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PHARMACEUTICAL APPLICATIONS OF NEXT GENERATION PRINTING TECHNOLOGIES: A BRIEF LITERATURE REVIEW

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ABSTRACT: Next-generation printing or commonly known as three-dimensional (3D) printing (3DP), is a fabrication process of construction of a 3D object using a computer-aided design or digital 3D model. The 3D object is created layer by layer by depositing, joining, or solidifying a feedstock material such as thermoplastic polymer under the control of a computer-designed program. It is considered the latest technology that has the potential to address complex medical and pharmaceutical problems, such as prototyping essential medical devices, equipment, and novel drug delivery systems. The ability of 3DP to produce medications with accurate specifications tailored to the needs of individual patients has indicated the possibility of developing personalized medicines. The technology allows dosage forms to be precisely printed in various shapes, sizes, and textures, in a limited time period. In spite of many potential medical and economic benefits of 3DP, some technical and regulatory challenges are associated with the widespread application of 3DPin the pharmaceutical sector; those need to be addressed by proper research so that the benefit of this technology can be utilized fully. Along with 3DP, more advanced and sophisticated printing technologies like 4D/5D printing are also introduced and have already been explored in biomedical applications. However, the utility of these technologies in the pharmaceutical drug manufacturing process is still in the early experimental phase and gradually evolving. This review article illustrates the recent trends, challenges, and future prospects of 3D Pin pharmaceutical applications, along with the highlights of the ongoing transition from 3D to 4D/5D printing.

INTRODUCTION: Three-dimensional printing (3DP) is nowadays a well known advanced additive manufacturing technology used widely in various fields of technology, art, and science, however most importantly used in various pharmaceutical and medical applications like regenerative medicine, diagnosis, implants, developments of artificial tissues and organs, *etc.* **Fig. 1**.

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The fastest-growing demand for customized pharmaceuticals and medical devices makes the impact of 3DP technology increased rapidly in recent years.

The technique prints or manufactures one or more entities in a layer-by-layer manner with a 3D printer, and by adjusting the size and shape of each individual layer, a complex, solid object is formed from a digital model. It applies the additive shaping principle and based on that principle; it builds the physical 3D structures by successive addition of material [1, 2]. The main advantages of 3DP include high reproducibility, fast and accurate manu-facturing, personalized product series, superficial

modifications of a product at a designed level with no restrictions on its spatial arrangement, and convenient, cost-effective manufacture [3]. The most significant applications are found in regenerative medicine, artificial tissue, and organ generation, ophthalmological implants, 3D printed drugs, customized prosthetics, medical phantoms, and cancer research [1, 4]. There are mainly 3 types of 3D printing systems that are commonly used in pharmaceutical developments; printing-based inkjet system, nozzle-based deposition systems, and laser-based writing systems [5].

These printing technologies mostly differ in speeds and resolutions, but the main operating systems are based on either extrusion or powder/liquid solidification [4]. Among all these printing processes, extrusion-based printing like fused deposition modeling (FDM) and pressure-assisted micro-synringes (PAM) are widely used by researchers and manufacturers due to several advantages like low cost, ability to fabricate hollow objects, ability to print using a range of polymers with or without drug, ability to sustain drug release by altering the geometry and polymer, ability to print at room temperature, *etc.* [6] However each of these techniques have their specific advantages and limitations. Regardless of these differences in material deposition mechanism, the basic method of function is the same. A computer-aided design (CAD) file is prepared based on the desired 3D model, then the 3D printer follows the instructions of the CAD file and builds the object in a specific shape and size by moving the print head along the 3D directions [7]. The materials used as ink formulation covers a wide range of compounds from plastics, metals, ceramics or a combination thereof, making the process highly versatile [2].

Within the last decade, patient-centric personalized drug development has been under considerable attention. It was focused on novel dosage forms and technological processes. Growing demand for customized devices combined with an expansion of technological innovation drives the major progress in personalized medicine to meet the anatomical needs of patients [4]. Within many discoveries introduced into the pharmaceutical and biomedical market, 3DP technology has revolutionized the area of personalized medicine. 3DP offers many novel strategies and approaches in the field of novel drug delivery systems in suitable dosage forms, and gradually it is becoming of much interest in the pharmaceutical industry. Recently engineered solid dosage forms with complex inner structures, geometries, surface texture, multiple combinations of drugs, and many different types of drug delivery systems like oral control released systems, microchip, pills, implants, rapidly dissolving tablets, multiphase release dosage forms, *etc*. have been developed using this technology [8-13]. 3DP technology showed many industrial benefits over conventional technologies in designing and fabricating novel drug delivery dosage forms. However, there are some technical and regulatory challenges and limitations associated with the widespread application of this technology in the pharmaceutical sector [14].

