BioChemMed

Technium BioChemMed Vol. 3, Issue 2 pp.1-14 (2022)
ISSN: 2734-7990
www.techniumscience.com

Types of 3D Printers Applied in Industrial Pharmacy and Drug Delivery: *Review Article*

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Abstract. The promising technology depend on using 3D printers' machines (3DPs) might be considered a modern approach in drug industry and delivery. A 3D printer may define as a machine which fabricates 3D models or products using computer aided design (CAD) software programs. These printers can create a single copy of an item that is too complicated and very difficult to produce by using traditional manufacturing methods. Moreover, it has ability to make products with complex internal structure geometries with lower cost and time. Recently, 3D printers have been involved into printing bio-products, custom pills and organs for transplant. This review presents the types of 3DPs suitable for drug industry and delivery. There are several types of 3DPs are used in pharmaceutical fields including inkjet (IK) printers, fused filament (FF) type printers, extrusion and hot melt extrusion 3D printing, sintering by selective kind of laser (SLS), Stereolithography (SLA), melting by micro selective laser (SLM), binder applied jetting printing (BJ) and the laminated object engineering manufacturing (LOM).

Keyword: 3D printers, Pharmacy, Drug delivery, manufacture.a

Introduction

The 3D printer can be acquainted as kind of general-purpose machines which fabricate 3D geometry models or parts of devices and components via an additive manufacturing (AM) process after design it using (CAD) computer aided design software programs. It can generate a single copy of an item that is too expensive and difficult with traditional manufacturing[1]. 3D printing technologies can provide several advantages such as customizability and the capability to produce complex design of solid dosage forms with excellent precision and precision. 3DPs can formulate solid dosage forms with amendable diffusivities and densities containing various drugs and excipients. 3DPs can efficaciously overcome the problems concerning to the drug delivery of poor water-soluble drugs, peptides, delivery of robust drugs and the numerous release of multi-drugs. However, there are a number of issues that obstacle the uses of 3DPs in commercial sector, like the selections of best suitable excipients, binders and the pharma co-technical properties of the final desired products. Moreover, its use can improve the product complexity and introduce a complex pharmaceutical product: multilayered tablets or tablet within a tablet, osmotic dosage forms, multilayered systems, multi-particulate

system and others. Furthermore, various applications in pharmaceutical industry such as manufacturing of modified drug released dosage forms, oral dissolving tablet (ODT) containing high dosage of drugs, amorphous dispersions can be manufactured by hot melt extrusion and delivery of very low dose drugs (as low as 3 ng) [2].

Topical delivery systems can be also manufactured by 3DPs; niosomal hydrogel is an effective topical drug delivery system which showed a slight irritation in acne treatment. Niosomal hydrogel 3D printed and loaded with cryptotanshinone were prepared and sized below 150 nm with an entrapment efficiency ranged 67 and 71%. The loaded niosomes were added into the hydrogel which was then printed with specific drug dose, shape, and size using an extrusion-based 3D printer. The *in-vitro* release behavior of printed product was found to follow the Korsmeyer-Peppas model. Permeation and deposition studies showed significantly higher rates of transdermal flux and deposition. *In-vivo* anti-acne activity of 3D printed niosomal exhibited a greater anti-acne effect with no skin irritation. Enhanced skin hydration, wide inter-corneocyte gaps in the stratum corneum and a disturbed lipid arrangement may contribute towards the enhanced penetration properties of loaded drug[3]. Cooperatively, this study demonstrated that 3D printed niosomal products can be considered a promising drug delivery system in comparison with other conventional topical niosomal products[4,5] .

This review article aims highlight the most popular types of 3DPs and their applications in drug delivery and industrial pharmacy.

1-Fused Filament (FF)

