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Review Article

3D PRINTING IN PHARMACEUTICAL TECHNOLOGY: A REVIEW

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ABSTRACT

Three-dimensional (3D) printing is an additive manufacturing method, where successive layers of material are deposited or solidified to form a 3D structure. It uses computer aided drafting technology and programming to produce 3D object by layering material on to a substrate. A variety of 3D printing technologies have been developed to fabricate novel solid dosage forms, which are among the most renowned and distinct products today. The present review focussed on briefing various techniques, applications of 3D printing in pharmaceutical technology.

Keywords: 3D printing technology, Zip dose, Thermal-Inkjet printing, fused deposition.

INTRODUCTION

Three-dimensional (3D) printing is unique technology which uses computer aided drafting technology and programming to produce three dimensional objects by layering material onto a substrate [1]. It is a process of making three dimensional solid objects from a digital file.[2] Hence the process is called as additive manufacturing (AM), rapid prototyping (RP) or solid freeform technology (SFF).

Nowadays, 3DP could be extended throughout the drug development process, ranging from preclinical development and clinical trials, to frontline medical care.[3] When compared to the manufacturing process of conventional pharmaceutical product, it has a lot of advantages like high production rates due to its fast operating systems; ability to achieve high drug-loading with much desired precision and accuracy especially for potent drugs that are applied in small doses; reduction of material wastage which can save in the cost of production and amenability to broad types of pharmaceutical active ingredients including poorly water-soluble, peptides and proteins, as well as drug with narrow therapeutic windows[4]. Different types of drug delivery systems such as oral controlled release systems, micro pills, microchip, drug implants, fast dissolving tablets and multiphase release dosage forms have been developed using three-dimensional (3D) printing technology.[5] Hence, it is expected that three-dimensional (3D) printing technology could offer new approaches for developing novel pharmaceutical dosage forms.

TECHNIQUES IN 3D PRINTING

3D printing includes a wide variety of manufacturing techniques, which are based on digitally-controlled depositing of materials (layer-by-layer) to create freeform geometries.

Thermal Ink-Jet Printing

In thermal inkjet printing, the aqueous ink fluid is converted to vapour form through heat and expands to push the ink drop out of a nozzle.[6] It is used in the preparation of drug-loaded biodegradable microspheres, drug-loaded liposomes [7], patterning microelectrode arrays coating and loading drug eluting stents.[8] It is also an efficient and practical method of producing films of biologics without compromising protein activity. (Table 1)(Fig 1)

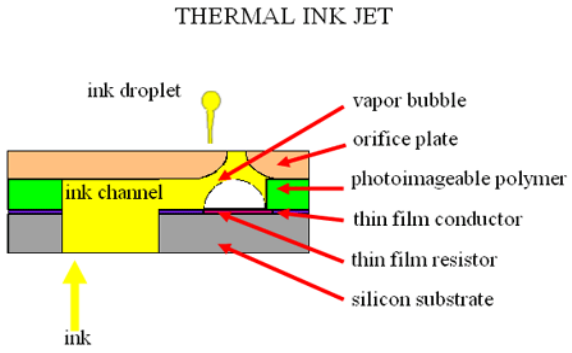

Fig 1: Thermal inkjet technique in 3D printing [9]

Table 1: Some of the drugs prepared by thermal inkjet printing

Sl.no	Drug	Dosage form	Application	Reference
1	Prednisolone	Tablet	Anti-inflammatory or Immunosuppressant	6
2	Salbutamol sulphate	Solution	Bronchodilators	10
3	Felodipine	Solid dispersion	Antihypertensive	11
4	Folic acid	Nano suspension	Anemia	12
5	Carbamazepine	Cocrystals	Antiepileptic drug	13
6	Terbutaline sulphate	Solution	Bronchodilator	14

Inkjet printing

In this technique, the Ink is deposited onto a substrate either in the form of Continuous Inkjet printing (CIJ) or Drop on Demand (DoD) printing, hence it provides a high resolution printing capability[15] (Table 2).Inkjet printing is also called as 'mask-less' or 'tool-less' approach because the formation of desired structure mainly depends upon the movement of inkjet nozzle or movement of the substrate for an accurate and reproducible formation. It has a low processing cost, rapid processing rates, generation of minimal waste, it gives CAD information in a 'direct write' manner and it process material over large areas with minimal contamination .[16] (Fig2)

