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Approaches of 3D printing in current drug delivery

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ABSTRACT

Three-dimensional printing (3DP) is predicted to be one of the most progressive innovations within the pharmacy. Nowadays, the use of 3D printing technologies in drug delivery systems has exponentially expanded, due to its potential advantages over customizing drugs in individually adjusted doses. 3DP empowers the precise deposition of medicaments and excipients, which might cause a change in perspective in drug configuration, production, and use. It can span the medication improvement measure, from the preclinical turn of events and clinical preliminaries to frontline medical care. Though 3DP technology represents the clinical and financial advantages, some specialized and administrative challenges limit its utilization of pharmaceutical products. Accordingly, there's a prerequisite for constant development and refinement in 3DP methods to beat current limits and work with patients' particular medical services with the utilization of customized drugs in the future. This article presents a few 3DP technologies appropriate for drug fabrications with their applications in the improvement of the drug dose structures, demonstrating the feasibility of this innovation in regular commercial production with regulatory assessment.

1. Introduction

The ongoing disease loaded in the current era has fuelled to development of new innovative concepts in drug designing and development, a better understanding of material sciences and manufacturing technologies to ensure the qualitative dosage forms. Though with the huge diversity of physicochemical and biopharmaceutical attributes of lead molecules towards target binding, considerable attention has been focused on formulation scientists for patient-centric product development with novel technological aspects. Among all the newer discoveries, three-dimensional printing (3DP) is witnessed as the most revolutionary and promising technology in the pharmaceutical and biomedical market. Three-dimensional printing (3DP) is believed to be a versatile tool for the paradigm shift of non-digitalized medical products into advanced 3D substances [1]. The International Standard Organization.

(ISO) defines three-dimensional printing as "the manufacture of objects through the deposition of a substance utilizing a print head, nozzle, or other printer technology." It has been used extensively in tissue and organ engineering, diagnostics, disease modelling, manufacturing of biomedical devices and the design and development of novel dosage forms [2,3]. It is utilized in the pharmaceutical industries as a process innovation technology to construct digitally controlled and personalized products by converting a concept into a prototype (additive manufacturing (AM)) using 3D computer-aided design (CAD) or a Magnetic Resonance Image (MRI) [4,5]. It is vigorous to plan and fabricate novel complex medication drug products with customized release trends and the individualized plan adjusted to address the patient's issue. 3D printing is otherwise called layered manufacturing, computer-automated manufacturing, rapid prototyping (RP), additive manufacturing (AM) or solid freeform technology (SFF) [6,7].

In the early 1980s, Charles Hull invented 3DP technology which was utilized in engineering, different non-clinical assembling regions, including automotive, aviation and consumer goods industries. However, it has been used extensively since the year 2012. The rapid advancement

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of the 3DP technology and the advent of flexible and biocompatible materials, facilitate the massive application of this technology in the pharmaceutical field [8,9].

In the early 1990s, the advancement of 3D printing innovation in the drug industry began at MIT (Massachusetts Institute of Technology, Cambridge, MA, USA) with a rapid prototyping strategy called "three-dimensional printing methods" designed and licensed by Sachs et al. [10]. 3D printing as a promising technology was determined by printing a variety of pharmaceutical formulations made up of poorly water-soluble drugs and proteins [11].

Spiratam® (levetiracetam) the first commercial 3D tablet was approved by the USFDA in.

August 2015, which opened another part of pharmacoprinting in drug manufacturing. This enables high-dose administration and rapid onset of action [12].

The focus of above-mentioned technology is on innovative approaches in the design of solid dosage forms for customized therapy, transdermal medication and biomedical utilization of additive manufacturing techniques such as implants, surgical models, bioprinted materials, and biorobotics, etc. Furthermore, because this technology may be used to create more predictable drug screening platforms with lesser cost in comparison to traditional screening methods used for drug products and devices, it can bring down the probability of failure at later stages of the new medication improvement process. Due to its numerous innate benefits over the conventional technologies like a customized and individualized formulation with adjusted dose, fabrication of highly accurate solid dosage forms on-demand manufacturing, more mechanized, fast and simple to utilize and cost-effectiveness, the 3DP technology has gained greater attention in recent years in novel drug delivery approaches, which is evidenced from various scientific databases such as Scopus, MEDLINE, EMBASE, Pub Med, Science.

Direct, DOAJ, etc. [13,14].

In this review, the focus has been done on certain 3DP technologies that are suited for pharmaceutical designing, suitability in the development of dosage forms, broad regulatory acceptance and demonstration of the technological viability in commercial production.

2. 3DP technology in pharmaceutical formulations

Based on the energy source, material source and other mechanical characteristics various 3DP methods have been designed. Printing-based inkjet (IJ), nozzle-based deposition, and laser-based writing systems are the most prevalent 3DP technologies for pharmaceutical applications which are additionally parted into subtypes dependent on materials and energy sources Fig. 1 [15]. A concise outline of the overall characteristics of each 3DP technology is delineated in the following sections.

2.1. Printing Based Inkjet System

Inkjet printing is a broad word that refers to various methods for digitally controlling the generation and positioning of small liquid drops. Continuous Inkjet printing (CIJ) and Drop on Demand (DoD) printing are the two promising of inkjet technology, which are distinguished by the physical process that produces the drips.

