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A REVIEW ON: 3D PRINTING IN PHARMACEUTICAL TECHNOLOGY

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Abstract

The 3D PRINTING technology has paid attention towards medical devices industry and pharmaceutical industry due to its applications on various platforms in health care industry. 3D printing is using computer- aided design to plan fast prototyping. The technology allows easy process drug combinations that are required and tailored dosing. It becomes one of the most new and beneficial tools serving as a technology of good manufacturing of developed dosage forms, tissue engineering and disease modeling. It is a valuable strategy to overcome some challenges of conventional pharmaceutical processes The recent introduction of the first FDA approved 3D-printed drug has fulfilled interest in 3D printing technology, which is set for revolutionize the healthcare. Since the use, the rapid prototyping (RP) technology has evolved to such an extent that it is currently being used in a wide range of applications including in tissue engineering, dentistry, construction, automotive and aerospace.

Keywords: *3D printing, Novel drug delivery, personalized medicine.*

1. INTRODUCTION

3D printing plays an important role in multiple active ingredient dosage forms, where the formulation can be a single blend or a multi-layer printed tablets having a sustained release properties. This reduces the frequency and number of dosage form units consumed by the patient on a daily routine. 3D printing technology has a great potential in an individualized dosage form concept i.e the polypill concept. [1] This brings about the possibility of all the drugs required for the therapy into a single dosage form unit. Three-dimensional printing is a technology which uses computer aided drafting technology to produce three dimensional objects by layering material onto a substrate.

3DP can be used throughout the drug development process, starting from preclinical development and clinical trials, to the medical care. 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 agreeable to broad types of pharmaceutical active ingredients that include poorly water-soluble, peptides and proteins, as well as drug with narrow therapeutic windows.[2]

An action or process of manufacturing of objects through the deposing of a material using a print head, nozzle, and or another printer technology. In this technique 3D model are used for preparing the parts in the process of joining materials layer by layer. In novel drug delivery system 3D printing are used for viable tablet production. These tablets are manufactured in such a way that are capable of satisfying regulatory tests and matching the standards of commercial tablets. [3]

HISTORY

Additive manufacturing fabricating methods of 3D plastic model with photo hardening polymer were invented by Hideo Kodama of Nagoya Municipal Industrial Research Institute; here the UV exposure area is controlled by scanning fibre transmitter or mask pattern. [4]In 1984, Check Hull of 3D systems corporation developed a prototype systems based on a process as a systems based on a process known as Stereo lithography. The team of umbrella was gaining additive manufacturing and wider currency in the decade of the 2000's.This technique in field of pharmaceutics was in practise by inkjet printing a binder solution was passed on powder bed, therefore binding the particles together was given the credit to the semi-liquid binding solution. The process was continuously repeated until the final desired structure was obtained. This first happened in the early 90's at the MIT (Massachuset Institute Technology). [5]

In 1989,S.Scott Crump, a patent was filed on another 3D printing technology: fused deposition modeling, where a extruded polymer filaments heated into a semi-liquid state were extruded through a heated nozzle and deposited on a build platform layer and layer to harden. Inkjet printing was the method used to manufacture Spritam (levetiracetam) tablets for oral use, the first 3D printed drug approved by the Food and Drug Administration (FDA) in 2016 by Aprecia Pharmaceuticals. 3D printing is more advanced in the fields of automobile, aerospace, biomedical and tissue engineering than in the pharmaceutical industry where it is in its initial phase. FDA encourages the development of advanced manufacturing technologies, including 3D printing, using risk-based approaches. [6]

STEPS INVOLVED IN A 3D PRINTED DOSAGE FORM

Pharmaceutical product is designed in three dimensions with computer aided design. Converting the Design into a machine readable format or a Data which describes the external surface of the 3D dosage form. The computer program then Divides this surface into several different printable layers and transfers those layer and layer to the machine. [7, 8]

Advantages Delivery of 3D Printed Drug

- High drug loading ability when compared to conventional dosage forms.
- Accurate and precise dosing of potent drugs which are administered at small doses.
- Due to lesser material cost of production reduces.
- Suitable drug delivery for difficult to formulate active ingredients like poor water solubility, drugs with narrow therapeutic window.

