highly porous scaffold of the 3D tablet permits rapid disintegration, even at large doses of up to 1000 mg of API, when placed in the oral cavity with a limited quantity of water. The advantage associated with this form of 3D tablet is the reduced time lag for the onset of action as a high amount of drug remains available in the oral mucosa for absorption. Moreover, this type of dosage form can initiate a new way of fabricating a drug for individuals who have difficulty in swallowing a tablet [35, 47].

4.4. Hollow Structure Tablets: Chai *et al.* introduced a new way of increasing the solubility and bioavailability of the poorly soluble drug (Domperidone) through 3DP technology. HPC filament, a hydrophilic carrier, was used as a solid dispersion to load domperidone and printed it into a hollow structured tablet. Its shape was mainly determined by the infill percentage and the numbers of shells which may influence the inner part and outline structure, respectively. While reducing the former during the printing process results in raised porosity, thus enhancing the dissolution rate. Increasing the latter leads to increased strength and weight of the tablet. Thus, these tablets can improve efficacy and decrease the frequency of drug administration [145].

4.5. Nanosuspension Strategy: Jana *et al*. used inkjet printing technique to fabricate a nanosuspension formulation of folic acid, a model for sparingly water-soluble drugs. They prepared a folic acid suspension (10%) by using mortar and pestle of folic acid added to Tween 20 (3% w/w). The study's findings suggested that, compared to folic acid micro-suspension, the dissolution rate and saturated solubility of nanosuspension were considerably raised by up to 12.5% and 57%, respectively. Thus, a more precise and faster dissolution profile can be created by preparing the nanosuspension. Moreover, under ambient conditions, the printed dosage forms have been reported to be physically and chemically stable [146].

4.6. 3D Printed Buccal Film: Contrary to other biomedical materials, peptides and proteins cannot be produced conventionally and administered orally and thus, represent enormous pharmaceutical challenges. They retain their structure and are unstable in gastrointestinal fluids, and thus, have insufficient efficacy and bioavailability. Miguel *et al*. used the thermal inkjet printing technique and fabricated buccal oral film. They demonstrated that contemporary printers can favorably print this buccal film, and following printing, there was no change in the enzyme activity or structure of protein [147].

4.7. Pediatric-printed Tablets: Scoutaris *et al.* introduced a 3D indomethacin tablet for pediatric patients. A thermoplastic polymer, Hypromellose acetate succinate (HMPCAS), was used to incorporate indomethacin and fabricate a 3D tablet through extrusion technique. They reported that the printing technique allows the manufacturing of 3D tablets in various shapes (ring, bottle, bear, heart, and lion-shape) with adequate sweetening. They further demonstrated that indomethacin has a capacity of immediate release, irrespective of its shape. Thus, this formulation may be an assuring alternative for conventional indomethacin tablets, thereby enhancing adherence in the pediatric population [148].

4.8. SEDDS (Self-Emulsifying Drug Delivery System): An isotropic combination of surfactant, oil, co-solvents, and the drug is termed as SEEDS. It is used for increasing the bioavailability of the drug by enhancing the membrane permeability and solubility of less soluble drugs [149]. It is formulated through 3DP by laying a layer of a molten and self-emulsifying combination of celecoxib and gelucire on an inert tablet made of HPMC films [150].

5. Challenges and Limitations of 3D printing Techniques: Though 3DP is associated with several advantages, including the capacity to fabricate complex structures, design flexibility, simplicity of use, and fabrication of tailor-made products, it is still not developed enough to be used in real-world settings. There are many challenges and drawbacks that need to be answered. Moreover, the requirement of further technological advancement is required.

The challenges that require additional analysis and exploration include anisotropic mechanical properties, a limit on the part size, low manufacturing efficiency, poor accuracy, high costs, the building of overhang surfaces, warping, stringing, pillowing, under-extrusion, over-extrusion, layer misalignment, gaps in the top layers, mass production, and limited availability of biomolecules [151, 152]. Some of the limitations and challenges associated with 3DP technology are:

5.1. Void Formation: The formation of the void results from decreased bonding between the consecutive layers leading to decreased mechanical performance [151, 152]. An example includes the use of the FDM technique results in the formation of the void between the fabricated layers leading to delamination and anisotropic mechanical properties [152–154]. The type of 3DP process and the material used determine the quantity of porosity created by void formation. Thus, to limit this effect, Paul *et al*. assessed the change in void formation due to nozzle geometry and demonstrated that the performance of cylindrical nozzles was inferior to the rectangular nozzles [155].

5.2. Stair-stepping: It is described as a layering error or staircase effect in the fabricated parts. It hardly holds any significance for the internal layer; however, it considerably alters the characteristics of the external layer. Though various techniques SLS can be used to limit or eliminate this error, they result in simultaneously increased cost and time of overall manufacturing process [156].

5.3. Anisotropic in Microstructure and Mechanical Properties: 3DP techniques fabricate the structures by laying layers on each other and simultaneously curing the photo resin, melting the powder bed, or the filament, ultimately leading to the generation of the thermal gradient. The 3DP usually leads to varying mechanical and microstructural properties together with build and other directions [157, 158]. Considering a scenario, the structures fabricated by FDM technique are stronger in the *x/y* direction than *z*-direction (build direction) [159, 160].

5.4. Small Build Volume: It is regarded as one of the primary limitations of the 3DP technique. Usually, the large parts are cut to subparts or scaled-down, which leads to increased manufacturing time and efforts. Moreover, in the majority of the cases, scaling down the model is not possible and less efficient. Following scaling down, the assembled subparts become bulky if mechanical fasteners are used or have lesser strength if adhesives are employed [159]. Until recently, 3DP has not been favorable for large-scale industrial fabrication [161].