CIJ printing includes the discharge of a persistent stream of fluid through a nozzle of 50–80

μm diameter by using a high-pressure pump, which then breaks up under surface tension forces into a stream of drops, whereas in DoD the liquid is ejected from the print head only when a drop is required: the production of each droplet of 10–50 μm with a volume of 1–70 pL occurs rapidly in response to a trigger signal [16]. Drop-on-drop deposition and drop-on solid deposition are two subcategories of DoD technology. The printer head ejects the droplets onto each other in drop-on-drop deposition, resulting in a solid layer with great resolution. The drop-on-solid deposition is often known as drop-on-powder or drop-on-bed sedimentation, binder jetting, plaster printing, or powder bed 3DP because it spreads solid powder on top of a platform and sprays a liquid link, the binder, on the powders [17].

A liquid binder solution is dispensed over a flattened powder bed using an ink-jet head in this technique. Powder carrier particles can be bonded together by binders (organic/inorganic) to form an agglomerated product due to adhesion forces or hydraulic cement setting process [18]. There are numerous approaches to deliver a drop-on-demand (DoD) inkjet. The most common methods include thermal and piezoelectric. The ink is heated locally in thermal DoD (also known as bubble jet printing) and creates bubbles that eject ink. The quick change in form of the piezoelectric crystal causes a sudden volume change, resulting in an acoustic pulse adequate for ink ejection in piezoelectric DOD. While the thermal DOD approach is confined to volatile liquids, the piezoelectric DOD method can be employed with a wide range of liquids [19]. Inkjet printing exhibits product transition via the innovation pipeline and exhibits a wide range of applications, where it can effectively enable continuous and semi-continuous manufacturing as well as a faster feed of the innovation pipeline represented in Fig. 2 [20]. Pharmaceutical applications of inkjet printing in different formulations using API/polymers are illustrated in Table 1.

2.2. Nozzle-based deposition systems

To create a 3D object, nozzle-based deposition systems integrate the solid materials with the binder before 3D printing and direct deposit the mixture through a nozzle. This is broadly divided into two subtypes based on whether the process includes or excludes material melting: fused deposition modelling (FDM) and pressure-assisted microsyringes (PAM) [21]. Fused deposition modelling is a solid-based fast prototyping approach that builds a model by extruding material layer by layer. It is based on the heating and extrusion of a semi-liquid thermoplastic ink that is sequentially settled to obtain a 3D object using a removable scaffold. Low-cost manufacturing, compatibility of mixing pharmaceutical-grade polymers with APIs via hot-melt extrusion (HME), and the capacity to construct hollow objects are just a few of the benefits. This approach can be used to make a variety of dosage forms which include polymer in their formulations, such as implants, zero-order release tablets and so on [22,23]. Different Formulations prepared by FDM are narrated in Table 1.

PAM is another nozzle-based deposition system that uses a microsyringe to extrude viscous and semi-liquid materials; this can be released by compressed air. PAM technology allows the production of a microstructure of 5–10 μm or less [24]. The viscous, semi-liquid ink is deposited layer by layer according to a pre-designed 3D form using a microsyringe moved by pressure generated by an air piston. Several works of literature on the pharmaceutical application of PAM are illustrated in Table 1.

2.3. Laser-based writing system

Stereolithography (SLA) was the first created laser-based liquid resin polymerization technology and it is currently widely utilized in rapid prototyping. It is the method of computer regulated laser beam, used to make liquid polymer/resin as solid, by this means creating a 3D structure. SLA has various advantages over previous methods of 3DP, the most notable of which is its incredible resolution and avoidance of thermal techniques that can destroy certain medicine molecules. Selective laser sintering (SLS) was developed more recently to avoid the usage of liquid photo-reactive substrates. A powder bed is treated with a high-powered laser, which melts a particular section of the powder bed. Again, all selected molten slices will splice to have the desired layer-by-layer architecture [25]. SLA offers a high resolution that enables the creation of intricate structures while also minimizing heating during the printing process, making it ideal for thermo-labile pharmaceuticals [26]. It has the wide application depicted in Table 1.