- Medication can be tailored to a patient in particular based on variation in genetics, differences in ethnic, age, gender and the environment.
- In case of multi drug therapy with multiple dosing regimen, treatment can be customized to improve patient adherence.

3D PRINTING TECHNOLOGIES

3D printing or additive manufacturing is a highly pleasing or attractive technology that produces 3-dimensional objects by constructing layers of the used material under the control of computer software. It has established its ways in engineering and also in non-medical practices, and also in the automobile industries. It has an ability to produce complex shapes and geometries remains one of its major advantages in manufacturing. Recently its applications in medical devices, implants, tissue regeneration and pharmaceutical dosage forms etc. have been demonstrated with a wave of enthusiasm and its potential in personalized medicine.[9,10]

Types of 3D printing

1. Polypill concept

The concept of "polypill" refers to a single tablet that involves the combination of many drugs. This concept is mainly beneficial for geriatric population, as patients of this age are categorized to multiple disorders and hence multiple therapy is being suggested. [11, 12] This technology has been realized through the research in which five different active pharmaceutical ingredients with different release profiles have been formulated or made in a single 3D dosage form. Three drugs namely (pravastatin, at enolol, and ramipril) has to be printed in the extended release compartment. The drugs were physically separated by a permeable membrane of hydrophobic cellulose acetate. An immediate release compartment containing hydrochlorothiazide and aspirin were deposited on top of the extended release compartment.[13,14]The tablets used to illustrate that concept to put in or add something an osmotic pump with the drug captopril and sustained release compartments with the drugs nifedipine and glipizide. The room temperature extrusion process used to print the formulations used excipients commonly employed in the pharmaceutical industry. The combination of medicines such as nifedipine and glipizide could potentially be used to treat diabetics suffering from hypertension. [15, 16]

2. Inkjet Printing

In the inkjet printing an approach to a personalized medicine begins from the technique of computer-operated inkjet printing and includes use of inkjet printers. The practicing was done for pharmaceutical use by the replacing the ink with pharmaceutical solutions containing drugs and normal paper with edible sheets known as substrates. Dose changes are done by changing the number of layers printed in a given area or altering the area to be printed. The drug and excipients are designed in a ratio such that it has a potential or a power to print as microdots on an edible substrate. [17, 18]The two main printing types used under inkjet printing are thermal inkjet printers and piezoelectric inkjet printers Printing-based inkjet systems consists of two types of techniques: continuous inkjet printing and drop on-demand printing. In continuous inkjet printing, the liquid ink is passed through an orifice of 50-80 µm diameters which has a continuous ink flow. The liquid is made to flow and break into drops at a specific range of speed and size at regular time period using a piezoelectric crystal. These parameters are made in control by creating an electrostatic field. [19] Thus, the droplets are charged and are separated by "droplets of guard" to minimize the electrostatic repulsion between them. The electrostatic field that is being created

directs the charged droplets to the substrate. The drop-on-demand technique contains multiple heads (100–1000) and can use two types of translators, namely a thermal head or a piezoelectric crystal. The thermal head can be used only for volatile liquids, whereas the piezoelectric covers a wide range of liquids. [20, 21]

3. Fused Deposition Modelling (FDM)

Fused deposition modelling (FDM) is commonly used technique in 3D printing and also known as fused filament fabrication (FFF), in this the materials are soften or melted by heat to create objects during printing. FDM 3D printing helps in manufacturing of delayed release print lets without an outer enteric coating, and also helps to provide personalised dose medicines. [22,23] FDM 3D printing however, indicates several drawbacks of the system such as lack of suitable polymers, slow and often incomplete drug release the reason is the drug remain trapped in the polymers and the miscibility of the drug and additives with the polymers used was not evaluated.[24]

4. Drop-on-powder deposition

Due to the mixture of powder (bed) and binder (ink) they make a solid structure in a layer-wise manner. They allow the elimination of remaining volatile solvents for the stability of the final product Powder particle sticks due to the ink binder and results for the solidification.[25,26] Powder topology and material reactivity by binder are the main two characteristics of powder in the drop on powder deposition.