The Fused Filament FF (also named Fused Deposition Modeling FDM) is a method in which a thermoplastic filament that was molten is extruded via a heightedtemperature outlet or narrow nozzle and deposited layer-over-layer with fast solidification onto a form plate[6]. In this modern technique, pinch system and torque drives particular quantities of thermoplastic polymer thin filament into the liquefier plate or heater. The liquefier block temperature is fixed depend on the kind of filament and its melting temperature point and glass transition temperature. Hence, the melted filament is extruded via a heated nozzle and then solidifies onto the deposit on the buildup plate. The polymer flow is controlled by nozzle and the extruded material diameter depends on its orifice diameter. There is possibility to have one nozzle or more to print an item using fused filament. A couple polymers or more with various medicines can be printed at same time to manufacture drug delivery systems with multiple medicines. The thickness, degree of angle and gap size between layers are variables in the software of the3D printer. A simplistic illustration of FF is manifested in Schematic figure (1) [7]. Fused filament consider the most often applied 3D printing technique[8]. Currently, there is no FF printer has been specially designed for medicinal and pharmaceutical applications[9]. However, FF has been recently used for production of tablets and implants from filaments created by hot liquefy extrusion of numerous drug-polymer mixtures[10]. In addition, FF showed progress in the pharmaceutical industry because of the lower cost of printers and satisfactory of quality[11]. Moreover, many advantages can be obtained from FF printing technologies, such as manufacturing of different dosage forms such as capsules or tablets with perfect accuracy as well as several devices with quick and organized drug release properties[12].

Several polymers types have been enrolled for the production of platforms and implants however; few polymers are used for systems of drug delivery. The poly (lactic acid) (PLA),

ethylene vinyl and poly (vinyl alcohol) (PVA), acetate (EVA) polycaprolactone (PCL), acrylonitrile butadiene styrene (ABS), poly (methylmethacrylate (PMMA) are the commonly used polymers in FF printing. However, rheology and heat transfer characteristics of filament are the most significant criteria for selected materials which using in this type. Consequently, FF printing recorded some limitations such as lack of suitable polymers, slow and uncompleted drug release.

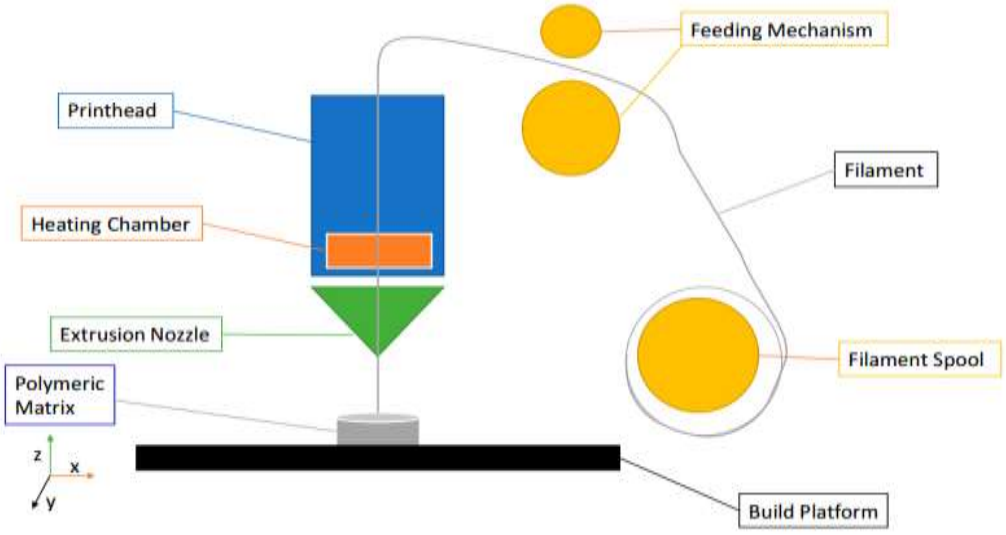

Figure (1): The fused filament cited from [7]

Control of printing variables offers interesting features to 3D printed products of drug. As projected, accuracy in dosage personalization which is one of important advantage of FF printing modern technology, as in the state of warfarin tablets. These tablets were printed in doses administered to rats, excluding the requirement to split tablets, as usually occurred during the treatments with this drug. Additional study projected to formulate floating sustained release tablets of domperidone (DM). DM is an insoluble weak base, can be studied to examine the potential of 3D printing floating tablets in improving of DM bioavailability and reducing frequency of dosing. DM was loaded into hydroxypropyl cellulose thin filaments by 3D-FF printing. The thin filaments were then printed into small hollow structured tablets which were capable to float *in-vitro* for around ten hours and high relative bioavailability compared with commercial tablets[13]. Other solid dosage forms called polypills of nifedipine, captopril and glipizide were produced by using extrusion 3D printing. Polypills contain osmotic pump of captopril and other separated compartments containing nifedipine and glipizide of sustained release profile. After taking polypill, the polypill is splited into a captopril pump and sustained released compartment because of degradation of the linking layers between them. Polypill can be containing five drugs which are difficult to be formulated by conventional methods [14-16]