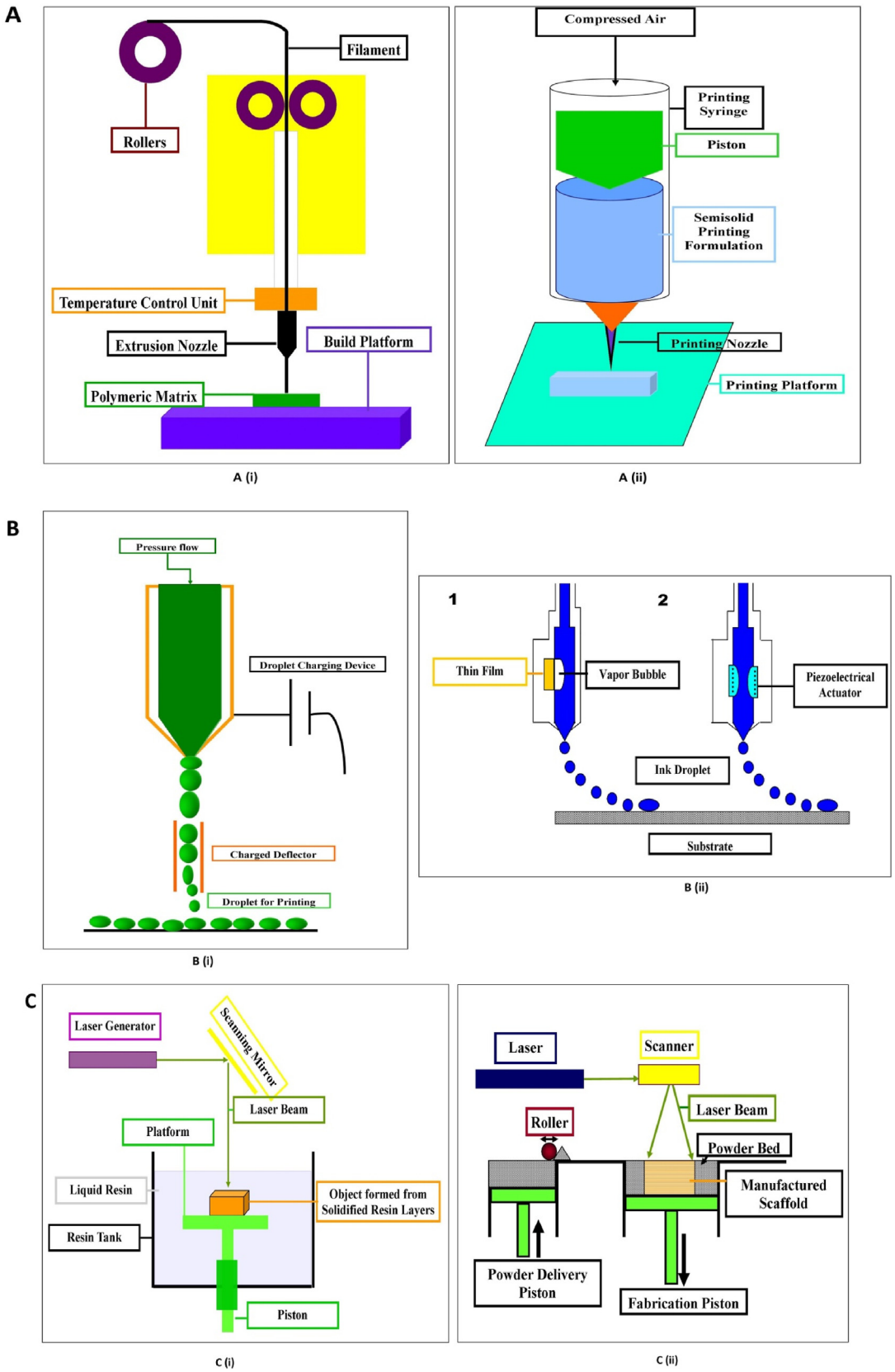

Fig. 1. Different 3D printing Techniques; A. Nozzle Based Deposition System: A(i) Fused Deposition Modelling (FDM), A(ii) Pressure-Assisted Microsyringes (PAM), B. Printing Based Inkjet System: B(i) Continuous Inkjet Printing (CIJ), B(ii) Drop-on-Demand Printing (DOD): 1.Drop-on-Solid Deposition, 2. Drop-on-Drop Deposition (Piezoelectric Technology), C. Laser Based Writing System: C(i) Stereolithography (SLA), C(ii) Selective laser sintering (SLS).

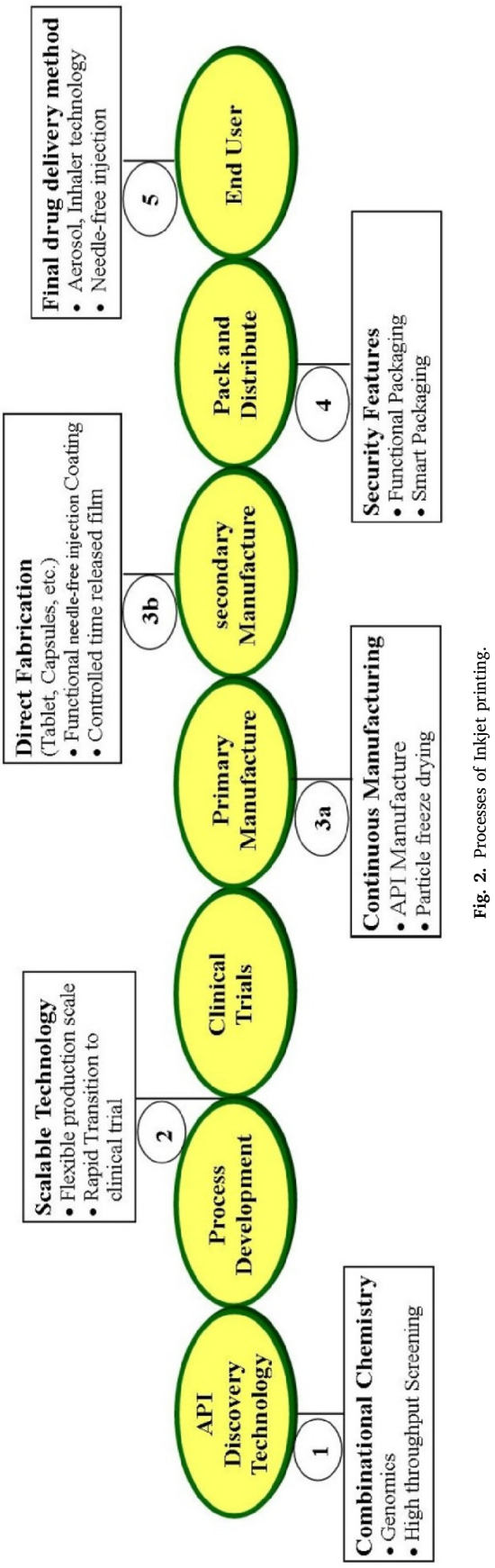

Fig. 2. Processes of Inkjet printing.