5. Drop-on-drop deposition

In a drop-on-drop deposition method, around 20 dissimilar loading geometrical shaped formulations fixed with nano carriers can be possible which offers a higher drug.[27] Polyethylene glycol [PEG] droplets of Ibuprofen were printed by Elele and co -workers. They then swallowed the material into a porous substrate which is formed by HPMC. The three-dimensional dosage form were created by superposition; the freeze-drying method was used to make a cellulosic derivative substrate and thus the three-dimensional printing was not used to make a final structure. To make a 3D printing PLA (polylactic acid) and PLGA polys(lactic-co-glycolic acid) are used in various methods such as drop-on-drop deposition, inkjet printing technique. [28,29]

6. Nozzle-based deposition systems

In Nozzle-based deposition systems mixing of drugs, polymers and other solid elements takes place prior to 3D printing. Direct writing is done, and computer-controlled manufacturing methods are used that place ink direct through a nozzle to create a 3D pattern layer-bilayer with controlled composition and designing.[30,31] Such systems may basically be divided into processes based on material melting and also on processes without material melting. Various methods have been suggested in bioengineering applications, and very few have been used in the pharmaceuticals field. An attention has been paid to SFF techniques based on pressure-assisted micro syringes (PAM) and hot-melt printing (HMP),also in free-melting and melting material processes.[32,33] The PAM printing method is based on removing a viscous semi-liquid material from a syringe to create a desired 3D shape. The process can be done in a continuous flow at room temperature. The dispenser is normally based on a pressured-air piston.

7. Laser-based writing systems

This method was the first that commercially presented SFF (solid freeform fabrication) techniques and developed in 1986. In the field of bioengineering, they are heavily was reviewed and used. To make a model, prototypes, patterns, and production parts using a photochemical process with the help of printing technology in the form of Stereolithography [SLA].[34,35]This

research came in exist during the 1970s, but the term was coined by Chuck Hull in 1984 when he patented his process, which was granted in year 1986. Stereolithography is a material which is used to make a medical model, and computer hardware and other sides. Which are very costly due to their property.[36]

8. Hot melt extrusion

Hot melt extrusion is the process of melting polymer as well as drug at high temperature and the pressure is applied to the instrument continuously for the purpose of blending. It is a continuous manufacturing process that includes several operations such as feeding, heating, mixing as well as shaping. In recent years, it has been proved that Hot Melt Extrusion have an ability to improve the solubility and bioavailability of poorly soluble drugs.[37,38]

9. Extrusion 3D Printing

Extrusion is the commonly and the simplest 3D printing technique that can used. In this technique the material is removed from the automated nozzle on to the substrate and it does not require any higher support material. The materials that can be removed are molten polymers, suspensions, semisolids, pastes.[39]

10. Selective Laser Sintering

Selective laser sintering is a quick manufacturing process which is based upon the use of powder coated metal additives, this process is generally used for rapid prototyping. And also for scanning and aligning particles in predetermined sizes and shapes of the layers a continuous laser beam are also used as heating source. The geometry of the scanned layers corresponds to various sections of the models established by Computer-aided design or from files produced by stereolithography. After scanning of the first layer the scanning of second layer is continued which is placed over the first, the process is continued from the bottom to the top until the product is complete. [40]The small particles is fused of plastic, metal, ceramic or glass powders into a mass that has the desired three dimensional shapes, this technology uses high power laser. Scanning the cross section or layers generated by 3D modeling program on the surface of powder bed, laser selectively fused the powdered material so that the powder bed is lowered by one layer of thickness. [41]Then a new layer of material is put into practise on top and this process is continued until the object is completed.

RISK ASSESSMENT DURING 3D PRINTING PROCESS

Risk identification is an important tool to prevent failure of quality control parameters like appearance, content uniformity, assay etc. Identification of risk involves through analysis of the process and process variables to assure that a quality product is being manufactured. Such a critical assessment was done by Norman et al. When a given printer is unable to print a given design, software control should be employed or used.

- Variability or changes in layer thickness has to be controlled by real – time layer thickness monitoring.
- Improper layering due to environmental conditions should be dealt with controlling the temperature and humidity of the manufacturing area.
- Inaccurate position during printing can be stopped by monitoring print head height and print head speed.
- Uneven layers can be avoided by checking powder water content and powder particle size distribution.
- Print head clogging can be prevented by ensuring particle size distribution and monitoring inkjet flow.
- Inconsistency in agglomeration or binding can be due to variations or

changes in surface tension or binder viscosity.

