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3D PRINTING: MODERN MEDICATION MANUFACTURE

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ABSTRACT

3D printing is the key for future advancement in pharmaceutical field and precise manufacturing of personalized dosage forms, implantable medical devices. It is a process where objects are manufactured by fusion or deposition of materials in successive layers under computer control. Since 1984 when 3D printing came to existence it has evolved itself and found its place in many sectors including medicine, architecture and recently in pharmaceutical manufacturing. After the approval of the first 3D printed antiepileptic drug by USFDA, it is now finding its place in establishments of personalized medicines. Personalization of medicine provides a wide range of benefit for the patients who need to take medications having narrow therapeutic indices or having a higher predilection to be influenced by genetic polymorphism.3Dprinting offers new opportunities for improving safety, efficiency and convenience of medicines. When seen from an industrial point of view 3D printing has increased productivity, its cost effective and it enhanced collaboration. The review highlights the different important 3D printing processes and the mechanism by which it works, the advantages and disadvantages of each process. It is concluded that 3D printing is the footprint for the manufacturing of personalized dosage forms and on demand fabrication of pharmaceutical products in critical situation may be an easy task in the future.

Keywords: 3D printing technologies, personalized medications, fused deposition modelling, laser based printing technology, inkjet printing system

INTRODUCTION

The evolution of printing technologies has resulted in three dimensional printing of objects where a depositing or binding material is deposited layer by layer onto a substrate **[1]**. The traditional "one-size-fits-all" concept of treatment is becoming a thing of past and getting replaced with new therapies which are personalized to an individual. Thus we are shifting towards the personalized medication from the traditional therapy, as according to National Health Service (NHS) report the traditional treatment pathway is ineffective for 70 % of patients **[2]**. 3D printing became a major disruptive technology in pharmaceutical field with the innovative production of bespoke objects of virtually any shape and size and of complex geometries.

For the design and controlling of fabrication process, 3D printing uses computer aided drafting technology and programming. It utilizes a scanner that translate geometric features of a 3D object in digital data, a software for processing the digital data received from the scanner and a printer that manufacture desired object using a specific technology **[3]**.

With the introduction of 3D printing, manufacturing of certain oral dosage forms and medical devices has been made possible. It has also gained importance in the drug development process starting from preclinical to clinical stages and to frontline medical care **[4]**. 3D printing has a lot of advantage to state a few are the ability to accurately control the spatial distribution of API within the dosage form, high production rate, reduction in material wastage thus cost effective and manufacturing of narrow therapeutic index (TI) drugs and manufacturing of novel drug delivery systems **[5-8]**.

The present paper trying to describe about the 3D printing technologies, products being manufactured by this processes, advantages and disadvantages of this technologies.

3D PRINTING TECHNOLOGIES:

For the fabrication of pharmaceutical products, various printing technologies have been used in the past few years **[9, 10, 11]**. The printing technologies are extensively used in drug product research and development. With the introduction of 3D printing in dosage form design, leads to fabrication of personalized, multifunctional and novel drug products.

The three most advanced printing technologies widely used are:

- Printing based inkjet system
- Nozzle-based deposition system
- Laser-based writing system.

PRINTING BASED INKJET SYSTEM:

The technique where liquid droplets are placed onto a substrate in an organized manner using a computer aided pattern generating device is basically known as Inkjet based printing system. Lord Rayleigh's instability theory of 1878 is the fundamental or basics of inkjet printing which gives the explanation of breaking of liquid stream or jet into droplets **[12]**. This theory gives the two broad types of inkjet printing: a) continuous inkjet printing and b) drop on demand (DOD) printing. With these technologies different types of highly porous objects are manufactured.

a) continuous inkjet printing: It uses pressurized flow to generate continuous column of droplets(50-80µm) which gets charged up during its exit from the nozzle and with the help of electrostatic plates it is directed to towards the substrate and the waste are recirculated. The schematic diagram is illustrated in **Figure 1**.

Advantages: free from nozzle clogging problems, output faster.