The main disadvantage of 3DP is that this only takes into account the initial state of the printed structure and considers it static and inanimate [15]. To solve this problem, a new concept called 4D printing (4DP) was launched in 2013, allowing bioengineered constructs to be pre-programmed to evolve in a particular way after printing [16, 17]. Along with 4DP, 4D bio-printing or laser-assisted bioprinting has also recently emerged, which is a dedicated extension of 3D bio-printing that restructure the biochemical and biophysical compositions, in addition to the hierarchical morphology of different tissues using stimuli-responsive biomaterials and cells [18]. The major drawback of 4D printing is not able to print complex shapes having curved surfaces [1]. To overcome this problem, another new concept5D, printing (5DP) was introduced in 201619. 5DP technology is an extension of 3DP, also known as five-axis 3D printing, where the print head has the capability to move around from 5 different angles due to a movable flat terrain. This creates arched layers which are stronger than the traditional3D/4D printed flat layers [20].

This review describes the latest developments of some 3DP technologies suitable for pharmaceutical manufacturing, their advantages, and disadvantages associated with its utility based on current and future perspectives. The parallel development of higher next-generation printing technologies like 4D/5D printing technologies and their applications in medical and pharmaceutical manufacturing is

also discussed briefly. Lastly, it briefly summarizes the application of this technology in the ongoing crisis-response efforts to take on the COVID-19 pandemic situation generated worldwide for the past few months.

FIG. 1: DIFFERENT APPLICATIONS OF 3D PRINTING TECHNOLOGY IN MEDICAL AND PHARMACEUTICAL FIELDS

Applications of 3DP Technology in Novel Drug Development and Delivery: The principle application of 3DP technology in pharmaceutical developments pertains to novel drug development and delivery with correct dosage forms. The wide spread use of this application benefited mostly the rapidly growing personalized medicine field. Using this technology, various drug delivery systems can be developed with high accuracy and in short time, such as tablets, capsules, multilayered drug delivery systems, nano-suspensions, orodispersible films, transdermal systems, wound healing patches, vaginal and rectal delivery systems *etc.* [21-26] The most commonly used pharmaceutical active ingredients in these, include steroidal anti-inflammatory drugs, acetaminophen, caffeine, salicylic acid, antibiotics, paclitaxel, prednisolone, folic acid, insulin, captopril, curcumin *etc.* [4, 26] The ink formulations in 3D printers have been obtained from a number of both natural polymers like alginate, HA, collagen, chitosan etc. and synthetic polymers like PCL, PLA, PEG, PGA, diacrylate, PVP, PVAc, cellulose derivatives *etc.* [4] The main advantage of using synthetic polymers over natural polymers is that the synthetic polymers can be easily modified to meet specific requirements by optimizing mechanical and physicochemical properties, pH and temperature responses and they can be functionalized with various biomolecules. Sometimes blended polymers (natural+synthetic) are also used as bioinks to enhance and adapt cellular responses within 3D construct [1]. PLA is a biocompatible synthetic polymer that has recently been approved by the US Food and Drug Administration (FDA) biomedical applications such as tissue engineering, controlled drug delivery systems and orthopaedicim plants [27]. Many recent studies focus on the mechanical and biocompatibility / bioactivity properties of PLA or its blends after 3Dprinting [28, 29].

The first known 3D printed drug in tablet form, that was approved by FDA and was commercialized for the treatment of epilepsy is Spritam® by Aprecia Pharmaceuticals [30]. The drug (levitiracetam) was made by the layer-by-layer production system using ZipDose technique based on power bed fusion [31]. A year after Clark *et al.,* [32] in association with a British pharmaceutical company Glaxo-SmithKline conducted a study where inkjet 3D printing and ultraviolet (UV) curing were used to create a tablet Ropinirole HCL, a dopamine agonist drug used for the treatment of Parkinson's disease and restless legs syndrome. Using this set-up, batches of 25 tablets with a 5 mm diameter were produced.