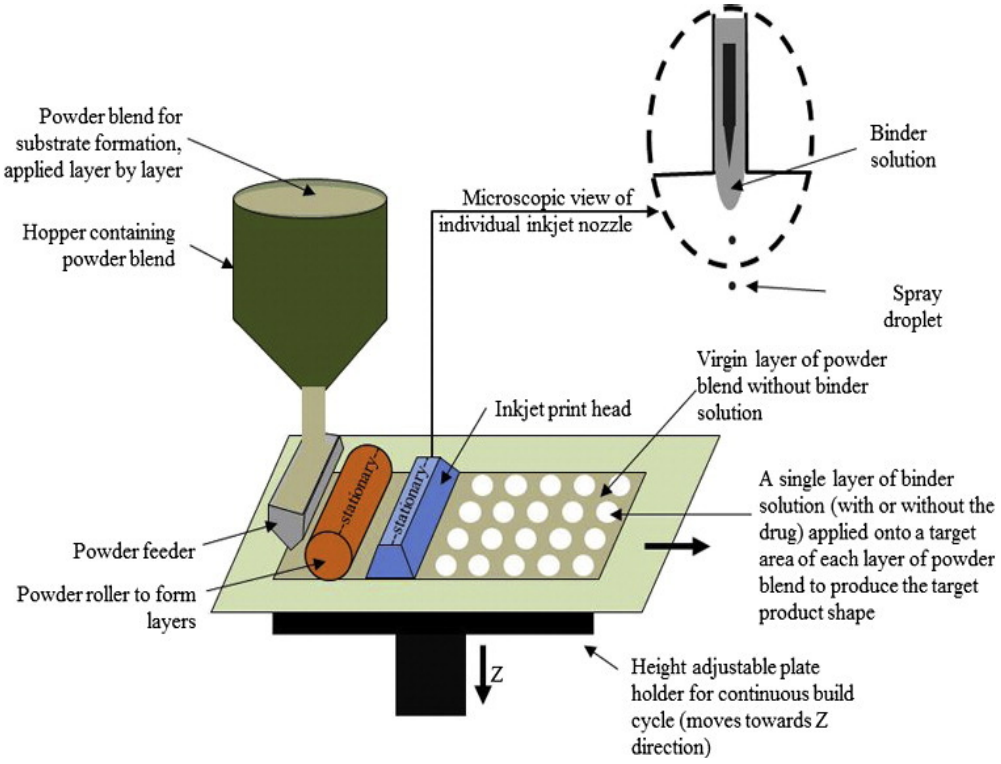

Fig 2: inkjet printing in 3D printing[17]

Table 2: Inkjet printing for pharmaceutical applications

Sl.no	Drug	Dosage form	Application	Reference
1	Felodipine	Microdots	Antihypertensive	18
2	Polyvinyl pyrrolidone (PVP)	Microdots	Excipients	18
3	Insulin	Microneedle	Antihyperglycemia	19
4	5-Fluorouracil, curcumin and cisplatin	Microneedle	Anticancer agents	20
5	Paclitaxel	Microparticles	Anticancer agents	21
6	Fluorescein 5-isothiocyanate	Microparticles	Fluorescence	21
7	Loperamide	Tablets or capsules	Inflammatory bowel disease.	22
8	Caffeine	Tablets or capsules	CNS stimulant	22
9	Paracetamol	Tablets	Analgesics	23
10	Atenolol	Tablets ,sprays	Antihypertensive	24
11	Influenza vaccine	Microneedles	Against influenza viruses	25
12	Voriconazole and Itraconazole	Microneedles	Antifungal agent	26
13	Piroxicam	Capsules	Nonsteroidal anti-inflammatory	27
14	Lysozyme and Ribonuclease-A	Films	Antibacterial and Antiviral	28
15	Erythropoietin	Uncoated rubber stopper syringes	Anemia	29
14	Rifampicin	Implants , Nanoparticles	Antibiotic	30
15	Levofloxacin	Implant	Antibiotic	31
16	Folic Acid	Nanosuspension	Anemia	32
17	Nitroglycerin	Injection	Angina	33
18	Fenofibrate	Tablets	Anti Hypertriglyceridemia and Anti Hypercholesterolemia	34
19	Rapamycin	Tablets	Immunosuppressant	34
20	Ketoprofen	Tablet	Nonsteroidal anti-inflammatory	35
21	Rasagiline mesylate	Oral dosage	Antiparkinson agent	36