Disadvantages: due to recirculation a lot of ink are wasted

b) **Drop on Demand printing**: it is considered as more accurate and less wateful and droplets size of (10-50µm) are produced at a very high speed but as of required. It is broadly classified into two categories:

i) **Drop-on-Drop (DOD) deposition**: If the binding material is itself the droplets i.e the "printable fluid" and the binding structure are same material then the system is called Drop-on-Drop (DOD) deposition **[13]**. The mechanism of this system is that the droplets after ejecting from the nozzles are subjected to some form of thermal stimulus that leads to evaporation of the solvent and thus solidifying and acts as a support for the next drop to be jetted **[14]**. The physical properties of the ink plays an important role in controlling of the droplet size for instance the surface tension which is responsible for spherical liquid drops emerging from the nozzle and it should be within (30 – 70mN/m) **[15]**, the solubility of the incorporated materials and the vapor pressure of the system is highly impacted by the type of solvent, use of atleast one non-volatile solvent to prevent clogging of nozzle **[16]** and the optimal viscosity of the liquids. The schematic diagram is illustrated in **Figure 2**

ADVANTAGE: Objects printed by this system are of very high resolutions three dimensional structures.

DISADVANTAGE: limited availability of volatile solvents which should dissolve both the drug and binding material.

The absence of solid substrate leads to nozzle clogging and fluid leakage if the viscosity of the printable liquid is not optimized.

ii) **Drop-on-Solid (DOS) deposition:** when the droplets (binder ink) are deposited onto solid substrate(powder) to form a solid free form structure in a layer wise manner is termed as Drop-on-Solid (DOS) deposition. The binder ink helps the powder particles to adhere or solidify **[8]**. The active pharmaceutical ingredients or the drugs can either be in the liquid droplets or mixed in the powder bed. In this system the printhead which sprays the droplets (binder formulation) moves in longitudinal and transverse axis and then the powder bed and part being fabricated are lowered paving a space for new layers to be formed. The powder bed is replenished with powder with the help of levelling roller and these steps continues until the object is fully developed. The durability of the printed object is obtained through evaporation of volatile solvent by thermal sintering **[17]**. The powder topology and reactivity of binder solution and powder materials are the two powder characteristics which influences these techniques. The interaction between the binder ink and powder in this process is similar to the traditional method of wet granulation **[18]**.The schematic diagram is illustrated in **Figure 3**.

ADVANTAGE: average resolution of printed objects, materials used (powders and binder solutions) are already used in the manufacturing of solid oral dosage form thus making it easier for transition from traditional manufacturing methods to 3D printing.

DISADVANTAGE: particle size of the powder binding material is critical.

The two most common types of actuation with Drop-on-Demand printing system are:

- Thermal print-head
- Piezoelectric print-head.

Thermal print heads use resisters which upon getting electric pulses rises the temperature up to 300°C and forms vapor bubble in the ink chamber. The bubble thus formed expands and imparts the energy required for ejecting droplets for printing. Mostly water is used as solvent because of the high temperature generation in the system **[19]**.

Piezoelectric print-head uses a piezoelectric element like crystal or ceramic which on application of voltage shows deformation in shape that creates a pressure pulse to eject the ink out **[20]**. Piezoelectric print heads show certain advantages over thermal print heads in that substances are not exposed to high temperature and thus prevents degradation of thermoliable drugs and thermal print head are limited only to volatile solvents while piezoelectric print heads utilizes wide range of inks. The schematic diagrams for the print heads are depicted in **Figure 4**

NOZZLE BASED DEPOSITION SYSTEM:

The process where the binder solution is mixed with the solid components of system before 3D printing involves the nozzle based deposition system **[21]**. It is computer control manufacturing method that deposits ink directly from nozzle tip layer by layer to create 3D objects. These system needs to liquefy the materials by a heating/melting step for extruding through the nozzles of the printer. This system is usually divided into two process a) free-melting [pressure assisted microsyringes (PAM) and b) melting material (fused deposition modelling).

a) Pressure-Assisted Microsyringes (PAM):

The method of extruding semi-solid materials with the help of pressured air piston dispenser (3-5 bars) is called Pressure-Assisted Microsyringes (PAM). With the help of light exposure or drying the extruded materials needs to be solidify. Operation done at room temperature in a continuous flow pattern **[22]**. To obtain reproducible drug delivery system the major parameter to consider is the rheological properties of the extruding semi-solid materials.