Total printing time was 1.5 h or approximately 4 minutes per tablet. Curing time was an additional 7.5 min per batch. The researchers concluded that "UV inkjet printing has been demonstrated as a platform to produce solid oral dosage forms for the first time [32]." Nose-shaped masks, filled with salicylic acid, used as anti-acne agents, had been developed in a short and competent manner [33]. These are known as personalized tropical treatment devices. 3DP technology has also been used in chemotherapy for cancer treatment to reduce its side effects [34]. A construction of patches loaded with 5-fluorouracil, poly (lactic-coglycolic) acid and PCL had been successfully and efficiently printed and implanted directly into pancreatic cancer [35]. Another commercial use of 3DP technology has been seen in designing 3D printed polypill [36, 37]. Polypills are single personalized tablets made in combination of several drugs. These drugs are mostly designed for elderly persons who use poly medicines. **Table 1** summarizes the 3DP technologies applied in the development of pharmaceutical drug delivery systems and the suitable polymers exploited with various dosage forms [9, 32, 33, 35, 37, 38-68].

TABLE 1: SUMMARY OF DIFFERENT 3DP TECHNOLOGIES EXPLORED FOR THE DEVELOPMENT OF NOVEL DRUG DELIVERY SYSTEMS

3D Printing technology	Dosage forms	Polymers used	Model drugs used	Reference
Stereolithography (SLA)	Hydrogel	Polyethyleneglycol (PEG), Diacrylate	Ibuprofen, Riboflavin	38
UV-Inkjet 3D printed tecnology	Tablets	Cross-linked Poly(ethylene glycol diacrylate)(PEGDA)	Ropinirole	32
3D printer	Tablets	Polyvinyl alcohol l(PVA)	Paracetamol	39
FDM	Tablets	Polyvinyl alcohol(PVA)	Haloperidol	40
3D extrusion printer	Multi-active solid dosage form (polypill)	Polyvinylpyrrolidine (PVP), Sodium starch glycolate, Hydroxypropyl methylcelloluse (HPMC)	Aspirin, Hydrochlorothiazide Pravastatin, Atenolol & Ramipril	36
(FDM) and Hot Melt Extrusion (HME)	Tablets	Hydroxy propyl cellulose (HPC)	Domperidone	41
Fused deposition 3D printing	Extended release tablet	Polyvinyl alcohol(PVA)	Prednisolone	42
3D printer	Tablet implant	Methacrylicester copolymer (EudragitÒ E-100), cellulose powder (Avicel PH301)	Isoniazide	43
FDM	Nanocapsules	Poly(ε-caprolactone) (PCL)	Deflazacort	44
FDM and Hot Melt Extrusion (HME)	Compartmentalized shells	Polylactic acid	Rifampicin, Isoniazid	45
Fused deposition 3D printer	Oral pulsatile capsule	Polylactic acid (PLA) filament (L-PLA natural, ø 1.75 mm; MakerBot ®), Hydroxypropyl cellulose (HPC, Klucel®), Polyethylene glycol 1500 (PEG, Clariant Masterbatches, I)	Acetaminophen	46
FDM	Tablet	Polylactic acid	Hydrochlorthaizide	47
FDM and HME	Three compartment hallow cylinder	Polyvinyl alcohol (PVA) and Polylactic acid (PLA)	Hydrochlorthaizide, Mannitol	9
Ink-jet printer	Solid dispersion	Polyvinyl pyrollidone (PVP) k30	Felodipine	48
Desktop 3D printer	Bi-layer matrix tablet	Hydroxypropyl methyl cellulose(HPMC), Microcrystalline cellulose	Guaifenesin	49
Laboratory scale 3-DP™ machine	Capsule with immediate release core and a release rate regulating shell	Kollidon SR and hydroxypropylmethyl cellulose (HPMC), ethanolic triethyl citrate (TEC), PVP K17	Pseudoephedrine hydrochloride	50
Fused deposition 3D printer	Modified-release drug loaded tablet	Polyvinyl alcohol(PVA)	5-Aminosalicylic acid & 4-Aminosalicylic acid	37
Extrusion-based	Multi-active	Polyethylene glycol 6000, Hydroxypropyl	Captopril,	51