Fused deposition modelling (FDM)

Fused deposition modelling (FDM) is commonly used technique in 3D printing, in which the materials are soften or melt by heat to create objects during printing[37] (Fig 3),Hence there are several dosage forms listed in Table 3. FDM 3D printing helps in manufacturing delayed release printlets without an outer enteric coating, and also provides personalised dose medicines.[38]

FDM 3D printing however, indicates several limitations of the system such as lack of suitable polymers[39], slow and often incomplete drug release because the drug remain trapped in the polymers[40,41] and the miscibility of the drug and additives with the polymers used was not evaluated[42]

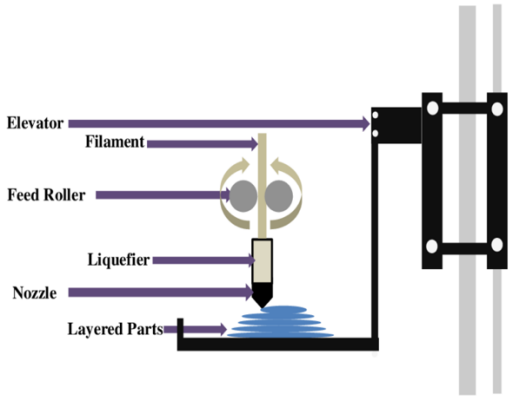

Fig 3: Fused deposition models in 3D printing[42]

Table 3: Some of the Pharmaceutical dosage forms by Fused deposition models

Sl .no	Drug name	Dosage Form	Use	Reference
1.	Domperidone	Tablet	Nausea, vomiting	43
2.	Ibuprofen	Tablet	NSAID	44
3.	Aminosalicylate	Tablet	Antibiotic	45
4.	Metformin, Glimepiride	Tablet	Antidiabetic	46
5.	Disopyramide	Tablet	Antiarrhythmic	47
6.	Theophylline	Tablet, Capsule	Lung diseases	47
7.	Paracetamol	Tablet	Antipyretic	48
8.	Budesonide	Controlled release tablet	Ulcerative colitis	49
9.	Diclofenac sodium	Tablet	NSAID	49
10.	Prednisolone	Extended release tablet	Immunosuppressant	50
11.	Enalapril maleate	Tablet	Antihypertensive	51
12.	Hydrochlorothiazide	Tablet	Diuretic	51
13.	Acetaminophen	Oral pulsatile capsule, Tablet MR	Antipyretic	52
14.	Captopril	Intermediate release tablets	Hypertension,CHF	52
15.	Budesonide	Capsule	Ulcerative colitis	52
16.	Nitrofurantoin	Catheter, Implant	Urinary tract infections	53
17.	Hydroxyapatite	Implant	Carrier	53
18.	Dye	Implant CR	Excipients	54
19.	Gentamicin sulphate, Methotrexate	General Device	Antibiotic and Anticancer	55
20.	Furosemide	Capsules IR, MR	Congestive heart failure	56
21.	Pravastatin	Tablet (IR, SR)	Lower "bad" cholesterol	57
22.	Atenolol, Ramipril		Anti -hypertensive	
23.	Aspirin		Nonsteroidal anti-inflammatory drug	
24.	Hydrochlorothiazide		Anti-hypotensive	
25.	Fluorescein	Tablet	Corneal ulcers and Herpetic corneal infections.	58
26.	5-aminosalicylic acid and 4-aminosalicylic acid	Tablet (MR)	Antibiotic	59
27.	Indomethacin	T-shaped (IU, SC rods)	Nonsteroidal anti-inflammatory	60
28.	5-Aminosalicylic acid	Tablets (IR)	Antibiotic	61
29.	Captopril		Anti -hypertensive	
30.	Prednisolone		Immunosuppressive drug	

Zip dose

Zip dose is the world's first and only FDA-validated, commercial-scale 3DP in new therapeutic areas for drug manufacturers. (Fig 4) It has a unique digitally coded layering and zero-compression processes, which is used for formulating a tablet with high dose and rapid disintegration .Hence it helps in overcoming a difficulty in swallowing.[62] Spritam® (Antiepilipsey drug) is an orodispersible tablet, marketed by Aprecia Pharmaceuticals based on powder bed fusion by layer-by-layer production system. In which it consists of the active ingredient, excipients and a binder liquid to produce a matrix tablet. [63]