ADVANTAGE: performed at room temperature, best suited for thermolabile drugs, high drug loading

DISADVANTAGE: drying steps are mandatory otherwise high risk of deformation or excessive droplet shrinkage, high chance of nozzle clogging, low resolution.

b) **Fused deposition modelling (FDM):** The method where thermoplastic materials are used as a starting materials which are drawn by gear system into printheads where it is heated up by heating elements/ liquiefiers into molten state for easy extrusion of the semi solid materials from the nozzle tip onto a build plate is called fused deposition modelling (FDM). The 3D structures can be obtained by the movement of the printhead in x and y axis and the platform can move vertically in z-axis. It is deposited in layer by layer fashion which needs to be fused to get the structure **[23]**. Materials to be extruded needs to be analyzed prior to extrusion for the rheological properties and other parameters like infill density, extruder speed, both nozzle and build plate temperature, nozzle diameter **[24]**. The schematic diagram is depicted in **Figure 5**.

ADVANTAGE: it is inexpensive and readily available, novel technique for development of personalized dosage forms (controlled and modified release profiles), designing of gadgets with complicated inner geometries

DISADVANTAGE: degradation of thermolabile substances, a limited number of low-dose thermostable API and biodegradable thermoplastic polymers can be utilized in this technique which limits its applicability in terms of flexibility.

LASER -BASED WRITING SYSTEM:

It is based on the principle that radiation helps in photochemical reaction where polymerization of photo-polymerizable materials takes place and thus forming the 3D objects. It is broadly of two types: a) Stereolithography b) Selective Laser Sintering.

a) **STEREOLITHOGRAPHY**: It is a computer control method where laser beams are projected towards the photo polymerizable resins/polymers which results in the solidification of the resin. At fixed interval when the resin is solidified to certain extent the platform is lowered along the z axis and the solidified layer is recoated with the resin and the process continues layer-by-layer until the desired 3D structure obtained **[25]**. The schematic diagram is depicted in **Figure 6**.

ADVANTAGES: high level of accuracy and resolutions, desired release pattern of customized drug delivery system obtained, implantable devices of desired shape is obtained and most important application in making of micro-needles.

DISADVANTAGES: availability of biocompatible photopolymerizable polymers are limited, low drug loading, carcinogenic and lot of resins wasted

b) **SELECTIVE LASER SINTERING**: It utilizes a digital monitoring device that directs the laser to draw a specific pattern on the powder bed. After the layer is sintered, a fresh layer is distributed onto the top of the formed layer and the process continues until the desired 3D structure obtained. The schemactic diagram is depicted in **Figure 7**

ADVANTAGES: High accuracy, complex geometries medical devices can be manufactured, support is not required.

DISADVANTAGES: expensive, lots of waste produced, porous and brittle.

APPLICATION OF 3D PRINTING:

The benefits of application of 3D printing in pharmaceutical industries are:

i. Medicines are produced at less cost since conventional methods uses lots of processes such as mixing, dry or wet granulations etc thus it increases cost efficiency.
ii. 3D printing technology is faster since multiple steps involved in conventional methods are eliminated thus it enhance productivity.
iii. High resolution, accuracy and reliability products can be obtained from 3D printing technologies.
iv. High drug loading capabilities as compared to conventional methods.
v. Active Pharmaceutical Ingredients which are difficult to formulate like poor water solubility and narrow therapeutic windows drugs can be designed into suitable drug delivery systems.
vi. Patient compliance is increased for those who face difficulties in

swallowing thus formulation easy disintegrating formulations.

vii. 3D printing technology helps in exploring ‘on-demand pharmacy’.

Some of the drugs which are formulated by the application of inkjet printing are shown in **Table 1**.

Some of the dosage forms prepared using extrusion based printing (FDM) are shown in **Table 2**.

Some of the dosage form prepared by laser based writing system (SLA) are shown in **Table 3**.

