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Review on 3D Printing of Pharmaceutical Solid Dosage Forms

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ABSTRACT

This article provides an overview of 3D printing technology in the pharmaceutical industry, focusing on its advantages, disadvantages, techniques and applications in the development of dosage forms for oral solids. The background of the review is the increasing interest in 3D printing technology and its potential to produce personalized pharmaceutical products. The research problem addressed is the need for a comprehensive understanding of 3D printing in pharmaceuticals, including its techniques and applications. The methodology includes a literature review on 3D printing technology in pharmaceuticals, covering techniques such as Laser-Based 3D Printing Systems, Inkjet-Based 3D Printing Systems and Extrusion-Based 3D Printing Systems. The context is the pharmaceutical industry's interest in developing new pharmaceutical dosage forms using 3D printing technology. Overall, this article serves as a handbook for various solid dosage forms developed using various 3D printing techniques and provides insight into the potential applications and implications of 3D printing technology in the pharmaceutical industry.

INTRODUCTION

3D printing is the production of a three dimensional (3D) object of any shape from a 3D model using additive processes where successive layers of material are placed under computer control. [1] With 3D printing, physical objects can be created from a geometrical representation by subsequent addition of material. [2] Charles Hull introduced 3D printing for the first time in 1980. [3] 3D printing technology originated as a technique of layer-by-layer manufacturing of three-dimensional (3D) structures directly from computer-aided design (CAD). [4] 3D printing impacts many industries such as automotive, architecture, education, medicine, commercial and consumer industries. [5]

3D printing is also called as rapid prototyping. [6] Using 3D computer-aided design (CAD), rapid prototyping is a collection of methods for quickly creating a scale model of a physical part or assembly. [7] Rapid prototyping has also been called solid free form manufacturing, layered manufacturing and computer-aided manufacturing. [8]

Drug delivery refers to approaches, formulations, techniques and systems to transport a medication within the body to safely achieve a desired therapeutic effect. Drug delivery is accomplished through the chemical composition of the pharmaceutical products, but may also be correlated with medical devices or drug-device combinations. Drug delivery techniques alter the drug's release profile, absorption, distribution and elimination, which improves product efficacy, safety, patient comfort and compliance. [9] By using three-dimensional (3D) printing technology, various drug delivery systems such as oral controlled-release systems, micro pills, drug implants, fast-dissolving tablets, and multiphase release formulations have been developed. Consequently, it is expected that 3D printing technology can provide new approaches to the development of new pharmaceutical dosage forms. [10]

The main objective of this article is to provide a quick understanding of an 3D printing, its advantages, disadvantages, 3DP techniques and polymers used in 3DP. This article also acts as a handbook for various solid dosage forms including tablets, capsules, caplets, implants and orodispersible printlets were developed using various 3DP techniques.

ADVANTAGES OF PHARMACEUTICAL 3D PRINTING

- 3DP enables precise control of droplet size, dose strength, complex drug release profile and multiple dosing.
- Precise dosing of potent drugs administered in small doses.
- Possibility to create tablets of all shapes and sizes.
- The possibility to determine the dose for each patient separately.
- Lower production costs because there is less material waste.
- High drug loading compared to traditional dosage forms.

DISADVANTAGES OF PHARMACEUTICAL 3D PRINTING

- Limited use of material
- Slow production process
- Unreacted substance in the final product
- In inkjet printing, the exact viscosity of the ink must be achieved.
- 3D printing machines are expensive.

3DP TECHNIQUES [11]

I. Laser-Based 3D Printing Systems

- Stereo-Lithography Apparatus (SLA)
- Selective Laser Sintering (SLS)

II. Inkjet-Based 3D Printing Systems

III. Extrusion-Based 3D Printing Systems

- Pressure-Assisted Micro syringe (PAM)
- Fused Filament Fabrication (FFF)

Stereo-Lithography Apparatus (SLA)

Stereo-lithography was one of the first 3DP techniques where radiation is passed through photo-sensitive polymers to initiate a photo-polymerization process. [12] SLA is a form of 3D printing technology used to create models, prototypes, patterns, and production parts layer by layer using photochemical processes where radiation causes chemical monomers to bind together to form polymers. These polymers then form a 3D solid body. [13] In this technique, computer-controlled laser beam is used to solidify a liquid polymer or resin, creating a 3D structure. SLA has several benefits over other forms of 3DP, chief among them being its superior resolution and the avoidance of heat processes that may be detrimental to s pecific drug compounds. [14] The pharmaceutical industry limits the use of this approach because of the increased laser energy input. [15]

