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Review on Applications of 3D Printing in Pharmaceuticals

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ABSTRACT:Three-dimensional (3D) printing is a revolutionary technology that uses computer-aided design software and programming to create three-dimensional objects by placing material on a substrate. Three-dimensional printing technologies is a new quick prototyping method in which solid objects are constructed by depositing several layers in sequence. It becomes one of the most innovatory and influential tools serving as a technology of precise manufacturing of developed dosage forms, tissue engineering, and disease modeling. 3D printing is an additive layer manufacturing technique, where consecutive layers of material are deposited or solidified to form a 3D structure. Medicinal substances are configured in three-dimensional with computer-assisted design module and transformed to a machine legible form which suggests the exterior emerge of the 3D dose form, then it sliced this surface into several different printable coats and convey these layers to the machine. Different 3D printing techniques have been developed and developed to fabricate novel solid dosage forms, which are among the most well-known and discrete products today. The 3D printing process desires to be espoused by the pharmaceutical sector and capable of exploring the marvels fetched by the approach. 3D printing can include very new possibilities to optimize medicine. The current review is an effort of briefing various methods (Thermal Inkjet printing, Inkjet printing, Fused deposition modeling, Extrusion 3D Printing, Zip dose, Hot melt extrusion, 3D printer, Stereolithography, Selective laser sintering, Laser-Based Writing System, Continuous Layer Interface Production, Powder Based 3D Printing), advantages, limitations, Principal of 3D printing, history, methods of 3D printing, materials of 3D printing, applications of 3D printing in pharmaceutical technology, challenges, risk assessment, prospect and patents of 3D printing.

KEYWORDS: 3D printing Technology, Manufacturing Process, Application, Challenges, Patent

I. INTRODUCTION:

3D printing, also known as additive manufacturing, is a method of creating a three-dimensional object layer by layer using computer design. Nowadays three-Dimensional printing is one of the fastest developing branches of technology, art, and science, and still broadens the applications. ISO defined 3D technology as the fabrication of objects through the deposition of a material using a print head, nozzle, or another printer technology. In this technique, 3D models are used for preparing the parts in the process of joining materials layer by layer. In a novel drug delivery system, 3D printing is used for viable tablet production. These tablets are manufactured in such away that they are capable of satisfying regulatory tests and matching the standard of the commercial tablet.[1]

3D printing plays an important role in multiple active Ingredient dosage forms, where the formulation can be a single blend or multi-layer printed tablets having a sustained release property. 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. 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 that 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 medical care. When compared to the manufacturing process of conventional pharmaceutical products, ithas 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 a drug with narrow therapeutic

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windows. 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 models are used for preparing the parts in the process of joining materials layer by layer. In a novel drug delivery system, 3D printing is used for viable tablet production. These tablets are manufactured in such a way that is capable of satisfying regulatory tests and matching the standards of commercial.[2]

Three-Dimensional Printing technology is a novel technique for rapid prototyping, which constructs solid objects by deposition of several layers in sequence. The introduction and application of 3D printing have promoted enormous innovations in many diverse fields, including the aerospace industry, architecture, tissue engineer, biomedical research, and pharmacy. It seemsthat3Dprintingtechnology will lead to a new approach to the next industrial revolution based on its versatility and diversity. Along with development and progress in science and technology, 3D printing technology gets mature enough so that anyone can apply it with open-source software at a relatively lower material cost. 3D printing technology has enabled unprecedented flexibility in the design and manufacturing of complex objects, which can be utilized in personalized and programmable medicine [10]. When compared to the manufacturing process of conventional pharmaceutical product, it has a lot of advantages like**Advantages**

1. Accurate and precise dosing of potent drugs which are administered at small doses.

2. Reduces the cost of production due to lesser material wastage.

3.Narrow therapeutic window.

4. Medication can be tailored to a patient in particular based on genetic variations, ethnic differences, age, gender, and environment.

5. High drug loading ability when compared to conventional dosage forms.

6. In the case of multi-drug therapy with multiple dosing regimens, treatment can be customized to improve patient adherence.

7.Suitable drug delivery for difficult to formulate active ingredients like poor water solubility.

8. Different materials can be used in the 3D models. It makes it very easy to create construction models or prototypes for a wide variety of projects within many industries.

9. The products with an excellent surface finish are produced.

10. High drug loading ability when compared to conventional dosage for

11. Due to lesser material cost of production reduces.[3, 11]

Disadvantages

1. The 3D printing technology is currently limited by size limitations. Very large objects are still not possible when built using 3D printers.

2. The cost of buying a 3D printer still does not make its purchase by the average householder possible. Different 3D printers are required to print different types of objects and the printers that can manufacture in colorare costlier than thosethat print monochrome objects.

3. As with all new technologies, manufacturing jobs will decrease. This disadvantage can have a large impact on the economies of third world countries especially China, which depend on a large number of low-skill jobs.

4. At present, 3D printers can work with approximately 100 different raw materials but it is not suitable when we compared with the enormous range of raw materials used in traditional manufacturing. More research is required to devise methods to enable 3Dprinted products to be more durable and robust.[1]

Limitations

- Nozzle problems are a major challenge as discontinuing the print head affects the structure of final products.
- Powder printing blocking is another obstacle.
- Probability of altering the finishing structure on to mechanical stress, storage condition adaptions, and the effects of ink formulations.
- Printer-related parameters and these effects on printing quality and printer cost [13].