Table 1: Application of inkjet printing in formulation of dosage form

S. No	Drug	Dosage form	Application	Reference
1	Felodipine	Microdots	Antihypertensive	26
2	Polyvinyl pyrrolidone (PVP)	Microdots	Excipients	26
3	Insulin	Microneedle	Antihyperglycemia	27
4	5-Fluorouracil, curcumin and cisplatin	Microneedle	Anticancer agents	28
5	Paclitaxel	Microparticles	Anticancer agents	29
6	Fluorescein 5-isothiocyanate	Microparticles	Fluorescence	29
7	Loperamide	Tablets or capsules	Inflammatory bowel disease.	30
8	Caffeine	Tablets or capsules	CNS stimulant	30
9	Paracetamol	Tablets	Analgesics	31
10	Atenolol	Tablets, sprays	Antihypertensive	32
11	Influenza vaccine	Microneedles	Against influenza viruses	33
12	Voriconazole and Itraconazole	Microneedles	Antifungal agent	34
13	Piroxicam	Capsules	Nonsteroidal anti-inflammatory	35
14	Lysozyme and Ribonuclease-A	Films	Antibacterial and Antiviral	36
15	Erythropoietin	Uncoated rubber stopper Syringes	Anemia	37
16	Rifampicin	Implant, Nanoparticles	Antibiotic	38
17	Levofloxacin	Implant	Antibiotic	39
18	Folic Acid	Nanosuspension	Anemia	40
19	Nitroglycerin	Injection	Angina	41
20	Fenofibrate	Tablets	Anti Hypertriglyceridemia and Anti Hypercholesterolemia	42
21	Rapamycin	Tablet	Immunosuppressant	42
22	Ketoprofen	Tablet	Nonsteroidal anti-inflammatory	43
23	Rasagiline mesylate	Oral dosage	Antiparkinson agent	44

Table 2: Application of extrusion printing (FDM) in preparation of dosage form

S. No,	Drug name	Dosage Form	Use	Reference
1	Domperidone	Tablet	Nausea, vomiting	45
2	Ibuprofen	Tablet	NSAID	46
3	Aminosalicylate	Tablet	Antibiotic	47
4	Metformin, Glimepiride	Tablet	Antidiabetic	48
5	Disopyramide	Tablet	Antiarrhythmic	49
6	Theophylline	Tablet, Capsule	Lung diseases	49
7	Paracetamol	Tablet	Antipyretic	50
8	Budesonide	Controlled release tablet	Ulcerative colitis	51
9	Diclofenac sodium	Tablet	NSAID	51
10	Prednisolone	Extendedrelease tablet	Immunosuppressant	52
11	Enalapril maleate	Tablet	Antihypertensive	53
12	Hydrochlorothiazide	Tablet	Diuretic	53
13	Acetaminophen	Oral pulsatile capsule, Tablet MR	Antipyretic	54
14	Captopril	Intermediate release tablets	Hypertension,CHF	54
15	Budesonide	Capsule	Ulcerative colitis	54
16	Nitrofurantoin	Catheter, Implant	Urinary tract infections	55
17	Hydroxyapatite	Implant	Carrier	55
18	Dye	Implant CR	Excipients	56
19	Gentamicin sulphate,Methotrexate	General Device	Antibiotic and Anticancer	57
20	Furosemide	Capsules IR, MR	Congestive heart failure	58
21	Pravastatin	Tablet (IR, SR)	Lower "bad" cholesterol	59
22	Atenolol, Ramipril	Tablet (IR, SR)	Anti -hypertensive	59
23	Aspirin	Tablet (IR, SR)	Nonsteroidalanti-inflammatory drug	59
24	Hydrochlorothiazide	Tablet (IR, SR)	Anti-hypotensive	59
25	Fluorescein	Tablet	Corneal ulcers and Herpetic corneal infections.	60
26	5-aminosalicylic acid and 4-aminosalicylic acid	Tablet (MR)	Antibiotic	47
27	In domethacin	T-shaped (IU, SC rods)	Nonsteroidal anti-inflammatory	61
28	5- Aminosalicylic acid	Tablets (IR)	Antibiotic	62
29	Captopril	Tablets (IR)	Anti -hypertensive	62
30	Prednisolone	Tablets (IR)	Immunosuppressive drug	62

Table 3: Dosage forms prepared by laser based writing system (SLA)

S. No.	Drug name	Dosage form	Use	Reference
1	Paracetamol	Oral modified release tablets	Antipyretic	63
2	4-Aminosalicylic acid	Oral modified release tablets	Antibiotic	63
3	Salicylic acid	Anti-acne patch	Psoriasis	64