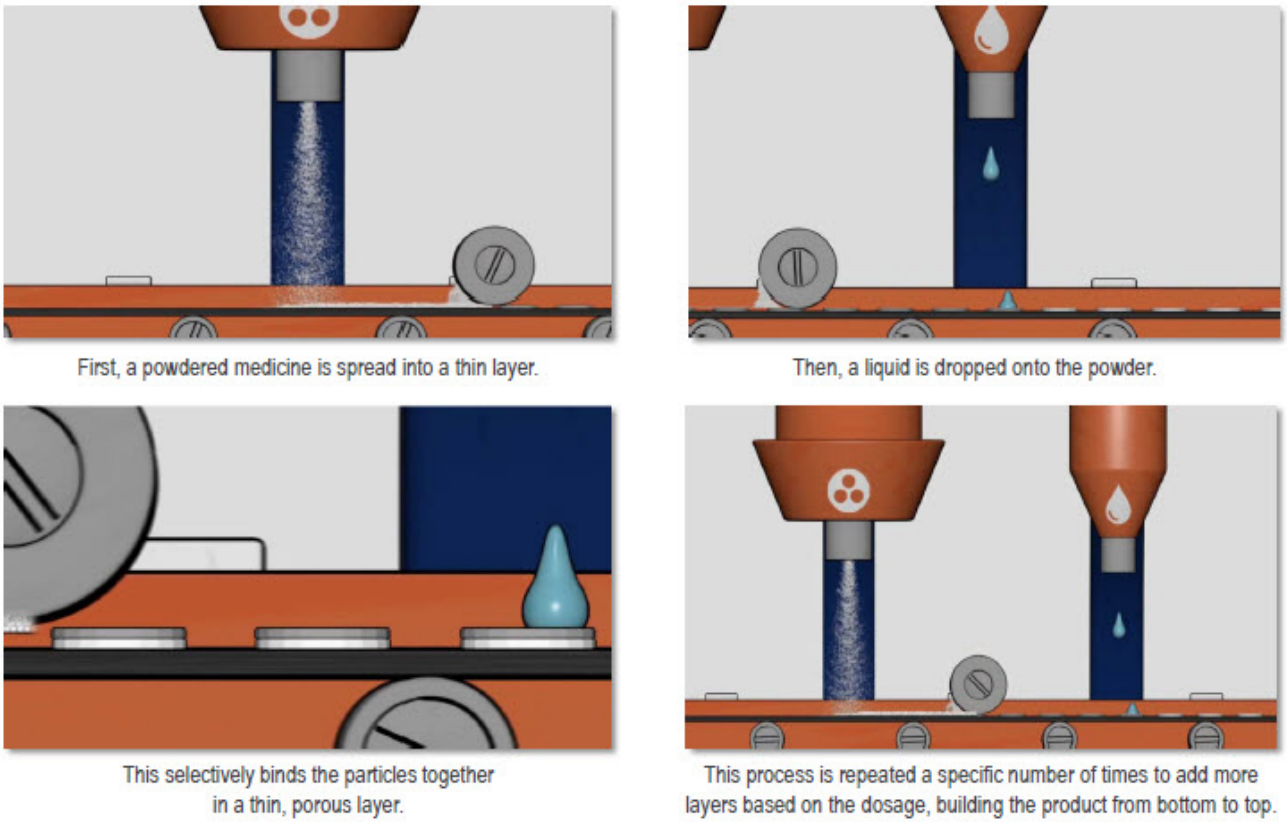

Fig 4: Zip dose technique in 3 D printing[64]

Extrusion 3D printing

In this technique the material is extruded from the automated nozzle on to the substrate and it does not require any higher support material. It is only used to fabricate tablet containing Guaifenesin as expectorant. The materials that can be extruded are molten polymers, suspensions, semisolids, pastes. [65, 66] (Table 4)