Optimization of the process, improving the performance of the device for versatile use, selections of appropriate excipients, post-treatment method, need to be addressed to improve the 3D printed products performance and to expand the application range in novel drug delivery systems are the most challenges in the application of 3 D printing. Few 3D printing techniques may produce relatively porous structures and uneven shapes of dosage forms. For example, when the fused deposition modeling technique is utilized, the use of only thermo-stable drugs and the few available compatible excipients is a regulating step. Also, with stereolithography, the challenge lies in the possible drug degradation due to the exposure of materials to UV light that induces polymerization reactions [14].

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In terms of technological hurdles, and comparison, to traditional manufacturing methods, the major shortcoming of all 3D printing methods is its yield of production. While a conventional tableting process can produce more than 15 000 tablets per minute using one press, the production time for 3D printing can vary from an average of 2 min up to 2 h (depending on the process used) to produce just one tablet. Even though this limitation may hinder industrial production, one can argue that the greatest strength of 3D-printed pharmaceutical products is the possibility of bringing production closer to the patient, which means printing on a small scale locally in pharmacies or hospitals. Other general problems that may arise in most 3D printing methods include the variability in layer thickness, the relatively limited material choices, as well as the presence of unreacted starting-material in the final formulation [15].

Principle of 3D printing

The principle behindhand a 3D printer can be expected to be parallel to a regular printer. The 3D printer consists of an extruder that moves horizontally on an axis which is held on top of two axes that allow it to move back and forward in an x-y plane to create the base of the object. These two axes are involved in the sides of the printer. The only alteration is the 3D printer has a base that moves vertically along the z-axis to create the layers over the object. Whereas printing the first layer the extruder remains at the top and moves only in 2D. The base that holds the substrate will decrease in height so that the next layer could be built upon it. The process is repeated following the computer-aided drafting instructions until the object is built layer by layer. This procedure is denoted as additive manufacturing, rapid prototyping (RP), or solid freeform technology. 3D printers are used to print various porous scaffolds with controlled chemistry, interconnected porosity, and special shapes. These prints are biodegradable and proved to be ideal for drug delivery abilities. Some of the highly complex structures incorporating living cells can be created by this technique and have gained popularity and applicability in cancer management. Dissimilar types of drug delivery systems such as oral controlled release systems, micro pills, microchips, drug implants, fast-dissolving tablets, and multiphase release dosage forms have been developed using 3DP technology [8].

Steps involved in a 3d printed dosage form

Three-dimensional printing involves three major steps.

a.Modelling **b.** Printing **c.** Finishing

(a) Modelling: Virtual blue print from computer-aided design.

(b) Printing: 3D printer read the design and lay down a successive layer of materials.

(c) Finishing: After printing the support are removed or dissolved to get the final product

1.Pharmaceutical product is designed in three dimensions with computer-aided design.

2. Design is converted to a machine-readable format that describes the external surface ofthe 3D dosage form.

3. The computer program then slices this surface into several distinct printable layers and transfers that layer-by-layer to the machine.[8].

History

Additive manufacturing fabricating methods of the 3D plastic model with photo hardening polymer was invented by Hideo Kodama of Nagoya Municipal Industrial Research Institute; here the UV exposure area is controlled by scanning fiber transmitter or mask pattern. In 1984, Check Hull of 3D systems corporation developed a prototype system based on a process as a system based on a process known as Stereo lithography. The team of the umbrella was gaining additive manufacturing and wider currency in the decade of the 2000s. This technique in the field of pharmaceutics was in practice by inkjet printing a binder solution was passed on the 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 ’90s at MIT (Massachuset InstituteTechnology). In 1989’s Scott Crump, a patent was filed on another 3D printing technology: fused deposition modeling, where 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 Sprit am (levetiracetam) tablets for oral use, the first 3D printed drug approved by the Food and Drug Administration (FDA) in 2016 by ApreciaPharmaceuticals. 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

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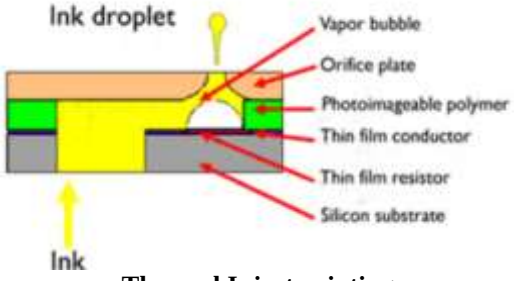
advanced manufacturing technologies, including 3D printing, using risk-based approaches. After the start of the 21st century, machines of 3D printing sale out very rapidly and their price has been dropped gradually.