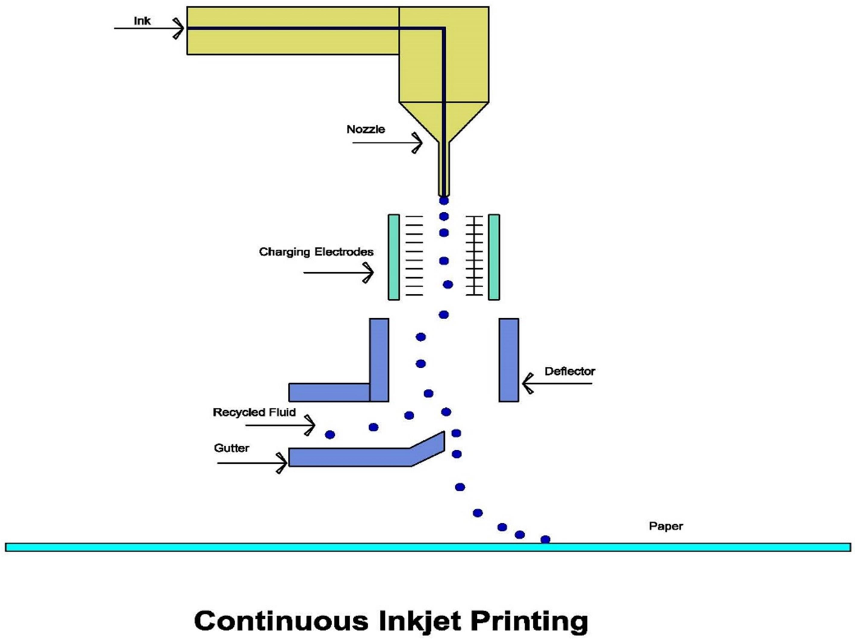

Figure 1: Schematic diagram depicting continuous inkjet printing

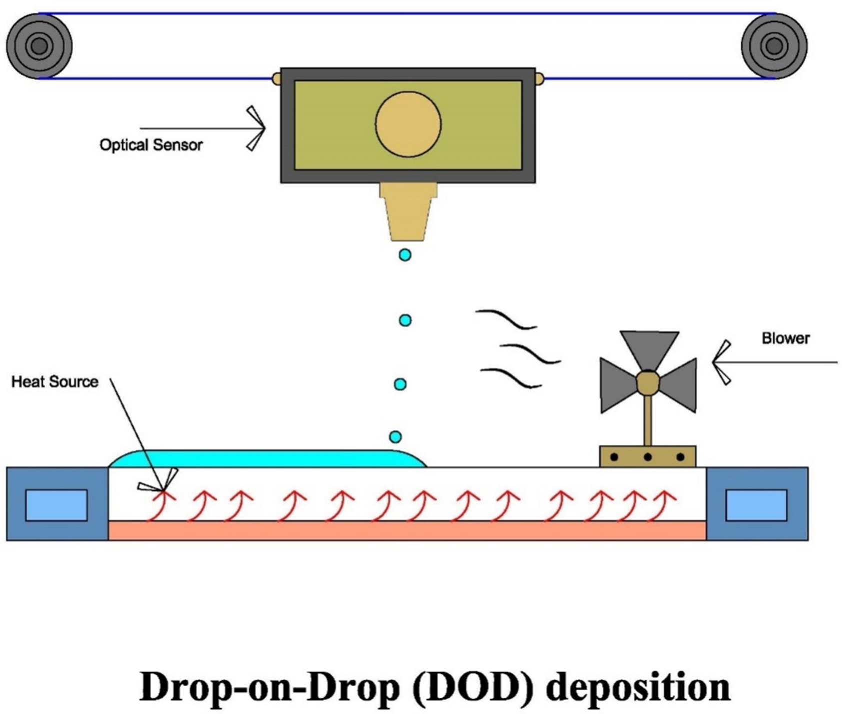

Figure 2: Schematic diagram depicting Drop-On-Drop (DOD) Deposition

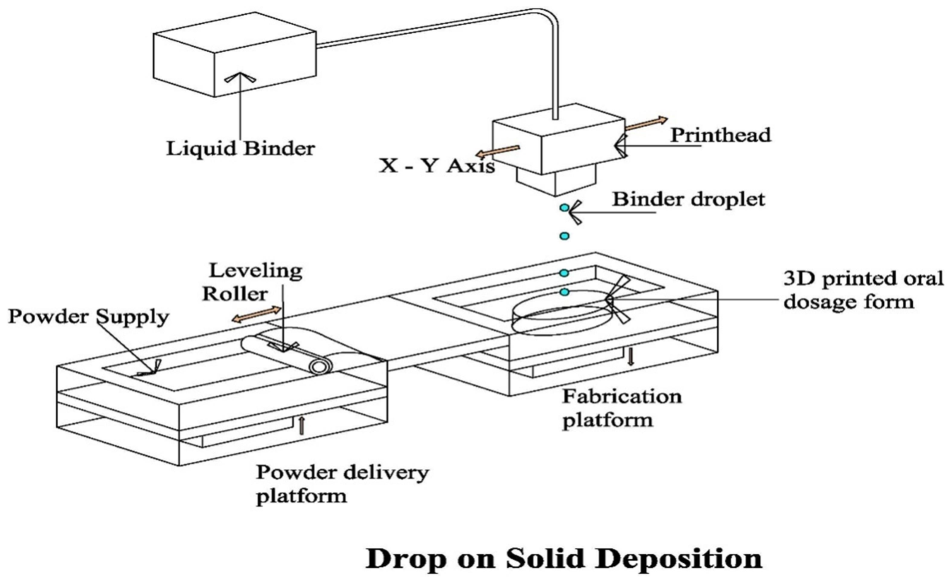

Figure 3: Schematic diagram depicting Drop-On-Solid (DOS) Deposition