Continuous Liquid Interface Manufacturing (CLIP) is an altered version of SLA. This technique is ongoing and continuous rather than layer-by-layer pattern and requires a pool of liquid photopolymer resin. By this technology, objects can be created almost 100 times faster than other commercially available 3DP methods. [16] In CLIP, printing speed and resolution are very high compared to traditional SLA. [17] Digitally controlled UV light emitter is commonly used to collect polymers. These UV emitters scan the superficial of liquid polymers and resins that are photo-polymerizable. After polymerization, the 3D printer makes a surface of solid resins that matches the depth of the previous polymer layer.

Advantages:

- Extensively employed in the production of medical devices and drugs with prolonged release.
- Enhances the solubility of poorly soluble drugs
- Opted for the manufacturing of multi-layer polypills

Disadvantages:

- Not suitable for light-sensitive drugs
- May be related to material toxicity issues

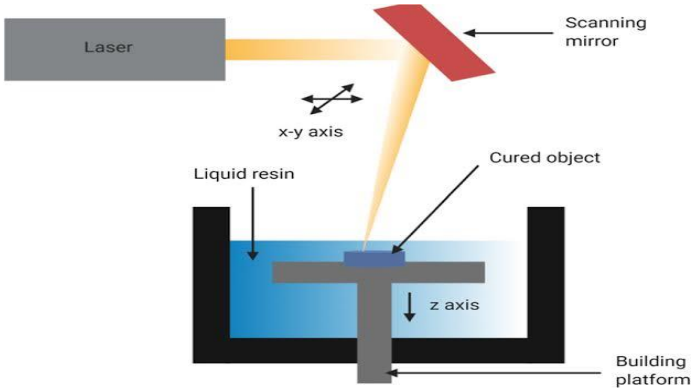

Figure 1: Stereo-Lithography printing process

Advantages:

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- Enhances the solubility of poorly soluble drugs
- Opted for the manufacturing of multilayer polypills

Disadvantages:

- Not suitable for light-sensitive drugs
- May be related to material toxicity issues

Selective Laser Sintering (SLS)

Dr. Carl Deckard and Dr. Joe Beaman invented this method in the mid-1980s. [18] Using a laser as an energy source to sinter powder materials such as nylon or polyamide, SLS is an additive manufacturing process that creates solid structures by binding the materials together and automatically orienting the laser to a space specified by a 3D model. SLS utilizes a laser to bond with powder particles from the powder bed.

During printing, a laser is directed to draw a specific pattern on the powder layer's surface, creating a three-dimension structure. Now, it is used for the industrial production of plastic, metal and ceramic items. [19]

SLS is one of the newest developments in the 3D printing industry.

To create the desired 3D structures, it just takes one step in which a laser sinters the powders in layers. As the layers are sintered, the powder layers move down and the reservoir layers up to form new layers, and the new layers are then piled on top of the previous layers. [20]

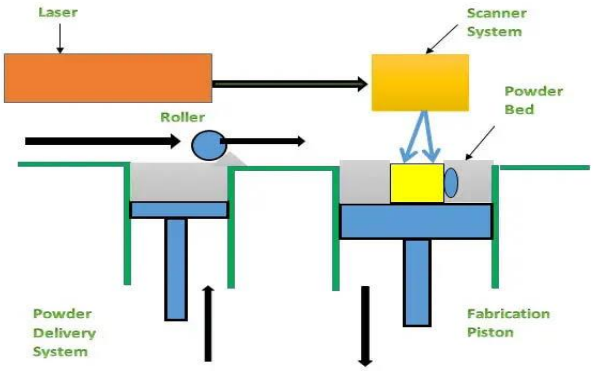

Figure 2: Selective laser sintering printing process

Advantages:

- Can form highly porous dosage forms (dissolves quickly)
- High resolution method to create complex geometries

Disadvantages:

- May not be suitable for light- and heat-sensitive drugs
- Needs post-treatment
- Needs careful control of powder properties

Inkjet-based 3D printing systems

Ink jet printing is one of the most popularly used 3DP technologies.