II. METHODS OF 3D PRINTING:

3D printing includes a wide variety of manufacturing techniques, which are based on digitally – controlled depositing of material (layer by layer) to create freeform geometries. The widely used 3D printing technologies are as follows: -

1. Thermal inkjet printing.
2. Inkjet printing
3. Fused Deposition Modelling
4. Extrusion 3D printing
5. 3D printer
6. Hot Melt Extrusion (HME)
7. Powder bed 3D printing.
8. Stereo-lithographic 3D printing [4]
9. Selective laser sintering
10. Continuous layer interference production[3]
11. Three-Dimensional bio printing[9]
12. Digital light processing

1. Thermal Ink-Jet printing: In thermal inkjet printing, the aqueous ink fled is transformed to vapors state through heat, expands to push the ink drop out of a nozzle. It is used in the preparation of drug-loaded biodegradable microspheres, drug-loaded liposomes, patterning microelectrode arrays coating, loading drug-eluting stents. It is also an effective and applied method of generating films of biologics without negotiating protein activity. [4]



Thermal Inject printing

2.Inkjet printing

This approach to personalized medicine originates from the same technique of computer-operated inkjet printing. It was adapted for pharmaceutical application by the replacement of the ink with pharmaceutical solutions containing drugs and normal paper with edible sheets known as substrates. Dose alterations are done by altering the number of layers printed in a given area or changing the area to be printed. The drug and excipients are designed in a ratio such that it has the potential to print as microdots onto an edible substrate. The two main printing types employed under inkjet printing are thermal inkjet printers and piezoelectric inkjet printers.

Printing-based inkjet systems encompass two types of techniques: Continuous inkjet printing and Drop-on-demand printing. In continuous inkjet printing, the liquid ink is directed through an orifice of 50-80 am diameter creating a continuous ink flow. The liquid is caused to flow and break into drops at a specified speed and size at regular intervals using a piezoelectric crystal. These parameters are controlled by creating an electrostatic field. Thus, the droplets are charged and separated by "droplets of the guard" to minimize the electrostatic repulsion between them. The electrostatic field created directs the charged droplets to the substrate Inkjet drug printing offers a significant advantage of accurate control of dose combination and pattern of drug release. Ink jet printing requires the starting materials to possess certain characteristics mainly; particle size needs to be <1 µm to avoid clogging the printer head, viscosity needs to be < 20 cP, and surface tension between 30 and 70 nm/m for efficient flow.[2]

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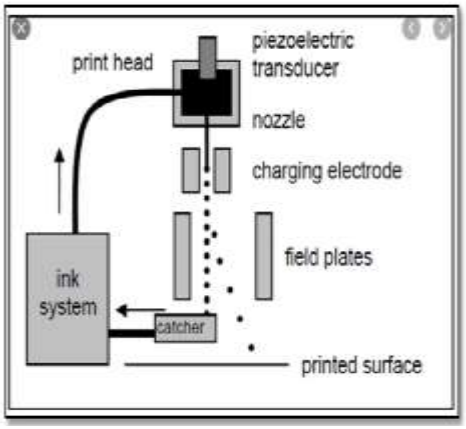


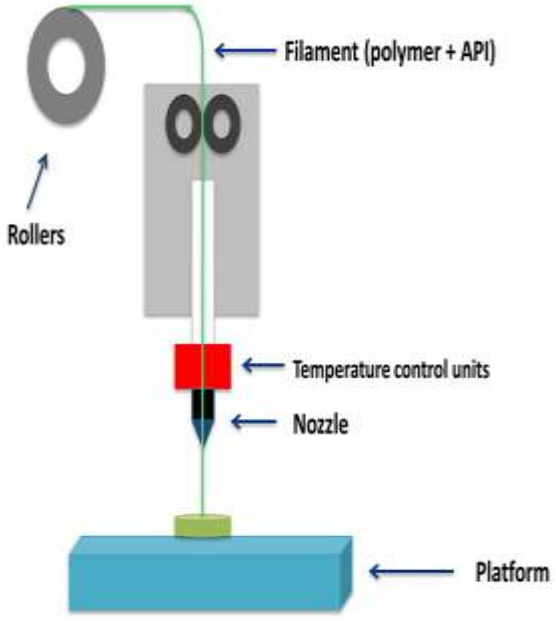
Inject Printing

3. FUSED DEPOSITION MODELLING

It is a commonly used technique in 3D printing, in which the materials are softened or melted by heat to create objects during printing. There are several dosage forms available by using FDM. 3D printing helps in manufacturing delayed-release print lets without an outer enteric coating, & also provides personalized dosed medicines.

Limitations – FDM 3D printing indicates several limitations of the system,

- Lack of suitable polymers
- Slow & often incomplete drug release because the drug remains trapped in the polymers & the miscibility of the drug & additives with the polymers used was not evaluate



Fused Deposition Modelling

4. Extrusion 3D Printing

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

5.3D PRINTER:

A 3D printer is a valuable tool that is used to create customized medication with tailored release profiles