5.5. Divergent from Design to Execution: Computer software is the primary tool to design a structure that can be 3D printed. However, the transformation of the software-generated design into a 3D-printed structure generally led to the incorporation of defects and inaccuracies, especially along the curved surfaces. A very fine tessellation can fix this issue to a certain extent, but the software processing and printing are complicated and time-consuming. Thus, post-processing steps such as heat, laser, chemicals, or sanding are used to remove these defects [160].

5.7. Compliance with Safety Standards of FDA: The drugs and medical devices manufactured with 3DP techniques must adhere to the regulations issued by the local FDA. As these 3DP techniques are comparatively new, the FDA is still to develop rules to regulate the use of 3DP in the healthcare sector. Moreover, the present rules are intricate and hard to comply with, thus, pharmaceutical companies are reluctant to employ the 3DP technology 58 fully.

5.8. Safety Aspects: Addressing the safety concerns is primarily important. Heating, extrusion, or fusion of some materials is associated with the probability of emission of toxic airborne matter, which can lead to the irritation of the respiratory tract or skin. Thus, hazardous exposure must be minimized by taking appropriate safety measures and following standard operating guidelines [162].

5.9. Clinical Pharmacy Practice: At present, integration of 3DP technology with hospitals services is associated with various challenges. Firstly, handling the technical aspects requires a highly-skilled technical operator based in hospitals, which is difficult to practice. Secondly, quality control of the fabricated formulations and non-destructive and feasible techniques must be

developed. Near-infrared spectroscopy and Raman confocal microscopy associated with process analytical technologies (PAT) have been highly precise in measuring drug distribution and concentration in tablets and oral films [163]. Thus, PAT helps to solve the issue of quality control. Moreover, setting up a 3D printer in hospitals is a costly affair.

In a hospital setup, the need of labeling and packaging of personalized medicine must be taken into account. Ideal printers that cater to the majority of the patients in a hospital setup are not known. Thus, an ideal 3D printer that is economical, user-friendly, and readily creates the desired dosage form for hospital use is required, and such technological advancements are need of the hour.

5.10. Miscellaneous:

5.10.1. Utilization of Limited Raw Materials: Limited number of biomaterials are compatible with the currently available 3D printers. Thus, there is a need to incorporate more polymers and materials in list [58].

5.10.2. Copyright Infringement: The probability of creating a replica of the original model or fabricating the counterfeit products is higher with advancement in 3DP technology, thereby resulting in an increased number of copyright violations [58].

6. Regulatory Aspects of 3D printing in Pharmaceuticals: Pharmaceutical companies have shown an interest in adopting the new technology of 3DP for fabricating several formulations, including tablets, suspensions, capsules, *etc*. and medical devices including implants, anatomical models, prosthetics, *etc.* [164].

Consecutively, FDA has approved various products such as drugs [131], and a range of medical devices consisting of prosthetics, anatomical models, reaction-wares, and orthodontic implants [165, 166]. The FDA made an attempt to bring a guidance document, particularly for utilizing 3DP in 2015 Guidance Agenda, but then skipped it entirely as documented in Guidance Agenda published in the subsequent year [164]. FDA approved few products manufactured via 3D printers through the contemporary guidelines related to drug products, 510(k) guidelines relating to medical devices associated with moderate risk and also emergency pathways. With the traditional guidelines, a new molecule is approved through a new drug application if it is proven effective and safe for use as cited in the label. As per the 510(k) guidelines, the device needs to be comparable [164].

A device is said to be considered comparable if in comparison to the originator device, a) it has similar indication of use, (b) similar technical properties, (c) similar intended utility but distinct technical properties and does not result in distinct query of effectiveness and safety, and (d) the knowledge shared with FDA proves that the device is at least as effective and safe as the approved originator device [167]. FDA-approved 3D printed drugs and devices are Spritam® (leveriacetam) [165], Unite3D™ Bridge Fixation System [168], OsteoFab® (Patient-specific Facial Device) [169,] and 85 distinct products approved via 510(k) guidelines [170].

7. Future Prospectus: 3DP may emerge as a transformational technology that has the potential to become a necessary part of industrial manufacturing and households. The majority of the hospitals and pharmaceutical companies will probably install a 3D printer for quick and tailor-made products, including a variety of formulations, implants, and prosthetics. On-demand fabrication of products is certain to decrease the total expenditure of hospitals on healthcare products. Novel techniques will possibly evolve for customized medicine such that the entire formulation can be produced according to the requirement of a particular patient. 3D bio-printing of human anatomical structures can serve as models for physiological and toxicological studies involving animals, thus helping the drug discovery process. Comprehensive experimentation in the manufacture of artificial tissues and organs, including artificial heart, blood vessels, kidneys, skin grafts, artificial bones, etc., ignites hope for managing organ failure ailments.

CONCLUSION: 3DP technology allows to creation of tailor-made DDS from the perspective of a particular patient. Following the approval of 3DP technology by the FDA, the research involving the fabrication of oral dosage forms has grown exponentially. Various 3DP techniques permit the development of oral formulations that

increases the solubility and release of poorly soluble drugs. Following the present development of 3DP technology in the DDS, it is thought that the 3DP techniques can be combined with the conventional pharmaceutical techniques to elaborate the areas of 3DP application. Creating such hybrid systems can lead to the development of DDS that is patient-centric but results in low material wastage.

The quality, stability, and applicability of 3DP formulations are the major limitations discussed above. However, it is thought that 3DP technology will continue to progress and refine to produce safe and effective pharmaceutical preparations in the future from the patient and regulatory point of view.

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