printer	tablets (Polypill)	methylcelloluse (HPMC 2910) (hypromellose®),Croscarmellose sodium (CCS) (Primellose®),microcrystalline cellulose (MCC) (Pharmacel® 102) and sodium starch glycolate (SSG) (Primojel®)	Nifedipine & Glipizide	
3D printer	Complex matrix tablet with ethylcellulose gradients	Ethylcellulose(EC), Eudragit RS-100, Hydroxypropyl methyl cellulose (HPMC)	Acetaminophen	[52]
Inkjet printer	Implant with lactic acid polymer matrix	Poly(L-lacticacid)(L-PLA)	Levofloxacin	[53]
3D printer	Multi-layered concentric implant	Poly(D,L-Lactic acid)(PDLLA)	Rifampicin and Isoniazid	[54]
Micro-drop Inkjet 3DP	Nanosuspension	Tagat S, TPGS, Solutrol HS15, Cremophor EL, Cremophor RH 40, Lutrol F68	Folic Acid	[55]
Thermal Inkjet printer	Dosing drug Solutions onto oral films	Potato starch	Salbutamol sulphate	[56]
Commercial inkjet printer	Nanocomposite structure	Dimethyl sulfoxide (DMSO), poly(D,L-lactic-co-glycolic)acid (PLGA), Biphasic calcium phosphate(BCP)	Rifampicin and Calcium phosphate	[57]
3D Extrusion printer	Drug encapsulated film of PLGA and PVA	DL-lactic/glycolic copolymer (PLGA, 85:15), poly(vinyl alcohol)(PVP), dichloromethane (DCM)	Dexamethasone	[58]
Thermal Inkjet printer	Oral solid dosage forms	1,2,3-propanetriol (glycerol), ALPHAGLAS PTFE- coated fiberglass film(premium grade, B903)	Prednisolone	[59]
3D printer	Microfluidic pump	Polylactic acid bioplastic, Polydimethylsiloxane, polymer base	Saline solution	[60]
Stereolithography printer	Anti-acne patch	Polyethylene glycol diacrylate	Salicylic acid	[33]
3D printer	Biodegradable patch	Poly(lactide-co-glycolide), polycaprolactone	5-Fluorouracil	[35]
Fused deposition 3D printer	Immediate-release tablets	Methacrylic polymer (Eudragit E-100)	*5*-Aminosalicylic acid, Captopril, Theophylline & Prednisolone	[61]
Fused-deposition printer	T-shaped intrauterine systems and subcutaneous rods	Different grades of the EVA copolymer (ATEVA 1070, 1075A, 1081G, 1241, 1641, 1821A, 1850A, 1880A, 2821A, 3325A), polycarbonate (PC), polyetherimide (PEI) resin, polyphenylsulfone (PPSF), polyamides (Nylon), high-impact polystyrene (HIPS), high-density polyethylene (HDPE), polymethylmethacrylate (PMMA) and poly(ε-caprolactone) (PCL) (CAPA™ 6500)	Indomethacin	[62]
Electro hydrodynamic atomization technique	Patterned micron scaled structures	Polyvinylpyrrolidone(PVP), Polyethylene oxide(PEO)	Tetracycline hydrochloride	[63]
Fused deposition printer	Capsules for immediate and modified release	Hydroxypropyl methyl cellulose (HPMC),Ethyl cellulose(EC)	Acetaminophen and Furosemide	[64]
3D printer	Biofilm disk	Hydroxypropylmethylcellulose (Metolose), Polylactic acid, Methylcellulose	Nitrofurantoin	[65]
Multi-nozzle 3D printer	Capsule-shaped solid devices	Polyvinyl alcohol(PVA)	Acetaminophen & Caffeine	[66]
Fused-deposition printer	Capsule-shaped tablets	Polyvinyl alcohol (PVA), Budesonide powder, Eudragit1 L100, Triethyl citrate (TEC)	Budesonide	[67]
Stereolithographic 3D printer	Modified-release tablets	Polyethylene glycol diacrylate	4-aminosalicylic acid & Paracetamol	[68]

Challenges of 3D Printing in Novel Drug Development and Delivery Systems: Even though the 3DP technology offers several advantages in designing pharmaceutical products over conventional manufacturing methods, there are also some limitations that can hinder the progression of this technology to commercialize. It faces technical challenges like optimization process, improving the performance of the product for versatile use, selections of appropriate raw materials, post-treatment measures, *etc.* [69] There are concerns include technical difficulties associated with printing of large volumes of materials, slow printing times, availability of materials are limited at present because of the recent arrival of this technology and high cost of the 3D printers [1]. Also, to attain the quality of 3D products, some essential technical parameters are required to be optimized like printing rate, printing passes, line velocity of the print head, interval time between two printing layer, the distance between the nozzles and the powder layer, *etc.* [70, 71] It is also important for post-processing after prototyping like drying methods, as it has major impact on the quality of the finished 3D printed products [72-74]. To increase the drug loading capacity in 3D printed processed tablet, uniaxial compression and suspension dispersed methodologies are adopted, but this technique suffers from increased complexity and clogging of spray nozzle [75, 76].