2. Stereolithography (SLA):

Stereolithography (SLA) is a vat polymerization technique. The principle steps SLA processes can be described as an ultraviolet (UV) light applied over layers of the fluid in a

container with selectively solidification. The UV light and upper irradiations react with a photo initiator molecule (PI) in the prepared resin. The chemical polymerization reaction is a locally stimulant acting, just in the open space. Following the improving the first made layer in that method, a fresh prepared resin superfine film is applied carefully [17]. Consequently, the item incrementally cultivates layer-over -layer. This technique can be categorized according to the irradiation method or incident light ray direction. In order to obtain the resin solidification, the UV applied in 2 methods; either through below via a diaphanous color vat in the controlled worked surface approach or through overhead in the free surface approach. Irradiation technology can be applied by prominent the full pixelated drawing onto the thin layer in digital light ray processing (DLP) - SLA or via scan processing of every small point of the selected cross-section by a laser beam in laser-SLA. This method utilizes a light-sensitive polymer solution. A chemical reaction named gelation occurs once the compounds are exposed to project DLP or UV[18,19]. During production, the device will emit the light in a desired pattern leading to gelation of the polymers as per the customary design. Before the first layer is printed a supporting structure is required to hold the product. After the first layer exposed to lights, it will solidify fast so the next layer can be attached and bonded on to the surface. After the printing is conducted, extra liquid materials and the supporting skeleton are removed. However, the SLA is considered as slow printing [20]. The current investigations recorded that the polymerization of photo-curable polymers can yield many dosage forms up to 28 in a single print cycle[21]. Platforms loaded with acetylsalicylic acid can be obtained by micro-SLA based on diode laser curing[22].

In addition, a micro manufacture for polymer micro size needles centered stereo SLA that can produce micro-needles using polymers. However, polymerization time, light intensity and chemical configuration of the resins had a significant effect on the construction speed and the engineering precision of the micro needles which have been investigated. Consequently, the diameter and the length of the micro needle are précised up on these factors. The tip diameter and length of micro needles were restrained to be between 520 μm and 40 μm, respectively[23]. For oral administration, micro-reservoir devices containing polymers with sizes about 300μm can control drug release. This micro-reservoir assembly has been made-up with simple shapes by SLA [24].

3. Selective laser sintering (SLS)

Like to SLA, this technique acts by lasers beam. The powder is disseminated in form of a thin thickness layer on a platform inside chamber. The laser moves a cross-section designed of the 3D geometry model with rise the temperature of the powder to just lower or exact the degree of melting degree point of the powdered material. The materials particles fused together by mechanical way to form single solid part. The unused powder back up the part in printing span and removes the need for devoted support structures. The build work platform let down by single layer into the working chamber, usually from 50 to 200 microns, and a re-coater applies a new one powder layer on the top. Then, the laser starts to scan the following cross-section of the shape. This procedure replications for each single layer until geometry is completed, and the completed part left-hand to make cool down progressively inside the device. After parts have been cooled, the worker take away the build chamber from the laser printer and carries it to a cleaning place, separating the printed parts and removing of the extra powder [25]. Although there are many advantages of this method including precision and high resolution, fast production, no need for supporting structures and greatly controllable internal microstructures, there are several drawbacks such as, it is expensive cost, post-processing

required, high energy input causing degradation of drug and excipients and wastage of un-sintered powder(recycling).