3. 3D printing landscape

3D printing is a Cutting-edge technology that is helping designers to re-think the design for leadership development, new customized formulations, etc. This is accomplished through shortening the design cycle of developing new ideas and concepts, receiving valuable input, and improving the design to make decisions.

In this technique, an idea is reversed into a prototype using 3D computer-aided design (CAD) files, allowing for the production of digitally controlled and personalized products [47].

Virtual 3D design of an object is prepared using digital elegant software like Onshape, Solid works, Creo parametric, Autocad, Autodesk Tinker cad, BRL-CAD, Free CAD, Open SCAD, Wings3D, 3D Slash, Sketch UP, Fusion 360, etc [48]. Using MeshLab, Google SketchUp, plugin, STL-viewer, and Netfabb Studio software, this advanced model is then adapted to (.STL) digital file format, which stands for standard tessellation language or stereolithography [49]. Slicing is the ahead interaction of changing over the 3D model into a stack of flat layers. Slicing is done using slicing software like Matter Control, Ultimaker Cura, Slic3r, Octo Print, idea Maker, etc. [50]. Slicing software depicts these layers as straight developments of the 3d printer extruder fixation laser or same. By slicing the design into a sequence of 2D horizontal cross-sections with the help of specialist slicer software installed in the 3D printer, the standard tessellation language (.STL) file is turned into a G file. The next step is to choose a suitable material for 3D printing. Filaments consisting of various materials are used in 3D printers. 3D printers use filaments as their "ink". 3D printing may be done using a wide variety of materials like plastics, ceramics, resins, metals, sand, textiles, biomaterials, glass, food and lunar dust, etc. When the model is loaded into the computer, it sends instructions to the 3D printer for layer-by-layer material deposition. By extruding molten plastic through a small nozzle, a 3D printer works. It moves accurately in response to computer commands. After printing one layer, the printer waits for it to dry before printing the next layer on top, Fig. 3. This process continues until we achieve the desired product [51].

4. Pharmaceutical applications of 3D printing

As 3D printing innovation is getting more open to drug researchers and the first 3D printed tablet Spritam was endorsed by FDA in Aug 2015; utilizing 3D printing technology to foster drug items has acquired critical interests in the drug industry and academic. Drug utilization of 3D printing has two expected bearings to carry the drug item improvement to unfamiliar regions, one is the assembling of medication conveyance frameworks with refined constructions and the other one is customized medication. 3DP has been witnessed wide application in pharmaceutical fields due to its potential advantages like enhanced productivity, complex drug release profile, multiple dosing, single-step process with low cost and customization/ personalization of drug delivery. This modernized technology is very useful tool for more precise drug dispensing with the tailored release of drug to address the unique need of the individual patient. Moreover, personalized medicine is an unprecedented opportunity of 3D printing to cater the challenges for treatment of heterogeneous diseases. Various formulations including oral solid dosage forms, implants, microneedle and hydrogel etc. with suitable examples are described below.

4.1. Oral solid dosage forms

Tablets have been broadly inspected for the possibility of 3DP advancements in drug fabricating. By and large, tablets delivered by 3DP techniques can be ordered into two gatherings: single API tablets and various API tablets. Particular instances of every class are portrayed in the following two areas, individually.

At first, 3DP innovation was applied to manufacture straightforward quick delivery (IR) tablets including a solitary API. FDM technique was

Table 1
Different categories of 3D printing with suitable examples.

3D printing technology	Formulation	Study aim	API	Excipients	Refs
Binder jet printing	Tablets	Fabrication of fast-dissolving drug delivery device	Paracetamol and alizarin yellow (dye)	Colloidal silicon dioxide (SiO2), mannitol, polyvinylpyrrolidone (PVP) K30, and lactose	[27]
	Tabular device	Fabrication of novel drug delivery devices	Methylene blue and alizarin yellow (dyes)	Polycaprolactone (PCL) and polyethylene oxide (PEO)	[28]
	Cubic tabular devices	Development of near zero-order release dosage forms	Pseudoephedrine	Kollidon SR, hydroxypropylmethylcellulose (HPMC)	[29]
Pressure-assisted microsyringes (PAM),	Tablet	On-demand manufacturing of immediate release	Levetiracetam	polyvinylpyrrolidone-vinyl acetate copolymer (PVP-PVAc)	[30]
	Semisolid extrusion	Controlled release oral drug delivery	Ramipril	Kollidon VA64 and Kollidon 12 PF	[31]
FDM	Tablet	Rapid Drug Release	Haloperidol	Kollidon(®) VA64, Kollicoat(®) IR, Affinsiol(™) 15 cP and HPMCAS	[32]
	Caplets	Evaluate microstructure and drug release characteristics of PVAbased caplets	Paracetamol or caffeine	Polyvinyl alcohol (PVA)	[33]
	Intravaginal ring	Medical devices	Clotrimazole	Thermoplastic polyurethanes	[34]
	Tablet	Controlled drug release	Isoniazid (INZ) and rifampicin (RFC)	hydroxypropyl cellulose (HPC), hypromellose acetate succinate (HPMC – AS)	[35]
	Tablet	Fabrication of modified-release tablets	4-amino salicylic acid (ASA) or 5-ASA	PVA	[36]
Semi-solid extrusion	Tablets	high drug loading levetiracetam	levetiracetam	Hydroxypropyl cellulose (HPC-M)	[37]
	Suppositories	Self-Emulsified Drug Delivery System	Tacrolimus	Gelucire 44/14 and Gelucire 44/16	[38]
	Tablets	Controlled-release	Glipizide		[39]
	Hydrogel	Gummy drug formulations for paediatric use	Lamotrigine	Gelatin, HPMC	[40]
Selective laser sintering (SLS)	Amorphous printlets	Solubility enhancer	Lopinavir	Kollicoat®, Candurin® NXT Ruby Red	[41]
	Tablets (printlets)	Solubility enhancer	Clindamycin Palmitate Hydrochloride	microcrystalline cellulose (MCC), lactose monohydrate (LMH)	[42]
Stereo lithography (SLA)	Novel indwelling bladder devices	Site specific drug delivery	Lidocaine hydrochloride	(Elastic Resin)	[43]
	Antihypertensive polyprintlet	Controlled release	Hydrochlorothiazide, Amlodipine, atenolol, Irbesartan	Poly(ethylene glycol) diacrylate, diphenyl(2, 4, 6-trimethyl-benzoyl) phosphine oxide (TPO)	[44]
Direct powder extrusion (DPE)	Tablet	Modified release	Tramadol	Hydroxypropylcellulose (HPC), Polyethylene oxide (PEO)	[45]
	Tablet	Modified release	Itraconazole	Hydroxypropylcellulose (HPC - UL, SSL, SL and L)	[46]