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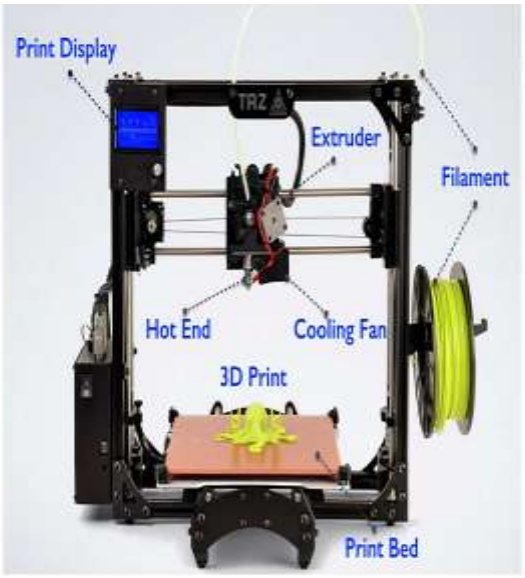
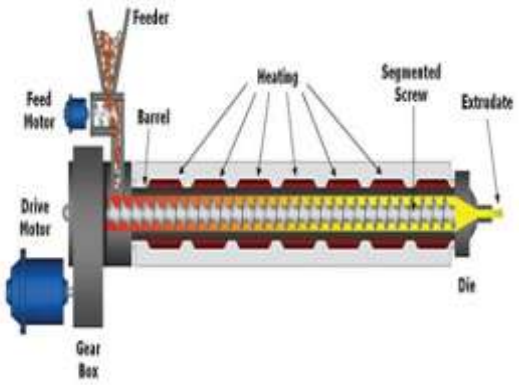
& the medication is changed as per the patient comfort



3D Printer

6. Hot-melt extrusion

Recently hot-melt extrusion (HME) was the main way of producing active pharmaceutical ingredient-loaded filaments. Drug amalgamation in the HME method involves pelletizing and grinding of commercially available filaments mixed with active ingredient(s) before a hot melt re-extrusion.The grinding process is important as it ensures that the API (powder) and polymer have similar particle sizes. Mixing pellets with drug powder would lead to poor encapsulation and subsequently poor drug loading [18].



Hot-melt extrusion techniques in 3Dprinting[32]

7.PowderBased 3D Printing:

This method customs powder jetting/powder bed to feast thin layers of powder and instantaneously apply liquid binder drops with inkjet printers. Th ink (binders and APIs or binder solutions) is sprinkled over a powder bed in a two-dimensional (2D) approach to make the decisive product in a layer-by-layer fashion. Th adaption of this approach into pharmaceutical manufacturing is at ease than other approaches as powder and binder solutions are broadly used in the pharmaceutical industry. The own disadvantages of this approach are; to remove solvent residues additional drying is required, during printing excess powder accumulates and contributes to wastage and due to the permeable designof the powder the drug delivery system's mechanical strength may poor.[3]

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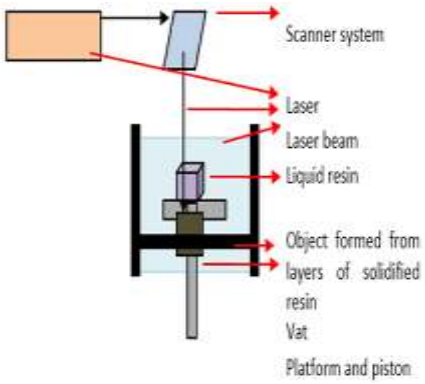
8. Stereo-Lithographic 3d Printing:

This technique involves the curing of photosensitive materials (photo polymerization to produce a 3D object. Scanning a focused UV laser over the top of a photopolymer sable liquid is a layer-by-layer fashion; SLA employs a digital mirroring device to initiate a chemical reaction in the photopolymer, which causes the gelation of the exposed area. This process is repeated layer after layer to build the entire part of the object. This occurs as unreacted functional groups on the solidified structure in the first layer polymerize with the illuminated resin in the next layer insuring adhesion & therefore, layer formation is done. Post printing processing is usually required to further curve the final product, to improve its mechanical integrity & to polish or remove the attached supports to the fabricated objects.

This technique however possesses a health hazard in the form of potential carcinogenic resins. This is also a very slow process. SLA printers are composed of a UV light beam, in the form of a laser, which transfers the energy into a liquid photopolymer sable resin. Baffles, axis X&Y, to transverse the surface of the liquid resin, to accurately represent the 3D model, previously designed, aid the UV light beam. When a layer solidifies, the lifting platform descends its position to the night of a new layer of a liquid resin, again beginning the procedure, until the manufacturing of the 3D product is finished in a layer-by-layer way.

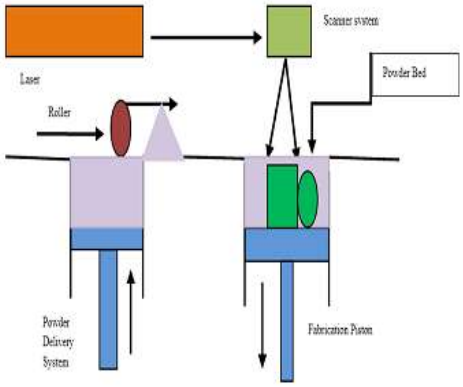
Here the thickness of the cured layers depends upon the energy of the UV light to which resin is exposed. The resin should be FDA approved for human use with the ability to solidify upon exposure to the laser beam.[4]



Stereo-Lithographic 3d Printing

9.Selective laser sintering (SLS)

Selective Laser Sinteringact as a way in the powder bed to bind. Th laser is designed to draw a specific pattern on the surface of the powdered bed during the printing process, thus creating a 3D structure. For example, Paracetamol is an Oro dispersible tablet prepared in this manner. It is currently used for industrial manufacturing of plastic, metallic and ceramic objects.