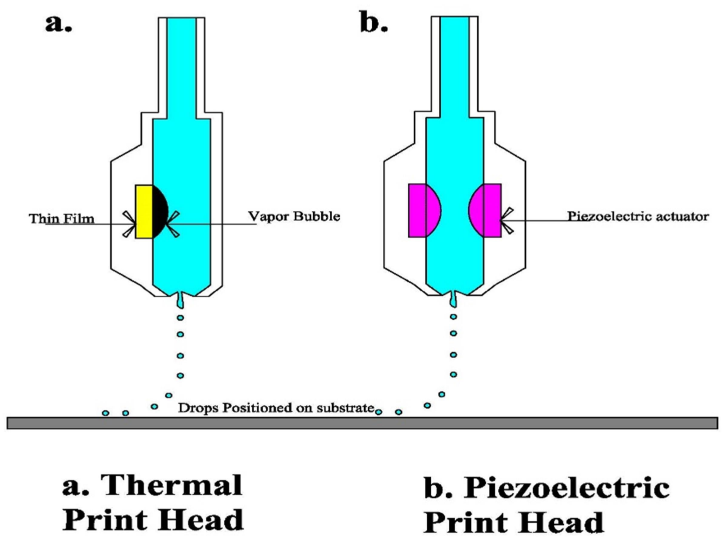

Figure 4: Schematic diagram depicting Print Heads- a) thermal print head b) piezoelectric print head

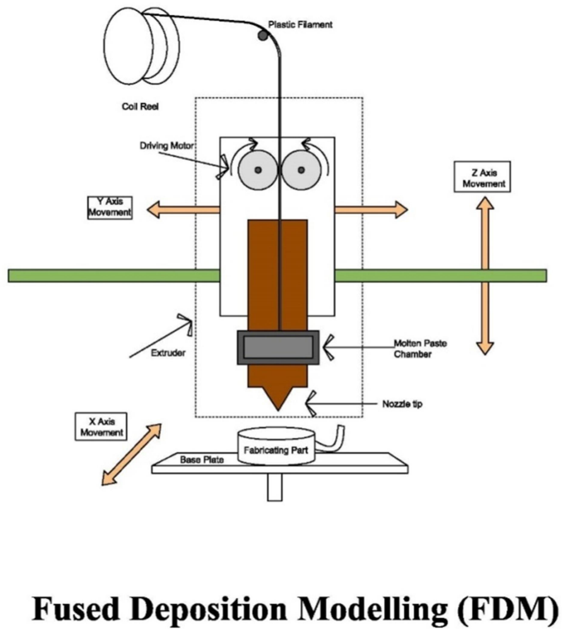

Figure 5: Schematic diagram depicting Fused Deposition modelling based 3D printing