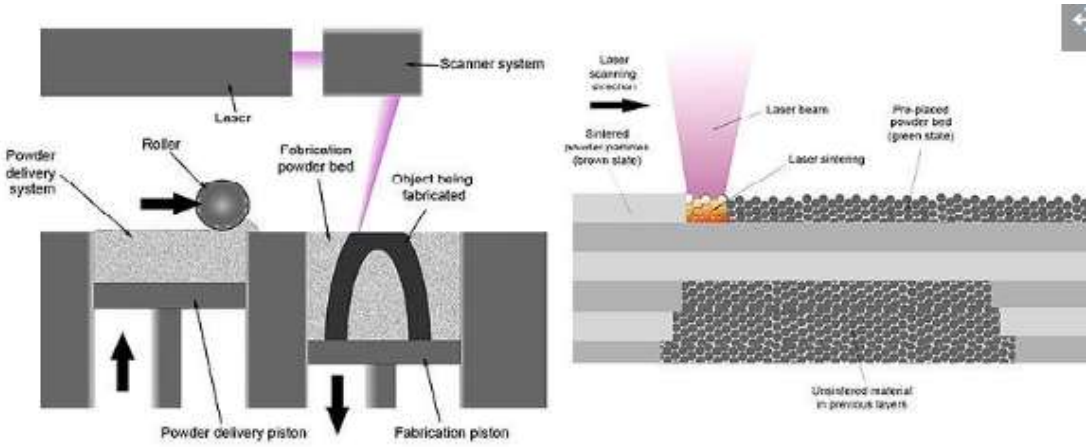

Figure (2): Selective Laser Sintering process (Image credit: Materialgeeza/Creative)

SLS applied in anticancer delivery systems. Polycaprolactone/fluorouracil implantable tablets were manufactured by SLS using different laser power levels. Initially, tablets provided a fast release of a great concentration of the drug at the specific site of cancer and following by controlled release [26].

4. Digital light processing (DLP):

Digital light ray processing (DLP)-that based technology 3D printing using projected light in order to polymerize specific materials to get the required product. This equipment has shown important benefits in increase of printing efficiency, resolution, and providing better features to the products. However, it has some disadvantages such as requirement of certain supporting structures, restrictive material selection, potential material toxicity, needs post-processing and it is costly equipment. DLP is depending on an optical semiconductor named a Digital Micro Mirror Device (DMD), the image is obtained from reflected light by using aluminum mirrors. The DMD is frequently indicated to as the DLP chip. This chip may have more than two million mirrors each, sizing less than 15 μm. These mirrors are designed in a matrix similar a photo mosaic that each mirror representing one pixel each part of it holds a very tiny, square photograph. One large image is created by blend the images together when its step away from the mosaic. The screen depends on the number of mirrors[27]. Moreover, repeatability and resolution of 3D printing processes can be influenced by several factors including the hardware, software, and material used [28]. DLP 1080p technique supplies more than two million pixels for factual 1920x1080p clear resolution that is broadly available[29]. The medical geometries have mechanical and physical properties with good shape. The printing development without great pressure, temperature, and high shear stress is produced by the small nozzle that made to be suitable for production living tissues with small cell damage. DLP technology allows fast printing in comparison with the laser-assisting 3D printing, which light spot by restricted onto the item. In this method a light is applied onto the precise resin thereby the entire layer is printed immediately. Materials used for DLP printing are types of polymers that convert from liquid state into solid form when a light is applied onto photosensitive liquid lead to polymerize to solid state. However, the chemical and physical properties of photosensitive materials

restricted their applications, and the majority of them are discordant and their monomers emitted unsafe vapors. Therefore, investigators have manifold the materials utilized for DLP-3D printing and they started to use PEGDA and GelMA inks because the biocompatibility and good polymerization effect for bio printing[30] .

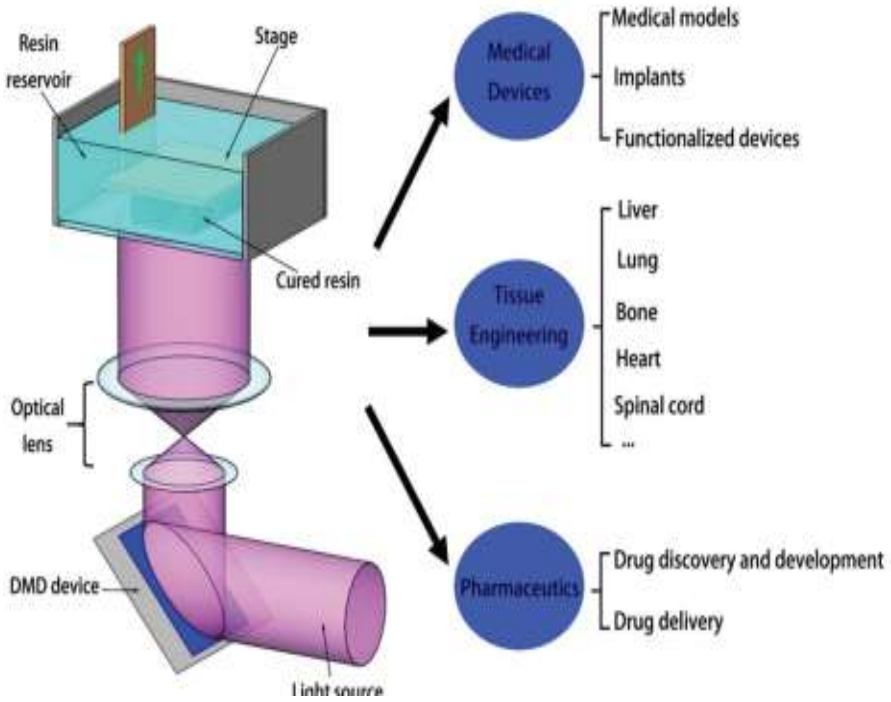

Figure (3) : Schematic diagram demonstration the principle of working and some application related to, DLP based 3D printing technique [30]