Major obstacles of polymeric 3D printed technology

Since the incorporation of 3D printing technology in pharmaceutical products is nowadays widely used in scientific communities, various numbers of polymers are used to verify the best probability of 3D printed optimized products. However, regulatory approval from USFDA remains of great concern to commercialize 3D printed products for human use. Major drawback of the 3D printed formulation filaments were also made in high temperature which might lead to instability for certain thermolabile drugs incorporating in 3D printed films. But this problem can be resolved by incorporating nano formulations of the drug in melted polymer, which results into Thermo protection of the drug. Another significant drawback is lower availabilities of fused deposition modeling (FDM); which could help in preparation of solid orals. The suitability & compatibility of polymers with FDM is a big concern in 3D printing technology. Since 3D printed formulations are mostly personalized in nature, hence it become very difficult to standardize the formulations.[42]

3D printing in pharmaceuticals

As per United States Government Accountability Office (GAO),3D printing makes 3D objectives from digital models, and its aim are to produce by layer by layer process.3D printing is gaining and increasing attention in pharmaceutical formulation as they produce different dosage from in various shapes, sizes & release various features.3D printing technology overcomes some challenges in conventional pharmaceutical preparation. Traditional pharmaceutical preparation involves milling, mixing, granulation, compression which may result in drug loading, drug release, drug stability and also in dosage form stability.

3D printing is necessary in pharmaceuticals for personalized dosing such as availability in variable dose, targeted therapy, orphan drug, and also needed to adjust dose based on diagnostic response.3D printing medicines are entering into the pharmaceutical market as they are potential to achieve personalized treatments of each and every patient. Personalized treatment is design by taking into consideration patient age, weight, pharmacogenetics and pharmacokinetic characteristics. Ex: Imagine there is an older patient who will have prescribed polypill per day but he forgot to take, it is solved by taking a single pill, if suddenly the patient will have serious problem and don't have time to go to the doctor or any specialized he has the facility to produce his required medicament by 3D printer. The variability is worldwide problem when treating patients having different medical history with varities of customs& necessities. This variability has been accepted as part of the therapeutic process all over the year, but now a day's new technologies for the optimization of treatments according to population subgroups, that are based on pharmacogenetics and pharmacokinetic profile. Pharmacokinetic features such as weight & age are necessary to dose adjustment to achieve the desired therapeutic effect.[43] Polymedicated patients have the risk of side effect, which can be minimized by intake of a single pill containing all the drugs required for the patient. This single pill can be produced by 3D printing technology. In this way 3D printing enters into the drug therapy. We have reached an era in pharmaceutical field whereby "one size does not fit all". Science medication should be individual i.e patient to patient. FDA approval 3D printing of drug product was given in August 2015. The Food and Drug Administration agency (FDA) granted the approval of Spritam, the first 3D printed tablet i.e for the treatment of epileptic seizures.[44]

Application of 3D printed drug

Commercially available 3D printed drugs

Spritam is marked by Aprecia Pharmaceuticals using the Zip Dose technique based on powder bed fusion. Spritam made by the layer-by-layer production system. The pharmacological efficacy of Spritam was found to be equivalent to conventional tablets. The great improvement is the solubilization time of Spritam was significantly reduced due to its porous and soluble matrix composition.[45]

Personalized topical treatment devices

Nose-shaped masks, loaded with salicylic acid, used for anti-acne treatments, have been developed in a short and efficient manner. The face of the patient was scanned and the taken image was projected to the autocad program, through which the nose section was selected. FDM and SLA, to determine which one was more favourable in terms of engineering, the morphological characteristics of the object, drug release, and the stability during printing. SLA was the most accurate technology for mask manufacture.[46,47]

3D Printing for cancer treatment

Chemotherapy has widely applied in cancer treatment but chemotherapy can cause side effect. Chemotherapeutic drugs have poor solubility in aqueous media; thus, they are administering through a different route. Currently, the construction of patches loaded with 5-fluorouracil, poly (lactic-co-glycolic) acid, and PCL have been effectively printed and implanted directly into pancreatic cancer.[47,48, 49]