For bio-printing, it is also essential to further develop more detailed *in-vitro* and *in-vivo* studies to assess the efficacy and, most importantly the safety concerns associated with the widespread application of 3D printed drugs, tissues, organs, and medical devices1. Since the technology is mostly based on computer-generated machine learning and most recently artificial intelligence-based models, technical, operational and systemical errors cannot be avoided. One has to take care and ensure the utmost accuracy in designing these models.

Despite these limitations and uncertainties, we have to understand that this technology is still in an early development phase and can be seen as a research subject. Till date, the only known 3D printed drug that was commercialized is known as Spritam® by Aprecia Pharmaceuticals, used for the treatment of epilepsy [30].

Future Prospects of 3D Printing: The initial developments and research studies clearly show the utility of 3DP technology in different medical fields, including the pharmaceutical sector. It depicts a prospective future of this technology in drug manufacturing. The significance of this technology in the pharmaceutical sector is growing inevitably. The technology has great potential in compiling personalized dosage forms that can play a remarkable role in personalized medicine [77]. Also, patients will reduce their medication load to one polypill per day, which will produce patient conformity [36, 37]. 3D printing technologies can change the pharmacy practice by allowing individualized medication and tailored specifically to each patient, although there are technical and regulatory hurdles that have to overcome [1, 69-76, 78]. Drug manufacturing and distribution is usually a costly process in the pharmaceutical industry. 3D printed tablet production can be done in localized conditions within the clinic or in the local pharmacies [79, 80]. Recently approved 3D printed tablet called Spritam® has created a benchmark for the pharmaceutical companies [30]. Many such investigations are already underway as many scientific articles can be seen in recent times to discuss 3DP technology or highlighting recent findings of 3DP technology. In a recent update, a coaxial needle extrusion 3D technology was used to print active pharmaceutical components and create combinations of controlled release of drugs [81].

Transition from 3D to 4D/5D Printing: Although the 3DP technology has several advantages in designing pharmaceutical products over conventional manufacturing methods, there are also some technical challenges that exist with the technology that has been already discussed in the previous section. Various methods have been developed to overcome these technical challenges and can be classified according to the formula applied to assemble the material or its physical state [82]. The most commonly used methods for processing pure polymers and polymer nano-composites for biomedical applications include stereolithography, inkjet, micro-extrusion, and laser-based printing [83]. Even after that, each of these methods has its own limitations [1]. The main disadvantage of 3DP technology itself is that this only considers the initial state of the printed

structure and considers it as static and inanimate [15], thus unable to build complex bio-structures. 4DP technology was arrived primarily to overcome this limitation and also to take care of some of the technical difficulties associated with the 3DP [17]. 4DP has the capacity to reshape or self-assemble with respect to time. It has 4 dimensions *i.e.*, x, y, z-axis, and a fourth dimension which is time. Unlike 3DP, 4DP uses the ability of shape and functionality transformation over time when exposed to intrinsic/external stimuli allowing a more precise replication of the dynamics of the indigenous issues and is based on the combination of smart biomaterials [16, 84-86].

4D printed material has the ability to act on certain parameters with respect to the environment like humidity, temperature, *etc.*, and it changes its shape according to the environment. 4DP technology has also included few technological advances over 3DP for printing adaptable objects [1, 87]. There are a few difficulties and limitations that also exist for the 4DP technology. The major disadvantage is that it is unable to print complex shapes having curved surface [1]. Also, it is observed that 4D printed materials are less stable with respect to environment temperature [88]. To overcome these difficulties of 4DP, another advanced printing technology was evolved based on 5 dimensions, known as 5D printing (5DP) [19]. 5DP is the latest printing technology in additive manufacturing in which both the print head and printable object rotate along with x, y, and z-axis altogether with five degrees of freedom [89]. It can produce curved layers or dipped shapes very precisely as per design restraints. In this process, the printed part simultaneously move while the printer head prints along the five axis. The printbed moves forward and backward along with x, y, z axis which allows the object to be printed from all 5 axes instead from only one point of printing [20, 88, 89].