Table 4: Different dosage forms prepared by Extrusion 3D Printing

Sl.no	Drug	Dosage	Application	Reference
1	Captopril	Tablet	Anti-hypertensive	67
2	Glipizide	Tablet	Anti-diabetic	
3	Nifedepine	Tablet	Anti-hypertensive	
4	Dexamethazone	Drug encapsulated film of PLGA and PVA	Arthritis	68
5	Aspirin	Multi- active solid dosage form (polypill)	Anti -inflammatory	67
6	Atenolol		Angina	
7	Hydrochlorothiazide, Ramipril		Anti-hypertensive	
8	Pravastatin		Cardio vascular disease	
9	Prednisolone	Tablet	Immunosuppressive drug	69
10	Polydimethylsiloxane (PDMS)		Surfactant	

3D printer

The 3D printer is a valuable tool which is used to create customised medications with tailored release profiles and the medication is changed as per the patients comfort. (Table 5)(Fig 5)

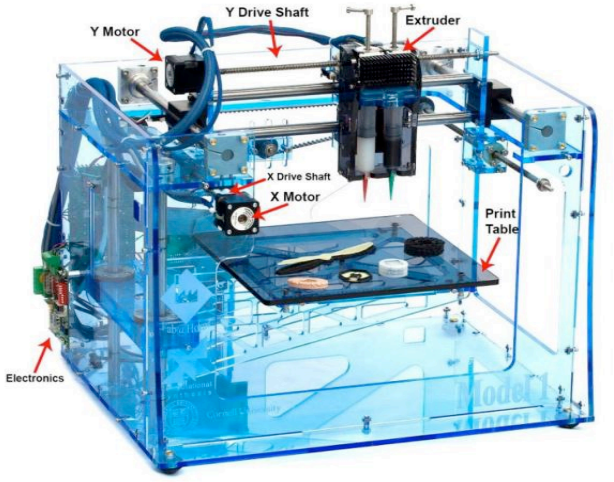

Fig 5: 3D printer used in 3 D Printing[70]

Table 5: Different drugs prepared by 3D printer method are

Sl.no	Drug	Dosage form	Application	Reference
1	Rifampicin, Isoniazid	Multi-drug implant	Antibiotic	71
2	Saline solution	Microfluidic pump	Electrolyte	72
3	Paracetamol	Fast-disintegrating tablets	Analgesics	73
4	Acetaminophen	Capsule-shaped solid Devices, fast disintegrating tablet	Analgesics	74
5	Caffeine	Capsule-shaped solid Devices	CNS stimulant	74
6	5-Fluorouracil	Biodegradable patch	Anti-cancer	75
7	Tetracycline, Vancomycin, Ofloxacin	Microporous bioceramics	Antibiotic	76
8	Chlorpheniramine maleate	Tablet	Antihistamine	77
9	Diclofenac sodium	Oral pulsatile tablet	Nonsteroidal anti-inflammatory drug	77
10	Fluorescein	Complex oral dosage forms	Corneal ulcers and Herpetic corneal infections.	78
11	Nitrofurantoin	Biofilm disk	Urinary tract infections	79
12	Polycaprolactone	Biodegradable patch	Manufacture of speciality Polyurethanes	79

Hot melt extrusion (HME)

Hot melt extrusion (HME) is the process of melting polymer and drug at high temperature and the pressure is applied in the instrument continuously for blending [80] (Fig 6).It is a continuous manufacturing process that includes several operations such as feeding, heating, mixing and shaping.[81] In recent years, it has proved that HME has the ability to improve the solubility and bioavailability of poorly soluble drugs [82]. (Table 6)

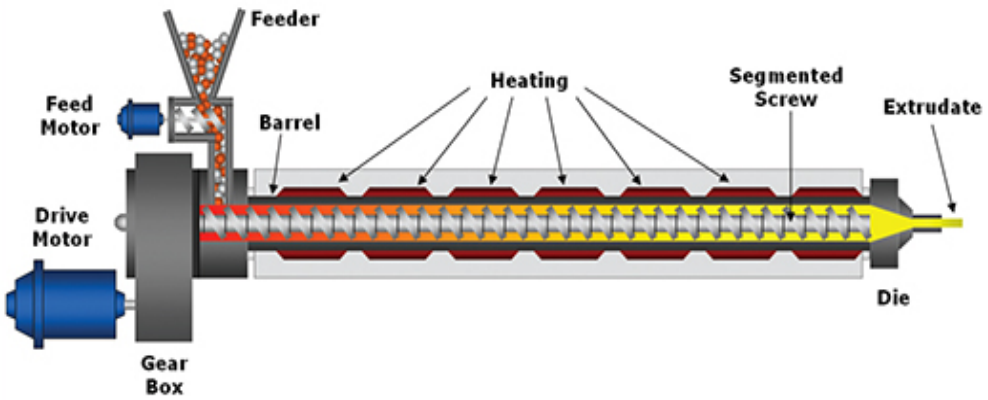

Fig 6: Hot melt extrusion technique in 3D printing[83]