In previous study, DLP-3D printers were applied in production of oral dosage forms. A digital micro-mirror modern device was used that accurately reflects and strong focuses ultraviolet (UV) ray light on the operated surfaces of photoreactive that polymerize in a layer-after -layer fashion. Poly (ethylene glycol) dimethacrylate (PEGDMA) and Poly (ethylene glycol) diacrylate (PEGDA) were used as photoreactive polymers and 1% loaded theophylline as a new model designed drug to formulate as tablets dosage forms. The printed tablets with adequate mechanical strength, weight variation, swellability, microscopic brow and drug release profiles were produced after adjusting UV intensity, exposure time, concentration of materials and layer thickness. Inclusive, this validates that DLP-3DP can be utilize as a platform for formulating oral tablets in various shapes forms and release profiles[31].

5- Micro selective laser melting

Micro selective laser melting (SLM) systems work depend on using powder of particle sizes from 20 to50 µm and a thickness of layer between 20 and100 µm. The resolution of SLM was influenced by factors include: particle size, diameter of laser beams and thickness of layer. The micro-scale SLM can be distinguished as a particle size < 10 µm, a layer thickness< 10 µm, a laser beam diameter < 40 µm [32].

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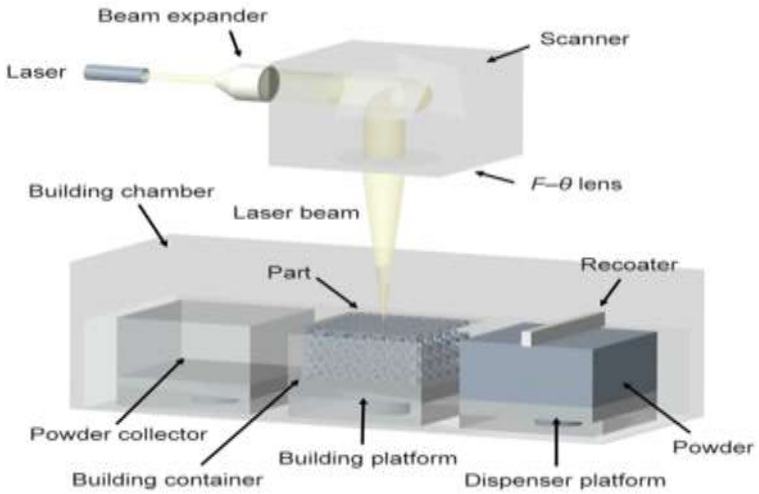

Figure (4): Schematic of the SLM process from [32]

In previous studies, SLM was used to manufacture and study samples, with complex internal pools and discharging micro-channels to act as an orthopedic surgery or dental implant. To improve the design and SLM considerations needed to release of micro-channels with lowest dimensional deviation to obtain a control of drug doses. Vertically channels had the smallest dimensional deviation from the impartial dimensions compared with horizontally-oriented networks. In addition, there was relationship between the density of energy with both roughness of horizontal surface and dimensional deviation, while no relation in case of the roughness of vertical surface. The study established the ideal conditions to design drug delivering implants containing hollow samples and releasing micro-channels equivalent diameter of ~271 μm, vertical surface roughness of(9.2 μm) , horizontal surface roughness (4.4 μm) and porosity 1.4% utilizing an internal contour (150 μm) and energy density (35.7 J/mm) [33].