3D printed polypill

The concept polypill allows the combination of several drugs in a single personalized tablet. It provides benefits over a poly medicated patient such as elder person. Numerous polypills using 3D extrusion printing have been successfully made and are used.[50,51]

FUTURE PROSPECTIVES

The future and development of pharmaceutical progress is represented by 3D printed drug manufacturing technology. 3D printing plays an vital and efficient role in the field of personalized medicine. It is used in modify nutritional products, organ, and drugs. Industries along with all society prefer 3D printing as a method for manufacturing medicine & healthcare product. 3D printing helps in the manufacturing of medications with continued research. Drug manufacturing and distribution is a costly process in the pharmaceutical industry. 3D printing tablet production is done within the clinic, local pharmacies or even in the patient home.[52,53]

Personalized medicines for which 3D printing technologies could find huge interest, is based on the biomolecules, which is more sensitive (e.g. solvent, temp, agitation) than familiar chemical entities. Personalized medicine will be a new option in the pharmaceutical field. It will reach new levels of possibility & pharmacist will be trained for this particular application of 3D printing. Most common medication become available in this way, patient will be able to reduce their medication load to one polypill per day, which will produce patient compliance.[54]

3D printing technologies can make changes in pharmacy practice by allowing individualized medication and tailored specifically to each patient, although technical and regulatory hurdles remain. However, freeform fabrication methods are generally associated with 3D printing.[55,56]In the area of biomanufacturing, these processes are mostly in use. The main agenda of discussion was to discuss the various methods possibly applicable in pharmaceutics.

These are progressive and fast growing techniques that can be used in 3D printing for customized drug delivery systems. 3D printing approach was used

to prepare the tablet firstly by Aprecia Pharmaceuticals in 2015 and accepted with FDA. 3D printing technique with ultraviolet (UV) curing was and is used by GlaxoSmithKline to formulate tablet for treatment of Parkinson's disease. They have the capability to change the pharmaceutical industry.[57,58,59]

In near future 3D printing approach will be utilized in many ways such as in fabrication 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.

CHALLENGES IN 3D PRINTING TECHNOLOGY

3D printing technology showed promising and efficient results in drug delivery applications, the technology is still under the developing stage. Hence it undergoes and faces many 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 an 3D printed products and to expand the application range in novel drug delivery systems.[60] 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.[61,62,63]

CONCLUSION

3D printing has become a useful for the pharmaceutical sector, leading to personalized medicine focuses on the patient's needs and effectiveness. 3D Printing technology is emerging as a new horizon for advanced drug delivery with built-in flexibility that is well suited for personalized/customized medication. 3D Printing technology will change or modify the pharmaceutical manufacturing style and formulation techniques.

However, to ensure that 3D printed medicines have the same efficacy, safety, and stability as the pharmaceuticals that are manufactured by the Pharmaceutical Industry there have been a significant barrier. Regarding the establishment of guidelines, laws, quality systems and safety as well as use and consumption of 3D printed medicines, it is a great challenge for the regulatory authorities entailing great obstacles, given the traditional requirements by the pharmaceutical sector. The FDA guidance entitled "Technical Considerations for Additive Manufactured Devices" provides the FDA's initial thinking on technical considerations associated with the processes, and recommendations for testing and findings for devices that include at least one additive manufacturing invention step.

In the near future 3D printing approach will be utilized to fabricate and engineer various novel dosage forms. Although commercial production of such novel dosage forms is still challenging; developing personalized medication, optimized drug release from dosage form, compacting or avoiding drug-drug incompatibilities, protection of biomolecules during manufacture, construction of multiple drug dosage form and multiple release dosage forms will be taken to a new era through 3D printing technology. The significance of 3D Printing technology in pharmaceutical sector is rising predictably.