Table 6: some of the drugs prepared by Hot melt extrusion technique are

Sl .no	Drug	Dosage form	Application	Reference
1	Paracetamol	3D-printed—cube, pyramid, cylinder, sphere and torus	Analgesic	84
2	Domperidone	Tablet	Parkinson's disease	85
3	Hydroxypropyl cellulose		Keratoconjunctivitis	
4	Rifampicin	Compartmentalized shells	Antibiotic	86
5	Isoniazid		Tuberculosis (TB) infections	
6	Indomethacin	Subcutaneous rods	Nonsteroidal anti-inflammatory	86
7	Ethylene Vinyl Acetate (Eva) Copolymers		Adhesive, sealants and coatings.	
8	Polymer Polyvinyl Alcohol (PVA), Mannitol and Hydrochlorothiazide (Hctz), Polylactic Acid (PLA)	Three-compartment hollow cylinder	Polymers	87
9	Indomethacin	T-shaped prototypes of intrauterine system (IUS)	Nonsteroidal anti-inflammatory	88
10	Ethylene Vinyl Acetate (Eva) Copolymers		Hot melt adhesives	

Stereolithography

Stereolithography is the technique in which a computer controlled laser beam is used to solidify the liquid polymer or resin, thereby creating a 3D structure[89] (Fig 7).SLA has some advantages over other types of 3DP, mainly it's remarkable resolution and the avoidance of thermal processes can be detrimental for certain drug molecules.[90] Some of the drugs prepared by Stereolithography are given in Table 7.

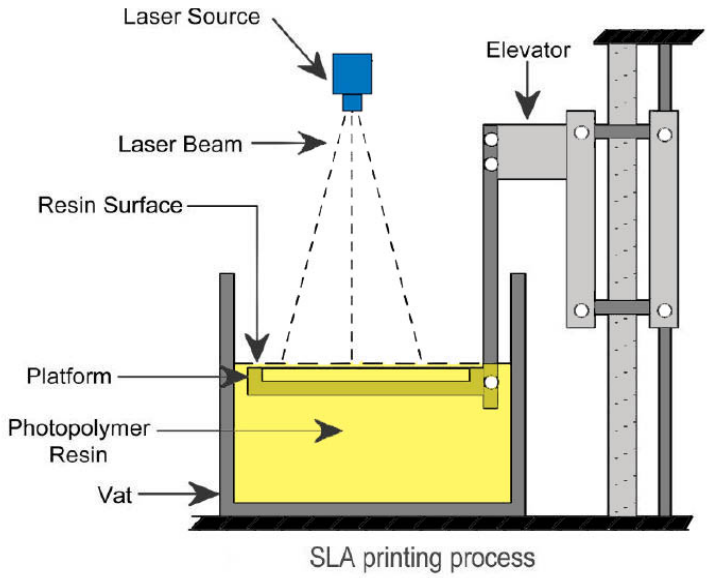

Fig 7: Stereolithography in 3D printing[91]

Table 7: Drugs prepared by Stereolithography are

Sl.no	Drug name	Dosage form	Use	Reference
1	Paracetamol	Oral modified release tablets	Antipyretic	92
2	4-Aminosalicylic acid	Oral modified release tablets	Antibiotic	92
3	Salicylic acid	Anti-acne patch	Psoriasis	93

Selective laser sintering

SLS uses a laser to bind together the powder particles from a powder bed. During the printing process, the laser is directed to draw a specific pattern onto the surface of the powder bed thereby creating a 3D structure (Fig 8). For example Paracetamol is an Orodispersible tablets which was prepared by this technique. It is currently used for industrial manufacturing of plastic, metallic and ceramic objects. [94]