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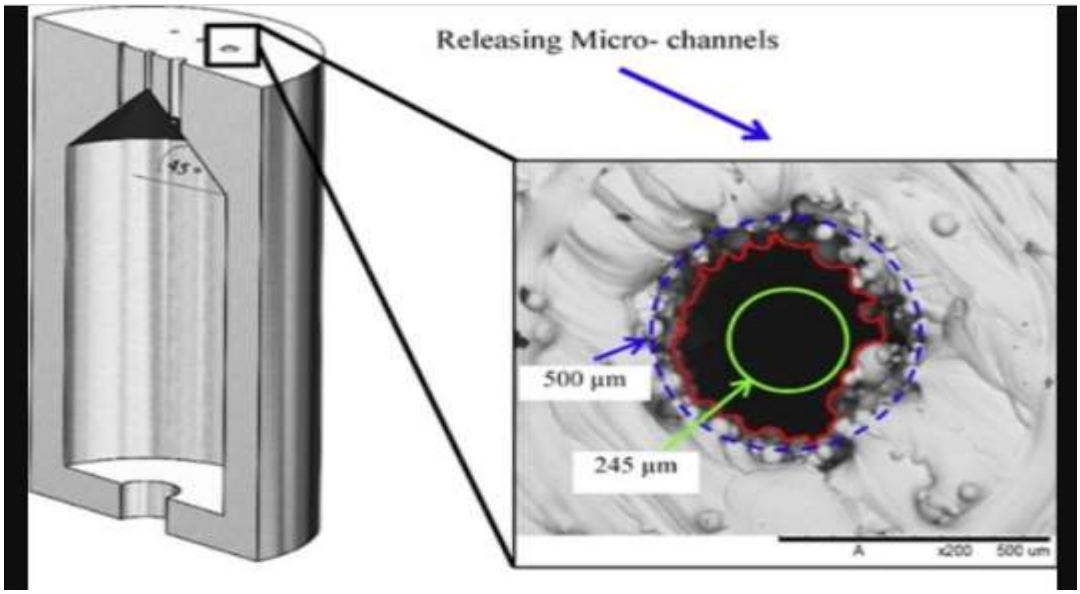

Figure (5): Micro-channels and internal reservoirs, designed by SLM [33]

6-Electronic beam melting (EBM)

Melting electronic beam (EBM) is approximately similar to the SLM process, that mechanism is depend on layer-by-layer technology[34]. An electron beam is involved in the fusion and melting of the powder particles instead of the laser beams in SLM. The powder bed is heated at high temperatures (>565° C) and long cooling periods are needed to reduce the temperature of powder bed after the finish of the build stage[35]. The EBM includes process parameters: beam scanning, beam diameter, beam focus, beam line spacing, beam power, velocity, plate heating, pre-heat temperature (including speed, power, and the number of the beam repetitions), scan strategy and contour strategies [36]. The process is slow and expensive. Moreover, limitations are in terms of the size of the objects in a structure frame /honeycomb, bigger in size than the designed substrate plate can be produced. However, the size of an initial layers of object should be a smaller than the substrate plate size. The EBM process occur in a vacuum atmosphere. Therefore, the parts' oxidation is generally obviated[37]. Additionally, if there is an adsorbed gas on the surface of powder will not cause the porosity creation in the EBM process.

However, it is unsuitable to develop alloys that have volatile elements such as Bi, Zn and Mg. In the EBM process, the cooling rate of the EBM process can be decreased extremely by increasing the powder bed temperature. In general, the hot bed temperature is around 560° C during the EBM process and the whole chamber becomes in high temperature after the building process that it may seriously require cooling period before the items can be pick up from the substrate plate[38].