4DP method is mainly used in manufacturing next-generation medical devices for targeted drug delivery, by enhancing the capability of already established 3DP technology in this field, where personalized medical treatments are important such as dentistry, implants, prosthetics, *etc.* [90] 4D-printed devices can contain pharmaceutical drugs and release them when the environment of the targeted location provides the correct stimulus. Few examples of such devices are 4D-printed containers [91], theragrippers that were particularly tested for the controlled release of drugs in the gastrointestinal tract [92], different types of stents [93-95], and splints [96-98] used in surgical procedures. 5DP technology is currently tested for manufacturing medical or surgical tools like mosquito forceps, monopolar diathermy, debakey forceps, deaver retractor, etc., those having complex curved-like structures [88]. 5DP can also be used to manufacture artificial body parts like hands, legs, lower jaw, teeth that have complex shapes of implants with high strength, as prosthetic implants [19, 88, 89]. Wide-scale applications of both 4D and 5D printing technologies are still in their infancy, and most of the activity now is still under research and development.

Application of 3DP Technology in Healthcare against COVID19: The global uncertainty created by the novel COVID-19 pandemic has pushed the world into a severe crisis that is still unfolding and gradually evolving. Healthcare systems are on a war footing path to handle the pandemic situation by increasing supplies of medicines, protective materials, and trained workers. Crisis-generated efforts are in action to assuage the shortages of essential medical supplies.

There is a need for more pharmaceutical factories to manufacture on-demand medicines and medical devices for a range of essential services in healthcare. In this context, a flexible advanced manufacturing network with mostly computational approach enabled by a distribution of 3D-printing factories has become a great potential, especially at this time of social distancing practices.

3DP technology has shown its capabilities in response to COVID19 by demonstrating its competitive advantage in this emergency situation [99-102]. It has stepped up to become a vital technology to support improved healthcare and our general response to the emergency at the present pandemic situation. The eminent manufacturers and researchers implicated the potential of 3DP technologies and channeled them for developing personal protective equipment like face masks, face shields, respirators, medical devices like ventilator valves, emergency respiration devices, testing devices, sample collecting devices like naso-pharyngeal swabs, *etc.* and other gadgets [101, 102].

Different types of 3DP technologies were used for this purpose like fused filament fabrication (FFF), FDM, selective laser sintering (SLS), stereo lithography (SLA), *etc.* [101, 102] As the vaccine development process against novel coronavirus are currently undergoing different stages, the healthcare professionals are treating their patients with the existing medical drugs.

To use the available drugs in the best way, it has been emphasized by the various professionals to adopt the novel 3DP technologies in delivering controlled healing chemical and organic compounds. Formulations based on micro-sized structures used for drug delivery using 3DP technologies are believed to be highly effective in curing patients suffering from pandemic [10, 53, 57, 70].

It is believed that long-standing health problems, generally observed in pandemic condition, may be solved by these systems that allow synchronized use of multiple drug components and other spatial models of drug deposition within the hydrogel or polymer matrix [33, 101, 102].

Focusing on COVID-19, these revelations of 3DP technologies can be lined up well with the current demands of personalized medicine in the pharmaceutical sector [100-105]. Although at present there are no specific antivirals drugs for the treatment of COVID-19, several already present and well-characterized antiviral drugs are being considered for therapies [106]. Soon, it may be possible to use these technologies to effectively and rapidly print drugs like lopinavir/ritonavir, remdesivir, hydroxyl-chloroquine, *etc.*, that are often being used now for the symptomatic treatment of COVID-19 patients and also as preventive medicine for health workers.

Although at present, very few studies are focused on the treatment of the COVID-19 patients as the current regulations are highly stringent due to the risk level, but this technology definitely has the potential to revolutionize the pharmaceutical industry by making faster research, development and production of drugs applicable to patients with COVID-19. The research activities will endeavor to categorize the 3DP technologies based on their superiorities in the fabrication of drug delivery systems as well as the formulation.

CONCLUSION: The utility of 3D/4D/5D printing technologies described in this review article shows the benefits of these technologies in the pharmaceutical industry, especially for the development of novel drug delivery systems. Although the development of these methods in the field of pharmacy is only in its early phase, but in the near future, these approaches will surely be utilized to fabricate and wangle various novel dosage forms to achieve optimized drug release profiles, develop effective personalized medicines, evade incompatibilities between multiple drugs, design multiple-release dosage forms, limit degradation of biological molecules and for many other purposes. Although commercial production of such novel dosage forms is still in a challenging phase, the scientists and researchers are certain that the modern pharmaceutical industry is seeing a turning point and that the 3DP of solid dosage forms are set to revolutionize the drug delivery systems.

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