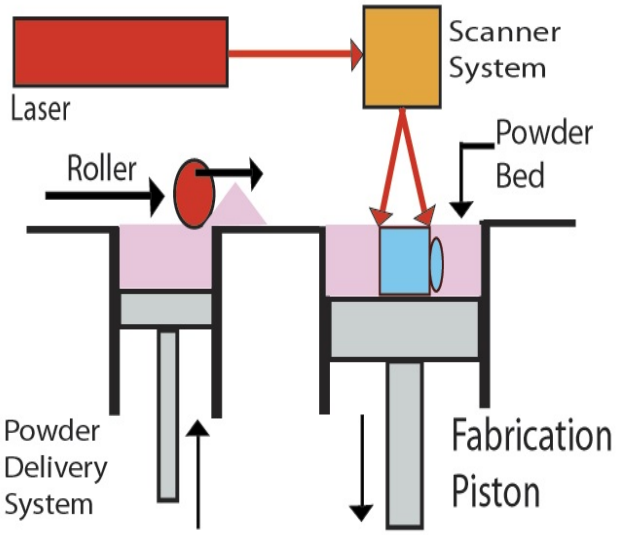

Fig 8: Selective laser sintering technique in 3D printing [95]

ADVANTAGES AND DISADVANTAGES

Use of 3DP has the advantage of adequate control on the spatial distribution of active pharmaceutical ingredients in the dosage form, which can help us to form a complex structure.[96] It also provides easy disintegration for patients who have difficulty in swallowing ,hence it increases the patient compliance.[97] There are basically 3 situations why this is on-demand in pharmacy because it includes printing directly on the implants or tissue scaffolds, printing "just in-time" in healthcare facilities or in other resource-constrained settings and printing low-stability drugs for immediate consumption. In all these scenarios, 3D printing technologies provide attractive solutions to explore on-demand pharmacy.[98]

Regarding possible disadvantages, there are several 3DP technologies based on the nozzle mechanism. Problems related to nozzle are a major challenge as stopping of the print head, which can affect the structure of the final product. Clogging in the case of powder printing is another hurdle. Other points of concern are the possibility of altering the final structure due to mechanical stress and storage condition alterations, the effect of ink formulations, printer related parameters and effect of these on quality of printing, cost of the printer. [99]

APPLICATION OF 3D PRINTING

3D printing applications are an enormous challenge, with potential use in a broad range of fields such as industrial design, aerospace, medical, tissue engineering, architecture, pharmaceutical and even food. [100]It mainly focus on two potential directions to bring the pharmaceutical product development to uncharted areas, one is the manufacturing of drug delivery systems with sophisticated structures and the other one is personalized medicine. It has expanded into the healthcare industry, where it's used to create dental implants. Now, there may be an opportunity to use it for personalized healthcare as well. It also fabricates a programmed release multi-drug implant for bone tuberculosis therapy. It also helps in Organ printing to produce cells, biomaterials, and cell-laden materials individually by layer by layer and directly creating 3D tissue like structure.

CHALLENGES IN 3D PRINTING TECHNOLOGY

Although 3D printing technology showed promising results in drug delivery applications, the technology is still under the developing stage. Hence it undergoes several challenges such as optimization process, improving performance of device for versatile use, selections of appropriate excipients, post treatment method, etc., to improve the performance of 3D printed products' and to expand the application range in novel drug delivery systems. Apart from the cost of developing new formulations or re-designing existing formulations through 3DP, the built-in flexibility may be a major source of liability from safety point of view. And to achieve quality 3DP products, many important parameters need to be optimized like printing rate, printing passes, line velocity of the print head, interval time between two printing layer, distance between the nozzles and the powder layer, etc.

FUTURE PROSPECTS

New possibilities in 3D printing may open up whole new opportunities for pharmaceutical research and bio-technology applications. In near future 3D printing approach will be utilized in many ways such as fabricate and engineer various novel dosage forms, achieve optimized drug release profiles, develop new excipients, avoid incompatibilities between multiple drugs, drug dosage forms, supporting delivery, limit degradation of biological molecules or helping to research cures. 3D printing could add a whole new dimension of possibilities to personalized medicine. In its most simplistic form, the idea of experts and researchers is to produce personalized 3D printed oral tablets. On demand printing of drug products can be implemented for drugs with limited shelf life or for patient specific medications, offering an alternative to traditional compounding pharmacies. In future it may lead to the innovation in garage biology. As the technology is still so new, there's a lack of regulation, safety and security concerns of 3D printing. So these problems can be overcome in nearby future

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