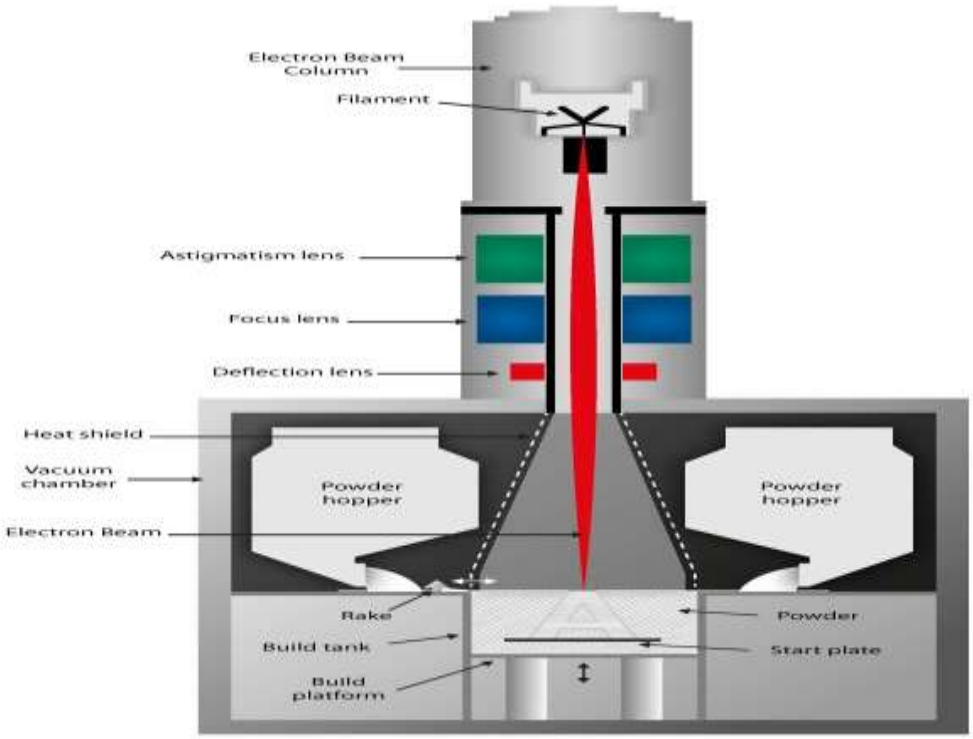

Figure (5): EBM process [39]

7- Binder Jetting

Binder jetting 3D Printing (BJ-3DP) was established by the innovators Ely Sachs and Mike Cima at the Massachusetts Institute of Technology in 1993 and both got an special license for the process in 1995[40]. In this technology (also called powder bed inkjet technique of printing), thin powder layers are distributed layer-over -layer, either by a powder jetting reservoir (powder jetting system), or by roller (powder layering system) then the layer. The first layer is made on the build surface platform after that piston moves down to the specific thickness of the next layer, then subsequent layers are made and merged together. The process is frequent numerous times till the pre-determined 3D object is created. The process sometimes requires improvement in the physical and mechanical reliability of the product and extra drying stages to remove the residual moisture. BJ -3DP permits switch over micro- and macrostructure of the parts allowing the manufacture of complex and very porous structures[42]. The significant parameters of BJ-3D printing are the diameter of nozzle, printing speed, droplet spacing, the frequency and velocity of the droplets. The mechanical strength of the product is effected significantly by the concentration of the binder[40]. The binder spreading and finally the porosity and strength are significantly affected by the droplet size of the binder[43].

Indomethacin as drug has been printed by binder jet in which powders are repetitively spread onto a form plate, and then inkjet a binder as a liquid to bind the powders in a prepared design. The pharmaceutical- powders physical properties and binders have been evaluated and a molding technique has been industrialized to choice suitable binder and powder for printing[44].
In material jetting (MJ) technology, the object is made by jetting thin layers of liquid photopolymer via a nozzle that moves horizontally over the build platform. Following the

3D design pattern the drops of material are deposited and an ultraviolet lamp moves over the objective directly and solidify the polymer. After the first layer is made, the platform goes down, and following layers are built on the previous one, forming the 3D object[45]. The most popular methods of make up the material jetting:

7.1. Drop On Demand (DOD): material jetting printer has dual print jets: one for deposit the build raw material and another for jet a dissolvable selected support material. The DOD printers work depend on a pre-designed track and deposit selected material in a point-wise fashion to form the specific cross sectional zone of a part. These printers use a fly-cutter that skims the build worked area after each layer in order to ensure an exactly flat and smooth surface before make the next layer. DOD equipment is usually used to create wax-like patterns for lost-wax casting/investment casting and mold making applications, production it an indirect 3D printing technique.

7. 2. Poly Jet by Objet: In this technique, the photopolymer can be selected and jetted in very thin layers onto a build mold in a similar approach compared to inkjet printing. Each type of photopolymer layer is treated by UV light directly after the existence [46]. The repetition of jetting phases, layer by layer creates completely cured paradigm that can be picked up and utilize directly. The gel used as support material, that is particularly designed to support complex design geometries.

7. 3 Nano- Particle Jetting (NPJ) by X Jet: This kind of material jetting technology, innovated by X Jet, uses a specific liquid, that has support nanoparticles or building nanoparticles, which is added into the printer as a cartridge and then jetted onto the build die in very ultra-layers of droplets. High degree of temperatures inside the build tray cause the molten to start evaporate leaving parts which fabricated from the building process.