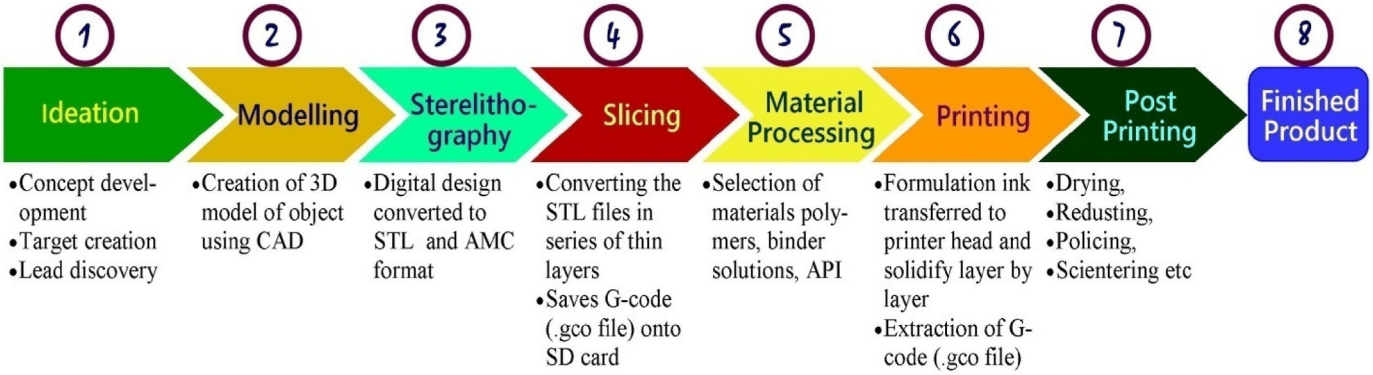

Fig. 3. Different steps of 3D printing.

received for delivering IR tablets, presumably because of its straightforward manufacturing methodology. Specific instances of single API IR tablets acquired by utilizing the FDM technique have been investigated [52,53].

It has been reported that 3DP technology can be used to prepare both low and high drug loaded-dosage forms. Theophylline-loaded (10% API) lower temperature FDM method was used by Okwuosa et al. to manufacture patient-specific IR Tablets [54]. Microdose formulations have been done by Arafat et al. using FDM printing technology. In this, capsular-ovoid-shaped tablets loaded with 200 or 400 μg of sodium warfarin were formed with 91.5%–102.4% dose accuracy [55]. Yan et al. developed Orodispersible films (ODFs) by semi-solid extrusion (SSE) 3D printing using levocetirizine hydrochloride as model drug [56].Using that FDM method, a thermoplastic polyurethane-based formulation (60% API) was invented [57]. A high dose of the drug (80% paracetamol) in an IR tablet was prepared using an extrusion-based 3D printer [58]. Recently, Cui et al. fabricated a high-loaded (96%) fast-release formulation of levetiracetam based on SSE technology using levetiracetam as the model drug [59].

3 D technology has been used to develop various modified-release tablets. FDM method to fabricate ER tablets has been reported by several kinds of literature.

In 2015, Skowyra et al. also used the FDM method to design extended-release tablets using prednisolone-loaded-polyvinyl alcohol filaments for attaining release up to 24 h [60]. Okwuosa et al. designed gastric-resistant tablets by implementing several shell-core designs with methacrylic acid and polyvinyl pyrrolidone (PVP) co-polymer for the core and shell structures, respectively [61]. Extended-release tablets of theophylline have been formulated using hydroxypropyl methylcellulose (HPMC) hydrogels [62]. Chai et al. developed intragastric floating sustained-release (FSR) tablets of domperidone incorporating hydroxypropyl cellulose (HPC) by FDM [63]. Controlled release formulations were fabricated using various 3d printing technologies. Alvaro et al. developed modified-release Budesonide dosage forms using polyvinyl alcohol filaments using HME [64]. Similarly, a controlled-release tablet of acetaminophen has been made by (HME) technology [65]. Haoyang Wen et al. fabricated stable gastro-retention and controlled-release formulation of ginkgolide using HPMC [66]. Vo et al. used hot-melt extrusion methodology in conjunction with 3D printing to invent a novel gastro retentive delivery system to customize the treatment of cinnarizine or other drugs having a narrow absorption window [67]. Controlled release tablets of glipizide were established by Qijun Li et al. The fabrication has been made by the hotmelt extrusion (HME) method using polyvinyl alcohol (PVA) [68].