Selective laser sintering (SLS)

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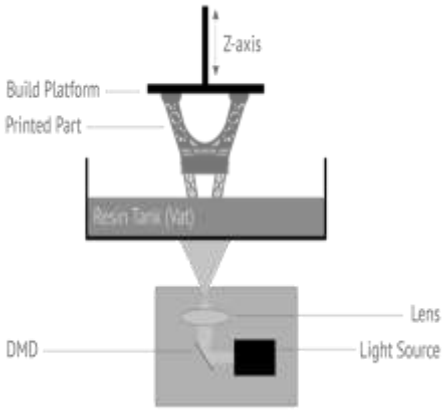
10.Continuous Layer Interface Production: It is an advancement in technology tothe speed of printing. But the method negotiates in the 3D structure manufacture through non-layer fashion. Th speed is amplified by the oxygen enclosing zone which assists and promises photo-polymerization. Inkjets print free-form structures that get hard drop-by-drop. Usually jetted materials are molten polymers, waxes, UV curable resins, and compound several component fluids. THz intact formulation desires to be formulated for jetting and rapid solidification.

11. Three-dimensional Bioprinting:
Three Dimensional bio printing includes all the variety of 3DP modes and is been is used in different pharmaceutical studies and tissue engineering .current treatment bone fracture and bone defects involve bone grafts or metal prosthetic implants which can be restrictive because of the substantial loss of tissue from surgery prolonged recovery periods and donor site morbidity, therefore, there is need for a novel method of treatment for bone fracture and defects [9]

12.Digital light processing (DLP)
In 1986 digital light processing is first described by Charles, a method that prints many layers by ultraviolet light to create 3D structures. The digital light processing technology is employing projection light to polymerize materials to obtain the predesigned structures. In comparison with other 3D printing methods, such as extrusion-based 3D printing methods and inkjet-based 3D printing methods, this method has significant compensations in printing resolution, efficiency, and working conditions. Hence, it can give many good features to the products [16,17]. Photopolymerization processes utilize liquid photo-curable resins, which undergo chemical reactions upon irradiation with light and fabricate solid objects, uses a projector to selectively expose and cure an entire cross-sectional slice of the photopolymerizable resin at each given time [19]



A schematic of a DLP 3D printer [16]

III. MATERIALS OF 3D PRINTING:

Polymers used in 3D printing for medical purposes:

1. Acrylonitrile Butadiene Styrene
One of the most widely used materials since the inception of 3D printing. This material is very durable, slightly flexible, and lightweight and can be easily extruded, which makes it perfect for 3D printing. It requires less force to extrude than when using Poly Lactic Acid, which is another popular 3D filament. This fact makes extrusion easier for small parts. The disadvantage of acrylonitrile butadiene styrene is that it requires a higher temperature. Its glass transition temperature is about 105℃ and temperature about 210 - 250°C is usually used for printing with acrylonitrile butadiene styrene materials.

2. Poly Lactic Acid
Poly lactic acid is derived from corn and is biodegradable another well-spread material among 3D printing enthusiasts. It is a biodegradable thermoplastic that is derived from renewable resources. As a result, Poly lactic acid materials are more environmentally friendly than other plastic materials. The other great feature of Poly lactic acid is its biocompatibility with the human body. The structure of Poly lactic acid is harder than the Acrylonitrile Butadiene Styrene material melts at 180-220°C which is lower than Acrylonitrile Butadiene Styrene. The polylactic acid glass transition temperature is between 60 – 65 ° C, so

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Poly lactic acid together with Acrylonitrile Butadiene Styrene could be some good options for any of the projects.

3. High Impact Polystyrene

High Impact Polystyrene filament is made from a High Impact Polystyrene material and it is another example of support 3D materials. This material is well spread in the food industry for packaging. It is also used to pack CD and to produce trays in medicine naturally this filament has bright white color and it is also biodegradable so there is no adverse effect when it is put in tight contact with a human or animal body. High Impact Polystyrene filaments have curling and adhesion problems, which can be reduced byusing a heated bed during printing. High Impact Polystyrene material can also be used as a support structure during the printing and then dissolved in a colorless liquid hydrocarbon Solution.[1]

IV. APPLICATIONS OF 3D PRINTING TECHNOLOGY:

Manufacturing industries have been using 3D printers for more than decades, but mostly to make prototypes rapidly & cheaply. The majority are used as functional models, prototypes, and casting patterns, or for presentation models. By using 3D printing technology, better things are being printed as finished goods, around 28% of the output of 3D printers is now final products rather than prototypes, & this is expected to rise to 80% in 2020. Hearing aids 3D printing technology for manufacturing hearing aids was introduced a decade ago & it has shortened the manufacturing process to three steps: scanning, modeling, &printing. Printers can print 65 hearing aids shells & 47 hearing aid molds within 60 -90 min. the printing speed helps manufacturers to adjust demand to supply. 3D printing technology is also used in the Automobile industry for making metallic parts components, alsouseful for making aircraft components (European aeronautic Defense& Space Company has developed the aircraft machine parts by 3D printing technology). It is also used to make Weapons, also to producepartsof sports gadgets or wearing sports things like shoes,etc. [4]

Medical application: 3D printing has been applied in medicine since the early 2000s. When the technology was first used to make dental implants & custom prosthetics. Since then, the medical applications for 3D printing have evolved concededly. Recently published reviews describe the use of 3D printing to produce bones, ears, exoskeleton, windpipes, jawbones, eye glasses, cell cultures, stem cells, blood vessels, vascular networks, tissues, & organs as well as novel dosage forms & drug delivery devices. It is also used in Dentistry to make the dental device.