It is separated into two categories:

I. Drop-On-Powder (DoP)

II. Drop-On-Drop (DoD)

Advantages:

- High resolution

- Low thermal effect

Disadvantages:

- Poor mechanical properties
- Difficulties of complex 3D geometries.
- Limited material selection

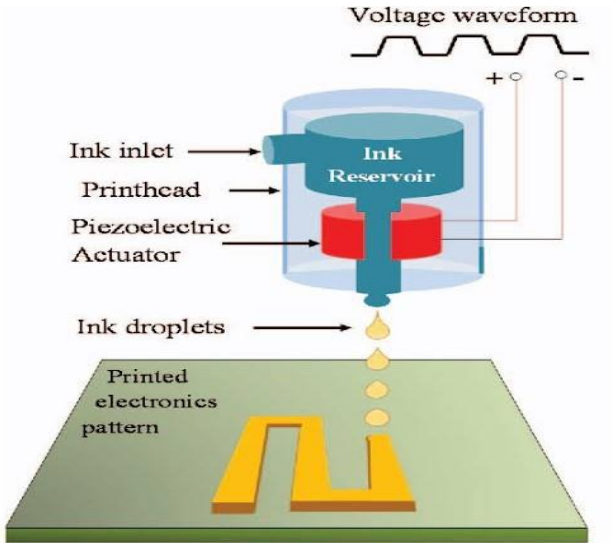

Figure 3: Inkjet-based 3D printing process

Drop-on-powder (DoP) deposition:

DoP deposition uses either a powder-coated layer with unbounded powder material or an inkjet printer to inject a liquid binder onto the powder layer to create 3D structures. This technique is influenced by two powder attributes:

(i) the topology of the powder

(ii) the reactivity of the material with the binder. [21]

From the topological attributes of the powder, the particle size was shown to be the most important factor affecting the grade of the final structure. The Drop-On-Powder technique is more suitable for the manufacturing of medicines. [22]

Drop-on-drop (DoD) deposition:

In this technique, liquid droplets are building materials that are deposited in a uniform pattern to the exterior of the substrate. The active ingredients (API) can be soluble in a liquid medium that behaves as a binder or made of powders that behave as a powder bed. The principle of interaction between the binding liquid and the powder bed is like wet granulation technology. [23]

This method can create microscopic methods for delivering drugs with different geometries and relatively enhanced drug loading. [24]

Extrusion-based 3D printing systems

Extrusion-based 3D printing method also noted as nozzle-based printing systems. Plastic filament is essential as the major printing material. It places plastic material layer by layer to design a 3D object using top-down construction. These systems are classified according to whether or not a heating system is required to melt the powder. This method can be of two main types:

(i) Pressure micro injector (PAM)
(ii) Fused filament fabrication (FFF) [25]

Nozzle-based deposition methods enable direct writing, which based on computer-controlled production methods that apply ink directly through a nozzle to generate a layer-by-layer 3D pattern with controlled composition. [26]

Advantages:

- Good mechanical properties
- Wide range of materials

Disadvantages:

- Materials are limited to thermoplastics
- Filament required

Pressure micro injector (PAM)

PAM is a technique in which powder and binder are mixed into a semi-solid material that is pressed at a pressure of approximately 3-5 bars. The material does not solidify immediately, but requires exposure to light or air to fully harden the material. [27] In PAM, certain solvents are used to produce a semi-solid material. After evaporation, the solvents form the intended final product at room temperature. These solvents are often toxic and may cause irrelevant damage by altering the stability profile of the API. [28]

This technique is based on extruding a viscous semi liquid material from a syringe to create the desired three dimensional shape. The procedure can be carried out in continuous flow at room temperature. [29] The rheological characteristics of suspensions, which are highly based on the type and amount of additives and the solid substance in the dispersion, can be considered a key parameter in realizing reproducible methods for delivering drugs. [30] In order for the paste to be uniform and homogeneous to prevent obstructing of the nozzle, it should be characterized by appropriate apparent viscosity, viscoelastic properties and yield stress in shear and compression. [26]