An expulsion-based 3D printer was utilized to manufacture paracetamol tablets with various calculations (lattice, ring and strong) from a solitary glue-based plan framed from paracetamol [69]. Notwithstanding quick or broadened drug discharge, 3DP innovation is appropriate for different kinds of altered delivery tablets. Utilizing three unique grades of hypromellose acetic acid derivation succinate (grades LG, MG and HG), enteric tablets were fabricated by the FDM technique to empower producing the deferred discharge tablets without the requirement for an external enteric covering [70]. Besides, 3D expulsion-based printing can manufacture gastro-gliding tablets [71]. Three-dimensional (3D) expulsion-based printing is presently the most encouraging way to deal with the assembling for the creation of multi-dynamic tablets with clear-cut and separate controlled delivery profiles for different medications. Khaled et al. created a polypill osmotic siphon with the medication captopril and supported delivery compartments with the medications nifedipine and glipizide. This mix of meds might be utilized to treat diabetics experiencing hypertension [72]. Tan et al. used 3D printing technologies and three distinct common drugs (paracetamol, phenylephrine HCl, and diphenhydramine HCl) to create drug tablets with personalized dosages, periods, and multiple drug permutations [73]. Robles-Martinez et al. successfully developed SLA 3D printer fabricated polypills containing six active ingredients with distinct drug release profiles [74]. Suxiao jiuxin orally disintegrating tablets were produced by Lin et al. by mixing DOP and traditional Chinese medicine [75]. This 3D-printed medicine improves the stability of borneol. Allahham et al. developed oral disintegrating print lets of ondansetron using SLS technology for the improvement of solubility and disintegration [76].

4.2. Implants

An implant can be a drug delivery system that contains effective drugs within a sustained release delivery matrix, benefiting patients who demand long-term medication treatment. An embed is a dosing structure containing dynamic medications inside a supported delivery conveyance grid, giving advantages to patients who need long haul treatment of medications.

For instance, microstructured embeds of levofloxacin display complex delivery profiles obtained from a solitary embed. This embed showed a bimodal profile, with pulsatile.

(day 5–25) and consistent state drug discharge (day 25–50) and afterward, the beat discharge started again on day 50 and proceeded up to day 80 [77]. By utilizing 3D printers, Wu et al. planned a multi-drug embed for the treatment of bone tuberculosis. Isoniazid and rifampicin, antitubercular agents have fused into each layer to get a particular grouping, shaping a multi-facet concentric chamber [78]. Wu et al. recently developed a 3DP-based multi-drug implant in which tobramycin (TOB) and levofloxacin (LVFX) as API were loaded and multilayered scaffolds were introduced (layers 0.4 cm3) for the treatment of chronic osteomyelitis [79]. This work explores the utilization of polycaprolactone (PCL) - based embed coatings as a novel procedure to delay the conveyance of hydrophilic mixtures from implantable gadgets that have been arranged by added substance fabricating (AM) [80]. An appropriate drug-loaded embed conveyance framework that can viably release antibacterial drugs within the postoperative injury zone and offer assistance repair bone infection is exceptionally noteworthy within the clinical treatment of bone imperfection by SSE and FDM technologies using ciprofloxacin (CIP) was a model drug [81]. Chaudhari et al. have developed skin patches with the incorporation of quercetin-PVP using FDM based on the HME technique to overcome the current drug delivery challenges [82].

4.3. Microneedles

A novel inkjet printing technique, a process for coating microneedle arrays made up of metal with three anticancer components such as curcumin, cisplatin and 5-fluorouracil, for transdermal drug delivery [83]. Farias et al. used stereolithography to design a cell-hydrogel having 3D printed methacrylate-based custom hollow microneedle assembly (circular array of 13 conical frusta) to evaluate the potentiality of cells named human hepatocellular carcinoma (HepG2) cells [84]. Economidou et al. designed 3D printed microneedle arrays by stereolithography (SLA) using a biocompatible resin for transdermal insulin delivery [85].

Notable novel drug delivery approaches have been accorded by 3D printing technology. Gastro retentive floating pulsatile drug delivery, transdermal drug delivery, microporous bioceramics, multiple pills, microfluidic pump etc. are the recent advancement so far which is illustrated in Table 2. Apart from the wide application in designing different formulations various recent signs of progress on customized drug delivery have been found in 3D printing technology. Personalized drug dosing, complex drug-release profiles, personalized topical treatment devices are becoming more popular because the key benefits behind are patient-centric design (tailored manufacturing), real-time analysis of dosage form simplified logistics and reducing wastage etc. These newer technologies have revolutionized the drug delivery system to address the unmet personalized needs of large groups of paediatric, geriatric, visually impaired populations [100,101]. Extensive research has been done, a few of which are depicted in Table 3. However, several polymers like polyvinyl alcohol (PVA), poly (lactic acid) (PLA), poly (caprolactone) (PCL), gelatin methacryloyl (GelMA), nanocellulose, chitosan, alginate, pectin, gelatin, alginate and chocolate are extensively used in 3D printing [107].