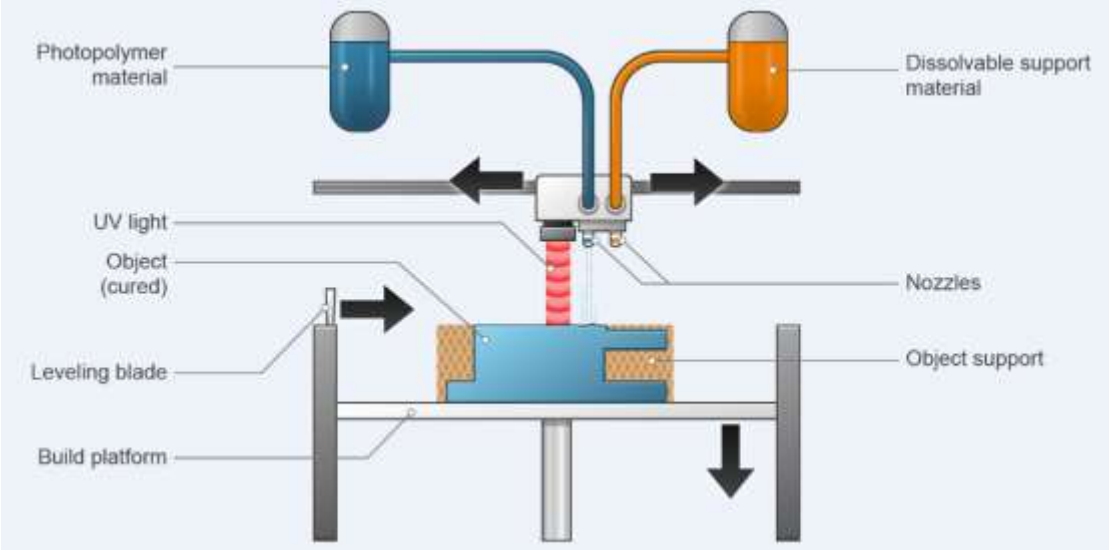

Figure (6): MJ printer cited from https://make.3dexperience.3ds.com/processes/material-jetting

8 . Laminated Object Manufacturing (LOM)

Manufacturing by laminated Object is used generally not for production but, for processes of rapid prototyping, it is a so fast and low-cost way to 3D print items in numerous kinds of materials. Material Sheets are bonded carefully together and precision cut in the exact

geometry according to the 3D model that sent from CAD software. Layers of plastic, adhesive-coated paper, or metal laminates are attached together and cut exactly to shape with a laser cutter or knife. A new layer is bonded to the earlier cut layer and a new one of cross section is created and also cut as done before. After that all layers have been laminated and cut, and excess material is detached to obtain the required finished model[47].
Items printed with this method may be furthermore modified by drilling or machining after printing. Usually resolution of layer for this process is determined by the feedstock of material and normally varieties in thickness from only one to small number of sheets of copy papel.

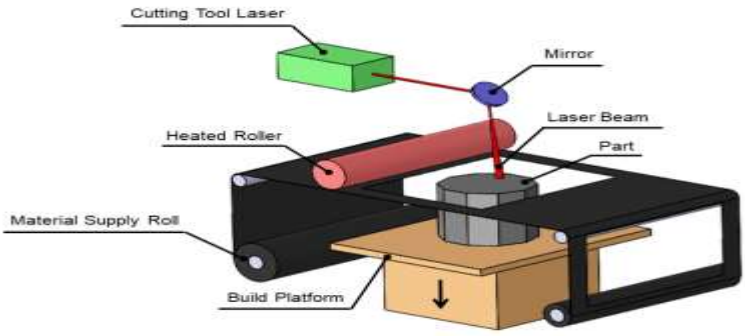

Figure (6): Laminated Object Manufacturing (LOM)[48].

9- Inkjet 3D printers

Inkjet (IK) includes two sorts, continuous inkjet 3DPs and drop-on-demand printing (DD). Continuous type generates a continuous thin ink stream over an orifice sized 50–80 µm diameter, by using a great pressure pump, whereas, DD type yields droplets (10–50) µm. Both categories hold a printer head and necessity to control the size, speed, and intermission of drop formations forms and viscosity [49]. Multi-layered drug delivery products can be formulated with retardant materials to obtain prolong and linear release such as acetaminophen, ethyl cellulose and hydroxypropyl methylcellulose[50]

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