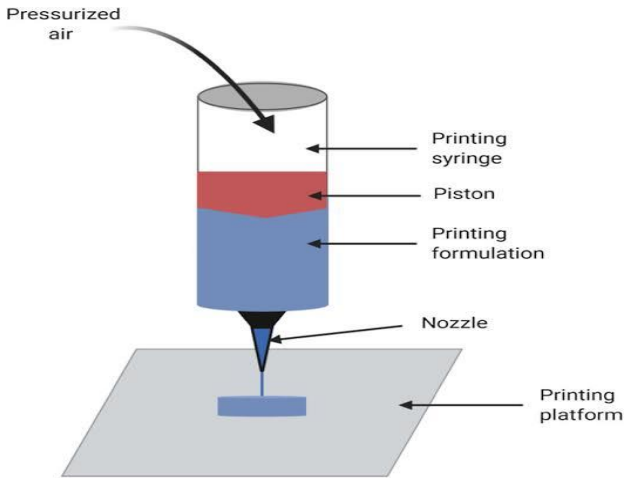

Figure 4: Pressure micro injector printing process

Fused Filament Fabrication (FFF)

Fused Filament Fabrication is also called as Fused Deposition Modelling (FDM). It is mainly used in the pharmaceuticals to generate an oral dosage form with a thin layer of material. [31] A continuous filament made of a thermoplastic material is used as a solid filament and fed through a transfer system to the moving and heated extrusion end of the printer. The material is converted into soft mass in the print head before being

extruded through the outlet. The extruded material solidifies practically rapidly after extrusion. [32]

Typical parameters that should be adjusted during the FDM process are infill density, extrusion speed and both nozzle and building plate temperatures. [33,34] The infill density is a parameter that determines the quantity of material filled into an object and is then associated to the porosity of the 3D structure. The infill density can vary from 0% to 100%, where 0% outcomes in a completely hollow object and 100% fill outcomes in a completely solid object. Printing speed and layer height are closely related. [35]

The temperature setting is relying on the standards of the thermoplastic polymer used. In fact, thermoplastic polymers are often used considering of their relatively low melting point, which allows them to melt at a viscosity high enough for construction but low enough for extrusion.

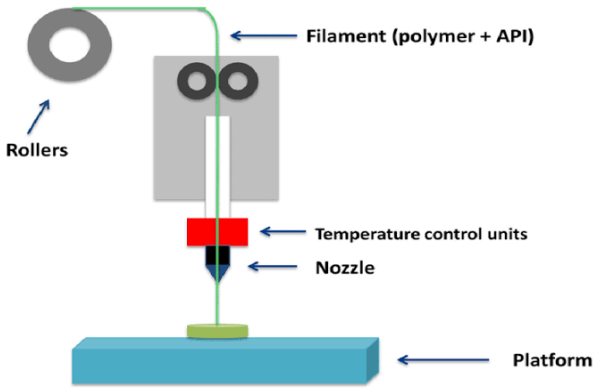

Figure 5: Fused filament fabrication printing process

Polymers used in 3D-printing technology

Table 1. List of non-biodegradable polymers used in formulation of dosage forms of solids along with 3DP techniques

Name of the polymer	3DP Technique	Dosage form	Refs.
Polyethylene glycol diacrylate (PEGDA)	SLA	Tablets	[36]
Polyethylene glycol dimethacrylate		N/A	[37]
Polypropylene fumarate-diethyl fumarate		N/A	[28]
Polyether ether ketone (PEEK)		Tablets	[38]
PA12 (Nylon)		Tablets	
Microcrystalline cellulose (MCC)	Drop-on-Powder	Tablets	[39]
Spray-dried lactose		Tablets	
Maltitol		Tablets	
Maltodextrin		Tablets	
Polyvinyl alcohol (PVA)	FDM/FFF	Tablets	[40], [41], [42], [43]
Polyvinyl pyrrolidone-vinyl acetate copolymer (Kollidon VA-64)		Tablets	[44], [45], [46]
Polyvinyl alcohol-polyethylene glycol graft copolymer (Kollicoat IR)		Capsules Tablets	[47] [46]
Poloxamer-407		Tablets	[46]
Polyethylene glycol (PEG)		Tablets	[46]
Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft co-polymer		Tablets Discs	[48] [49]
Eudragit E		Tablets	[33]
Eudragit RL		Tablets	[50]
Eudragit EPO		Tablets	[51]
Eudragit RL PO		Solid Discs	[52]
Eudragit L 100		Tablets	[49]
Eudragit L 100–55		Tablets	[46]
Eudragit RS		Tablets	[33]
Eudragit RS PO		Implants	[53]

3D-Printing Solid Dosage Forms

Researchers have been using three dimension printing (3DP) to produce dosage forms pharmaceutical solids and others for some decades. It has been researched to convert several medications into novel solid dosage forms via 3DP technology.