5. Global 3D printed drugs market (regulatory market)

The rising prevalence of chronic disease, combined with an increasing number of patients suffering from dysphasia around the world, is fuelling demand for instantaneous soluble drugs, and as a result, the market for 3D printed drugs is expanding. The global 3D Printed drugs market is estimated to achieve a market estimation of US$ 2064.8 million by 2027, growing at a satisfactory CAGR of 15.2% during the expected timeline (2021–2027) from US$ 638.6 million in 2019 [108]. The increasing adoption of customized medicines, intensive research activities, and the growing prevalence of dysphasia are the factors driving the 3D printed drugs market magnification Fig. 4. Furthermore, the global drug shortage associated with the COVID -19 pandemic, fuelled rapid growths in the

Table 2
Different formulations of 3D printing.

Printing technology/Printer type	Dosage forms/ Systems	Model drug used	Reference
deposition modelling (FDM)	Novel gastro retentive Floating Pulsatile Drug Delivery	theophylline	[86]
low temperature 3D powder direct printing process	Microporous bioceramics	vancomycin, ofloxacin and tetracycline	[87]
3D extrusion printer	Multi-active solid dosage form (polypill)	Immediate release compartment with aspirin and hydrochlorothiazide and three sustained release compartments containing pravastatin, atenolol, and ramipril.	[88]
Piezoelectric inkjet printer	Microparticles	Paclitaxel	[89]
deposition modelling (FDM)	Oral pulsatile capsule	Dronedarone hydrochloride and ascorbic acid	[90]
Laboratory scale 3-DP™ machine	Capsule with immediate release core and a release rate regulating shell	Pseudoephedrine hydrochloride	[91]
3D Printing	Nanocrystals	Indomethacin	[92]
Micro-drop Inkjet 3DP	Nanosuspension	Folic Acid	[93]
Commercial inkjet printer	Nanocomposite structure	Rifampicin and Calcium phosphate	[94]
3D printer	Microfluidic pump	Doxorubicin	[95]
3D printer	Biodegradable patch	5-Fluorouracil	[96]
3D printer	Biofilm disk	Nitrofurantoin	[97]
Stereolithographic printing	Ibuprofen-loaded hydrogels	ibuprofen	[98]
Fused deposition modelling	nanocapsules	deflazacort	[99]

Table 3
Novel applications of 3D printing.

Applications Area	Dosage Form	Method	References
Personalized Drug Dosing	A flexible-dose tablet for immediate and extended release	Fused deposition modelling 3D printing	[102]
	Starmix candy like formulations of indomethacin	Fusion deposition modelling 3D printing	[103]
Complex Drug-Release Profiles	Modified-release tablets of 4-aminosalicylic acid and paracetamol	Stereolithographic 3D printing	[104]
	Effect of geometry on drug release from 3D printed tablets	hot melt extrusion (HME)	[105]
	Nitrofurantoin model disk geometries	3D extrusion-based printing	[97]
Personalized Topical Treatment Devices	Nose-shaped mask, laden with salicylic acid, adapted to the morphology of an individual	Fused deposition modeling as well as stereolithography	[106]

pharmacy sector for 3D printing. The emergence of new industry players, as well as the release of a new 3D printer, components, and series funding in start-ups, are acting as growth catalysts. Some of the major players operating in the market include Aprecia Pharmaceuticals, LLC., GlaxoSmithKline plc, AstraZeneca, FabRx Ltd., Hewlett Packard Caribe, Merck KGaA, Cycle Pharmaceuticals and Tvasta.

FDA has launched several internal management sciences and research developments across the centers in response to the increased vigilance and exploration of 3D printed pharmaceutical drug products. This was done to improve understanding of the relationship between properties of the material and process parameters on 3D printed drug product quality. As of now, the FDA has investigated and governed 3D printed products in accordance with current regulations. Good Manufacturing Practice (GMP) guidelines for 3D-printed pharmaceuticals have not been established, but in 2017 the FDA established guidelines for 3D printing of medical device products. Aprecia Pharmaceuticals' Spritam (levetiracetam), an anti-epileptic drug, is the first and only 3D-printed pharmaceutical that received FDA approval in 2015 and is made using Aprecia's proprietary Zip Dose technology. FabRx Ltd., (M3DIMAKER) completed the world's first-in-human clinical study using their proprietary print lets technology, which relies on personalized treatment of children with rare metabolic diseases like polycythaemia, organic syndrome etc [109]. It was greatly achieved by Triastek, a 3D printing technology firm and Chinese pharmaceutical industry, has acquired Investigational New Drug (IND) approval for its first 3D printed drug substance, T19 for arthritis treatment from the US FDA (Food and Drug Administration) [110].