Pharmaceutical applications:

Pharmaceutical application for 3D printing is expanding rapidly &is expected to revolutionize health care. 3D printing technologies are already being used in pharmaceutical research & fabrication. Advantages of 3D printing include precise control of droplets size & dose, high reproducibility, & the ability to produce dosage forms with complex drug release profiles. 3D printing technology makes complex drug manufacturing processes more standardized, simpler & more viable. 3D printing technology is also a valuable tool in the development of personalized medicines. 3D printing technologies allow drug dosage forms, release profiles& dispensing to be customized for each patient. 3D printing can lead to drugs manufactured by "precision drug dispensing". The drug themselves could be tailored to meet various précised specifications & address the unique needs of individuals taking them. The application of 3D printing technology in pharmaceutical manufacturing could have the following potential benefits.[4]

- Potential use in improving the process, modifying performance for industrial design, aerospace, medical engineering, tissue engineering, architecture, pharmaceuticals.
- It mostly targets the two potential sites to rise pharmaceutical product development to unexplored areas, manufacturing sophisticated structures for the delivery and personalized medicine.
- In the Healthcare industry to create dental implants.
- On fabricating an organized release multi-drug implant for bone tuberculosis remedy.
- Helps in Organ printing, biomaterials, and cell-laden materials.[3]

Bio Printing Tissues and Organs

Organ printing takes advantage of 3D printing technology to produce cells, biomaterials, and cell-laden biomaterials individually or in tandem, layer by layer, directly creating 3D tissue-like structures. Researchers have used 3D printers to create a knee meniscus, heart valve, spinal disk, other types of cartilage and bone, and an artificial ear.[1]

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Customized Implants and Prostheses

Implants and prostheses can be made in nearly any imaginable geometry through the translation of X-ray, MRI, or CT scans into digital 3D print files. This approach has been used to fabricate dental, spinal, and hip implants.[1]

Anatomical Models

3D-printed neuroanatomical models can be particularly helpful to neurosurgeons by providing a representation of some of the most complicated structures in the human body.[1]

3D-Printed Dosage Forms and Drug Delivery Devices

In pharmaceutical industries, various techniques have been used and 3D printing is one of them in pharmaceutical research and fabrication due to the précis control of droplet size and dose, high reproducibility, and ability to produce dosage forms with complex drug-release profiles61. Complex drug manufacturing methods can also be standardized through the use of 3D printing to make them simpler and more viable. 3D printing technology could be very important in the development of personalized medicine.[1]

Unique Dosage Forms

The primary 3D printing technologies used for pharmaceutical production are inkjet-based or inkjet powder-based 3D printing. These technologies offer the ability to create limitless dosage forms that are likely to challenge conventional drug fabrication.3D printers have already been used to produce many novel dosage forms, such as microcapsules, hyaluronan-based synthetic extracellular matrices, antibiotic printed micropatterns, mesoporous bioactive glass scaffolds, nano suspensions, and Multilayered drug delivery devices.[1]

Personalized topical treatment devices Nose-shaped masks, loaded with salicylic acid, used for anti-acne treatments, have been developed shortly and efficiently. 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 favorable 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. [2]

3D Printing for cancer treatment Chemotherapy has been widely applied in cancer treatment but chemotherapy can cause side effects. Chemotherapeutic drugs have poor solubility in aqueous media; thus, they are administered 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.[2]

Application of3DP technologyto pharmaceutical dosage forms:

3DP technologies such as IJ, FDM, and SLS, are currently available for manufacturing adequate pharmaceutical dosage forms. In this review, the pharmaceutical applications of 3DP technology are focused on the oral solid dosage forms and transdermal delivery systems that seem to be undergoing relatively greater progress and are more suitable for wide applications of 3DP.[7]

Tablets Oral dosage formulations are the most preferred form of pharmaceutical products. Tablets and capsules are typical examples of widely used solid oral dosage forms. Particularly, tablets have been extensively examined for the feasibility of 3DP technologies in pharmaceutical manufacturing. Generally, tablets produced by 3DP methods can be categorized into two groups: single API tablets and multiple API tablets. Selective examples of each category are described in the next two sections, respective

Pediatric –Printed Tablets

A novel 3D printed designs such as minitablets and chewable dosage forms were established to serve the need for appropriate pediatric oral formulations with flexible dosing and easy administration. Formerly, FDM 3D printing technology was used to prepare baclofen mini caplets and indomethacin pediatric dosage forms with a Starmix® design demonstrating suitable taste masking properties. Besides, pediatric-pleasant chewable formulations were also developed using extrusion-based 3D printing technology, including Lego™-like tablets and chocolate-based dosage forms, overcoming the issue of swallowability and hence improving treatment adherence in children. At first, Goyanes et al. reported the manufacturing of isoleucine, for the treatment of a rare metabolic disease, into chewable formulations by using semi-solid extrusion 3D printing technology in a clinical location, letting the small-batch production of medicines at the point of dispensing. This was the first and only study so far that successfully probed the use of 3D printing in a hospital setting to prepare treatments at the dispensing point.