Table 2. List of drugs converted into novel 3DP solid dosage forms by using 3DP technology

S.No	Drug used	Dosage form	Type of 3D Technology	Name of the Polymer	Year	Refs.
1.	Ondansetron	Orodispersible printlets	SLS	Kollidon VA-64	2020	[54]
2.	Anhydrous caffeine	Tablets	FDM-hot melt extrusion	Hydroxypropyl cellulose + vinyl pyrrolidone-vinyl acetate (copolymer)	2020	[55]
3.	Ranitidine HCL	Gummies	Extrusion based 3D printer	Carrageenan + Xanthan gum	2020	[56]
4.	Theophylline	Tablets	FDM	HPMC + K4M	2020	[57]
5.	Isoniazid	Tablets	FDM-hot melt extrusion	Hydroxypropyl cellulose (HPC)	2020	[58]
6.	Rifampicin	Tablets	FDM-hot melt extrusion	Hydroxymethyl propyl cellulose acetate succinate (HMPCAS)		
7.	Paclitaxel + Rapamycin	Oral solid dosage form (hydrogel discs)	Extrusion based 3D printer	Poly (Lactic-co-glycolic acid) PLGA	2020	[59]
	lidocaine					
8.	Diltiazem	Caplets	FDM	Polyvinyl alcohol (PVA)	2019	[60]
	Diltiazem	caplets	FDM hot melt extrusion	Cellulose acetate (CA)		
9.	Pramipexole dihydrochloride monohydrate	Filaments and Tablets	FDM hot melt extrusion	Eudragit EPO + POLYOX-TMWSR N10	2019	[61]
				Eudragit EPO + POLYOX-TMWSR N80		
10.	Ciprofloxacin HCl	Tablets	FDM-hot melt extrusion	PVA	2019	[62]
11.	Metformin	Tablets	FDM	PVA	2019	[63]
12.	5-flourouracil	Tablets	Ink jet based DoP	2-pyrrolidone	2019	[64]
13.	Thiamine (vitamin B1)	Tablets	Water- based inkjet	Polyvinyl pyrrolidone	2019	[65]
14.	Paracetamol	Tablets	Extrusion based	Polyvinyl pyrrolidone	2018	[66]
15.	Ibuprofen	Tablets	FDM	Ethyl cellulose	2018	[67]
16.	Aripiprazole	Orodispersible film	FDM	PVA	2017	[68]
17.	5-flourouracil	Bio-degradable implants	FFF	PLA + polycaprolactone	2016	[69]
18.	Captopril	Tablets	PAM	PEG + CA	2015	[70]
	Nifedipine				2015	[71]
	Glipizide			HPMC		
19.	Theophylline	Tablets	FFF	HME + Polymethacrylate based copolymer or HPC + triacetin	2015	[72]
20.	Guaifenesin	Bi-layer tablets	Extrusion based	HPMC + polyacrylic acid (PAA)	2015	[71]
21.	Acetaminophen	Oral pulsatile capsule	Fused deposition 3D	Hydroxy propyl Cellulose	2015	[73]
22.	4-amino salicylic acid	Tablets	FDM	PVA	2014	[74]
	5-amino salicylic acid					
23.	Prednisolone	Tablets	FDM	PVA	2014	[75]
24.	Felodipine	Solid dispersion	Ink-jet printer	Polyvinyl pyrrolidone k30	2011	[76]

APPLICATIONS OF 3DP in Oral solid dosage forms

Controlled release

Release of drugs from dosage forms plays an important role in their subsequent absorption and therapeutic effect. Most oral formulations require immediate release (IR) for drug absorption. Sustained release allows the slow drug release, reducing fluctuations in drug levels associated with administration of multiple immediate release (IR) dosage forms at regular intervals. This may be of therapeutic benefit [77] and patient convenience. [78] The total surface area of traditional sustained-release tablets are reduced because they undergo a process of absorption in the gastrointestinal tract (GIT), ensuing in a non-constant release of drugs. Additive manufacturing overcomes this issue by making tablets with complex geometries. This allows not only for a sustained-release dissolution profile, but also for products with a customized release profile.