6. Challenges of 3D printing on formulation development

Despite the implicit advantages of 3DP technology in formulation development, the technical difficulties and complications imparting applications of 3DP are the availability of excipients, development of printing software and instruments, optimizing the mechanical properties of products, and the regulatory landscape. Relatively limited availability of excipients is the major hindrance for designing specialized dosage forms. Non-toxic, biodegradable, biocompatible and stable excipients are highly essential to the wide application of 3DP in formulation development. Further, with the increment of the more complex structure of dosage form, continuous updating of modeling and slicing software intended to design and inform its production must be required. The mechanical equipment, operating procedures, and control system need to be updated and optimized to prevent clogging or promote product uniformity. At present, 3D printers used in pharmaceutical formulation preparation do not meet good manufacturing practice (GMP) standards and thus need to be validated to ensure the product meets the required safety standards. The physicochemical parameters such as the viscosity and surface tension of the adhesives, fineness of the nozzle influence the performance of the products. Further, the quality control parameters of the dosage form are to be ensured to make the prepared formulations reproducible. In addition, post-printing processes such as drying methods, drying time, and drying temperature may also affect the appearance and quality of the products which are most important for 3D printing technologies based on DOP, FDM and SSE. Thus, it's essential to ameliorate the mechanical behaviour of products by optimizing printing outfits such as computer control programs, refining of adhesive nozzles and optimizing printing process parameters. In terms of regulation, many questions are surrounding how 3D-printed pharmaceuticals can be monitored and evaluated for quality. The FDA issued its final guidance on technical considerations for the regulation of 3D-printed medical devices in 2017; however, it may not apply to all 3D-printed medical devices as a separate assessment of safety and effectiveness may be required, especially for personalized products. In instances where products are customized to the patient, the question of whether 3D printing is classed as a manufacturing process or compounding would also impact regulatory guidance. Additionally, though the FDA authorized the first 3D-printed tablets, no regulations or guidelines regarding 3D-printed medicines are currently available. There remain several regulatory challenges, such as how the performance of 3D-printed pharmaceuticals should be measured or their quality controlled, though the FDA's Office of Testing and Research is currently working to answer those [111].

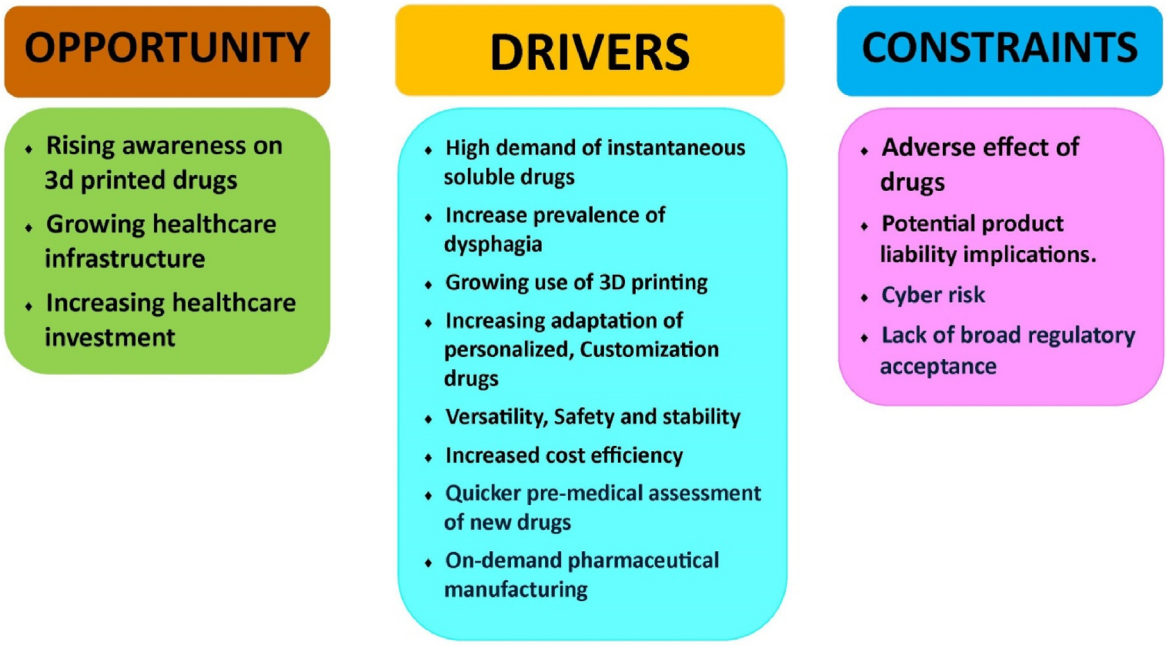

Fig. 4. Aspects of 3D printing.

7. Conclusion

3D printing innovation is a significant and likely apparatus for the drug design area, prompting customized medication zeroed in on the patients' requirements. It offers various benefits, for example, expanding the expense productivity and the assembling speed. 3D printing has reformed the manner by which assembling is finished. It further develops the plan fabricating and decreases lead time and tooling cost for new items. Without a doubt, this methodology turns into a helpful and likely apparatus for some patients as it brings the assembling near them and offers individualized treatment.

Late progressions in innovation and expanded research in the sector unquestionably can provide more secure and viable treatment while also creating opportunities for individualized medication. Albeit the 3D innovation is as yet in its early stages, this assembling technique is by all accounts an extraordinary instrument with greater adaptability in drug-producing and is probably going to alter drug conveyance frameworks to another level however, needs time to advance. The plan of different 3D printed drug conveyance frameworks to give exceptional and additionally redid arrival of medication moieties will make ready for custom-made dosing for customized medication treatment. The wide applications and limitless capability of 3D printing innovation in creating different medication conveyance frameworks are informed. 3D printing has shown its capability to foster creative medication conveyance frameworks wherein numerous medications are conveyed at various conveyance rates. Stereolithography, inkjet printing, and spout-based testimony frameworks, as well as laser-based composing frameworks are some of the common 3D printing strategies used in drug production. In nutshell this game-changing innovation is relied upon to discover sufficient room in certain medication conveyance frameworks, while it is difficult to predict the absolute substitution of existing items.

Conflict of interest

- All authors have participated in (a) conception and design, or analysis and interpretation of the data; (b) drafting the article or revising it critically for important intellectual content; and (c) approval of the final version.
- This manuscript has not been submitted to, nor is under review at, another journal or other publishing venue.

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