Single APITablets

Initially, 3DP technology was applied to fabricate simple immediate release (IR) tablets comprising a single API. In many studies, the FDM method was adopted for producing IR tablets, probably due to its

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simple fabricating procedures. Selective examples of single API IR tablets obtained by using the FDM method are reported in previous studies. Not only low drug-loaded dosage forms but also high drug-loaded dosage forms can be preparedusing 3DP technology. For example, a thermoplastic polyurethane-based dosage form loaded with 60% drug was successfully developed via the FDM method. Similarly, an IR tablet loaded with a very high dose of 80% paracetamol was prepared using an extrusion-based3D printer. In addition to IR tablets, 3DP is applicable to produce extended-release (ER) tablets. Skowyra et al. examined the feasibility of the FDM method to fabricate ER tablets using prednisolone loaded polyvinyl alcohol filaments, achieving the drug release up to24 h Another example of ER tablets prepared by the FDM method was reported by Alhijjaj et al., using polymer blends of polyethylene glycol, Tween 80, and polyethylene oxide with eitherEudragit® EPOor Soluplus.[7]

Multiple API tablets

To combine complex medication regimes into one, multiple APIs can be loaded in a single tablet, called a polypill. In recent studies, 3DP technology has been used to manufacture polypills showing controlled release profiles produced the polypill of captopril, nifedipine, and glipizide by using 3D extrusion-based printing, to treat patients withdiabetes, suffering from hypertension. This polypill was composed of a captopril osmotic pump compartment, joining layer, and sustained release compartments of nifedipine and glipizide After taking the pill, the joining layer was disintegrated quickly, thereby the polypill split into a captopril compartment and sustained release compartment. The captopril compartment showed zero-order drug release based on the osmotic release of the drug through a controlled porosity shell while the sustained release compartments released the drugs (nifedipine and glipizide) via diffusion through gel layers. They also applied3DP technology to fabricate a polypill containing fiveAPIs This polypill comprised two compartments showing independent controlled release profiles; one for sustained release and the other for immediate release.[7]

Implants

An implant is a dosage form containing active drugs within a sustained release delivery matrix, providing benefits to patients who need long-term treatment of drugs. While the traditional approach for implant development was mainly focused on extended and prolonged drug release, recent 3DP-based implants are designed to have complex micro- and macro-structures in a single device, for multi-APIsloading achieving more sophisticated drug release characteristics. For example, Huang et al. fabricated the implant of levofloxacin with a predefined microstructure, exhibiting complex release profiles from a single implant.

This implant displayed a bimodal profile, with pulsatile (day 5–25) and steady-state drug release (day 25–50), and then the pulse release began again on day 50 and continued up to day 80 [7] An implant is a drug delivery structure containing one or more than one active pharmaceutical ingredient loaded for continuous delivery to the targeted tissue, giving advantages to patients who need long-term treatment of medications. While the predictable approach for implant progression was mainly directed on expanded and delayed drug release, late 3D printing-based inserts are intended to have a complex matrix and large-scale structures in a solitary device, for multi-APIs stacking and accomplishing more advanced drug discharge characteristics. 3D printed implants were effectively established utilizing different technologies, like powder bed fusion technology, in designing rifampicin, levofloxacin implants based on the lactic acid polymeric matrix [37].

Microneedle design

Microneedles are a kind of transdermal drug delivery system, which has arrays of micron-sized needles on the surface of a matrix to enhance the skin penetration of biologically active molecules. Microneedle can be categorized into two types; hollow microneedle, and solid microneedle. The hollow microneedle is designed to be used to deliver liquids such as medicines to the blood vessels, while, solid microneedle is intended to be similar to a lancet for drawing blood [19]. In design studies, there are a few parameters that can be considered, such as the height of the needle, shape of the needle, materials, and the tip. All the parameters needed to be analyzed before undergoing the fabrication process. Previously, microneedle is made up of silicon, metals, polymers, glass, and silicon dioxide through micro-electro-mechanical system (MEMS) technology. Despite that, the fabrication period using MEMS technology is too long due to many processes that should be conducted [20]. Nowadays, the 3D printer technology has upgraded in terms of its resolution and accuracy that allow the printer to print using many materials and sizes in micron. The printing

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size is suitable for the size of the microneedle. Hence, many researchers introduce the use of 3D printers to fabricate microneedle, a Solid Works 2017 is used to design the microneedle. This study focuses on conical and pyramid design. In 2018, Luzuriaga et al. developed biodegradable microneedles by using a new technique called microfabrication, and FDM as a 3D printer with improved resolution, demonstrating that the printing parameters could be tuned to create microneedles of various shapes, lengths, and array densities, without a master template [21].