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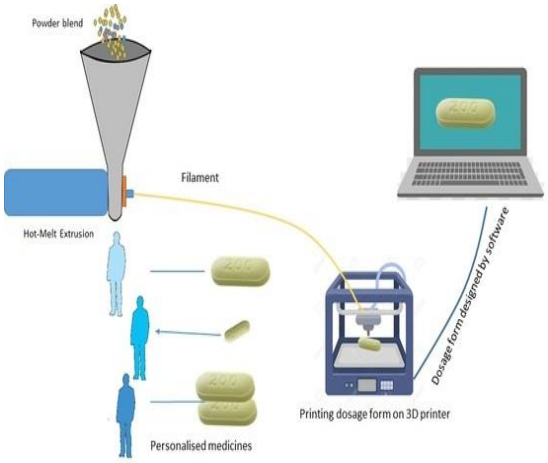

Fig1: 3D printing with Hot Melt Extrusion for Drug Delivery Systems

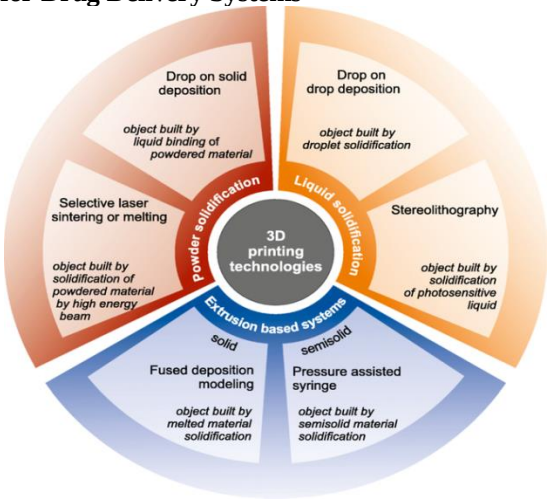

Fig 2: 3D Printing Technologies

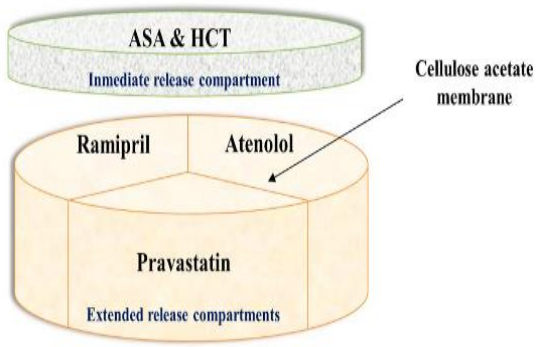

Fig 3: 3D Printed polypill

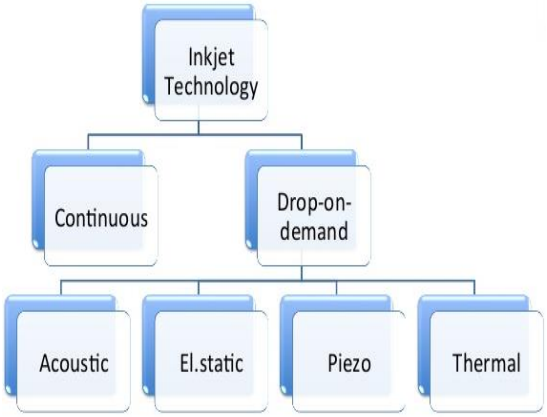

Fig 4: Types of Inkjet Technology

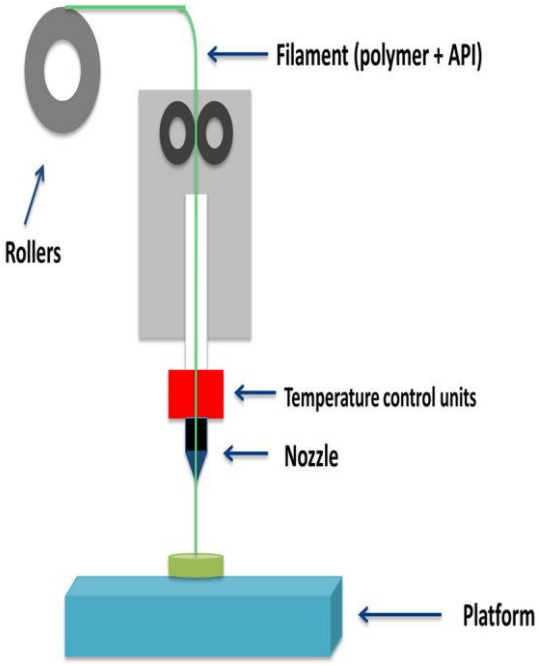

Fig 5: Fused Deposition Modelling (FDM) Printing Systems