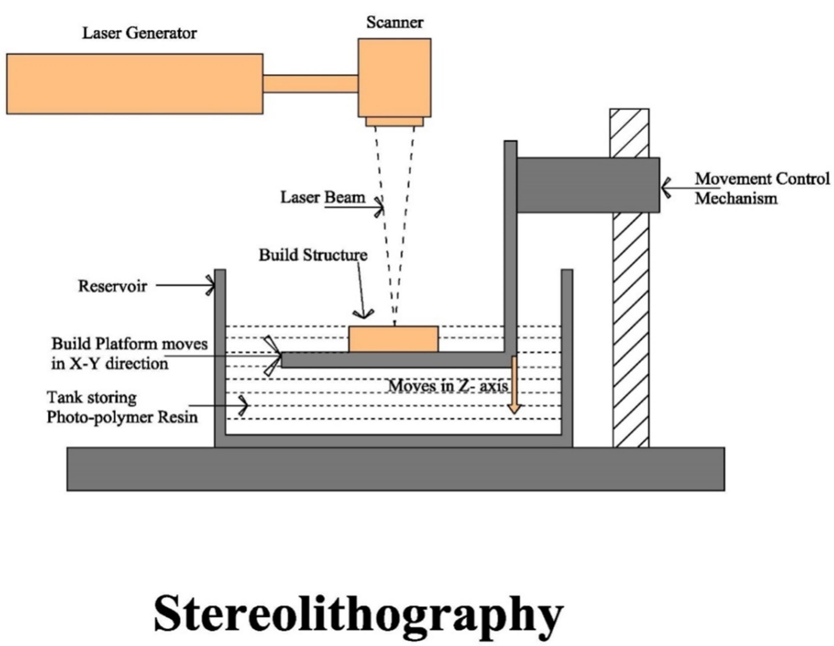

Figure 6: Schematic diagram depicting stereolithography (SLA)

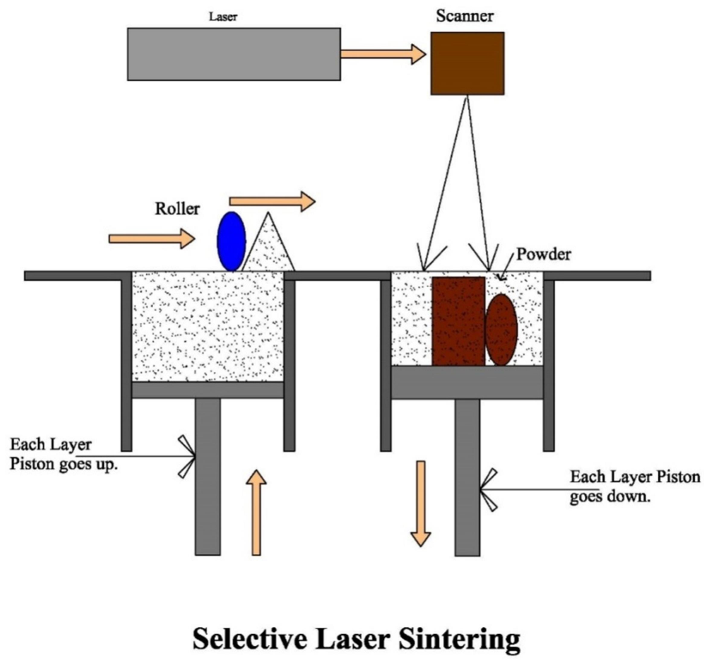

Figure 7: Schematic diagram depicting Selective Laser Sintering (SLS)

FUTURE PROSPECTS

3D printing technology is soon going to replace manufacturing and distribution of drugs by pharmaceutical companies by emailing databases of medication formulations to pharmacies for on-demand drug printing thus reducing the cost of medications. 3D printing technology helps in formulating drugs with narrow therapeutic index and complicated medical devices. Highly innovative products can be manufactured with multimechanism release behavior and combination drug products. 3D printing opens to new opportunities for formulating novel dosage forms, development of new excipients, multiple drugs incompatibilities can be removed etc. 3D printing technology is going to remove traditional one fit all type to personalized medication. In future these technology will be proved to be a blessing for development in medical research and medication formulations. Although these technology is now in its budding stage thus it has no such defined laws and regulations and has regulatory burdens yet seeing the advantages of these techniques the hurdles of regulatory process will be overcome and personalized medicines will be dominating the market.

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