Polypills

A greater number of patients, especially the elderly, are using polypharmacy, which has raised concerns about medication errors due to regime complexity. [79] Some conditions, such as cardiovascular disease requires multiple medications. An increase in the number of medications in an individual's regimen may be connected with poorer adherence and thus poorer health outcomes [80]. It would simplify an individual's medication, which would increase patient comfort and adherence [81]. Since, 3D printing is a precise process, dosage accuracy is not particularly important [82]. In addition, problems of incompatibility can be solved by chemically separating the drugs with a suitable excipient or by separating each drug into different parts of the tablet [83,84].

Oro-Dispersible

Oral route is the common and widely used route of administration by patients [85]. However, oral dosage forms such as tablets, capsules, and liquids may be troublesome for some populations, including children, the elderly, and patients with dysphagia [86]. Oro-dispersible tablets are fabricated to disintegrate in the oral cavity. It can be taken without water. Oro-dispersible tablets are linked with a porous structure, ensuing in a rapid dissolution profile. 3DP ignores high compressive forces required in the traditional production method, which leads to increased porosity in the structure and therefore rapid degradation.

Paediatric formulations

Children are a special group whose pharmacokinetic and pharmacodynamic properties differ from those of adults [79, 87 , 88]. Therefore, doses in this population must be carefully optimized to avoid adverse effects of toxicity. Syrups are dose-adjustable and available in paediatric formulations but are subject to dosing errors [89] and many have unpleasant tastes. A new solution to this problem is the miniprintlet, a 3D printed mini-tablet. Compared to syrups, mini-tablets are easier to dose due to the reduced taste and small size. In addition, doses can be adjusted with additive manufacturing (AM) by adjusting the amount of substance used [90]. This has been shown to be possible with SLS or FDM. Additionally, it is possible to combine different medicines into one miniprint, which makes administration even simpler.

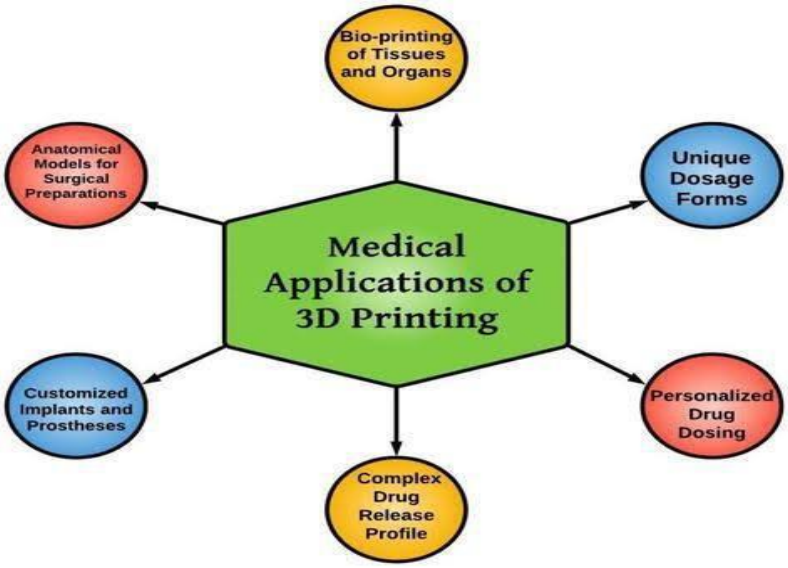

Figure 5: Applications of 3D printing in medicine

CONCLUSION

Researchers have been paying close attention to 3D printing technologies for a long time. The potential of this technique to create new, personalized solid dosage forms is increasing being recognized by researchers.FDA approved Spritam (levetiracetam), a 3D printed solid d osage form in 2015.As a result, new solid dosage forms were produced with much better qual ities.3D printing has shown to be a useful and innovative tool for the pharmaceutical business , helping to manufacture personalized medicine that is tailored to the individual needs of the p atient. Three-dimensional methods can expedite and reduce the cost of complex formulations.

Compared to conventional medications, this technology offers more sophisticated geometry, more accurate drug dosing and better drug distribution in space.

Number of novel medications will be designed and created soon with the use of 3D printing. The pharmaceutical industry's unfulfilled needs served as the catalyst for this new technology 's numerous uses in this field.

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