Preparation of rectal and vaginal delivery systems

Rectal and vaginal drug delivery via suppositories, pessaries, intrauterine devices, and surgical stents are used to provide drugs for local and systemic therapeutic effects. Highly professional methods are required to manufacture these dosage forms by the conventional approach, where the resulting systems need to be able to precisely fit the patient's anatomy [22, 23]. Accordingly, 3D printing was used to print such dosage forms by using a casting approach to produce suppositories and pessaries of castable resins and silicone polymers for the delivery of anti-inflammatory medicines. In another study, computer-aided designing modeling and prenatal ultrasound developed 3D printed personalized vaginal pessaries to identify the dimensional requirements for the treatment of stressful urinary incontinence showed improved therapeutic performance compared with conventional lines [24]

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Selection of polymers in 3D printing methods for drug delivery

3D printer technology has progressed as a novel "biomedical technique". Polymers are the spine in the formulation of 3D printing dosage forms because they are responsible for modifying the release rate and enhancing physical stability to incorporate active pharmaceutical ingredients. Polymers of natural and synthetic origin find applications for 3DP printing, natural polymers such as gelatin, collagen, alginate, and chitosan are usually utilized, but they frequently need cross-linkers which could be cytotoxic. Therefore, synthetic polymers have recently gained attention

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for 3D printing to avoid disadvantagesassociated with natural polymers.Polymers currently exploited for various 3D technologies are thermoplastic polymers such as polyurethane, polystyrene, polyethylene glycol diacrylate, PLA, and poly lactide-co-glycolide, poly ε-caprolactone (), polyamides, cellulose derivatives like ethyl cellulose and HPMC, and polymethyl acrylate (Eudragit)® polymers. Thermoplastic polymers are generally utilized in the fused deposition modeling methods, while any powdered polymers can be used in inkjet printing methods. Due to the utilization of high molecular weight thermoplastic polymer, FDM often leads to a prolonged-release pattern. The starting materials that could be used in SLA and techniques are thermostable heat processable polymers such as polyamides, polystyrene in addition to epoxy and acrylate-based resins[25].

Printer type/printing technique	Dosage forms/systems	Model drug used
Fused-filament 3D printing	Tablets	Fluorescein
3D printer	Tablets	Paracetamol
3D printer	Tablet implant	Isoniazid
Fused deposition 3D printer	Immediate-release tablets	5-Aminosalicylic acid, Captopril, Theophylline and Prednisolone
Fused deposition 3D	printing Extended-release tablet	Prednisolone
Fused deposition 3D	Modified-release drug-loaded tablet	printer 5-Aminosalicylic acid and 4-Aminosalicylic acid
3D printer	Complex matrix tablet with ethylcellulose gradients	Acetaminophen
3D printer	Fast disintegrating tablet	Acetaminophen
Extrusion-based printer	Multi-active tablets (Polypill)	Captopril, Nifedipine and Glipizide
Inkjet printer	Implant with the lactic acid polymer matrix	Levofloxacin
3D printer	Complex oral dosage forms	Fluorescein

Table 1: Examples of drugs fabricated by 3D printing technologies

V. CHALLENGES:

It shows promising results in drug delivery applications. It faces many challenges such as optimization process, improving the performance of the 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[38]. To attain the quality of 3D products, some essential parameters necessitate to be optimized like printing rate, printing passes, line velocity of the print head, interval time between two printing layers, the distance between the nozzleand the powder layer,etc[39,40] It is also important for post-process after prototyping like drying (hot air heat, microwaves and infrared) methods, as it has a major impact on the quality of the finished 3DPrinted products[41,43] To increase the drug loading capacity in 3D Printed processed tablet, uniaxial compression, and suspension dispersed methodologies are adopted, but this technique suffers from increased complexity and clogging of spray nozzle[44,45].

Risk assessment during 3D printing process:

Risk identification is an important step to prevent failure of quality control parameters like appearance, content uniformity, assay, etc. Identifying risk involves analysis of the process and process variables to assure that a quality product is manufactured. Such a critical assessment was done by Norman et al.

- When a given printer is unable to print a given design, software controls should be employed. Variability in layer thickness has to be controlled by real-time layer thickness monitoring
- Improper layering due to environmental conditions should be dealt with by controlling

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the temperature and humidity of the manufacturing area.

- Inaccurate position during printing can be avoided 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.
- Inconsistent agglomeration or binding can be due to variations in binder viscosity or binder surface tension.[4]

Need of 3D printing:

The use of 3D printing in pharmaceutical science can provide many benefits which include – cost-effectiveness; increased productivity; the democratization of design & manufacturing & enhanced collaboration.

Cost efficiency: The most important benefit offered by 3D printing is the ability to produce items cheaply. The conventional method of drug manufacturing is less cost-effective than 3D printing technology because conventional methods use a lot of processes for manufacturing (mixing, milling, dry or wet granulation, compression or molding, etc.)[4]

Enhanced Productivity: Thetraditional method of drug manufacturing uses various processes such as mixing, milling, dry or wet granulation, compression, or molding that making it time-consuming. But 3D printing technology is much faster than the traditional method of drug manufacturing because it does not have various processes like traditional manufacturing. In addition to speed, other qualities, such as resolution, accuracy, reliability & repeatability of 3D printing technologies, are also improving.

Environment friendly: 3D printing technology claims to have more environmental benefits than traditional drug manufacturing which needs a huge setup to manufacture a pill.Another beneficial feature offered by 3D printing is the democratization of the design & manufacturing of goods.[4]

VI. FUTURE PROSPECTS:

New possibilities in 3D printing may open up whole new opportunities for pharmaceutical research & Bio-technology applications. In new future,the 3D printing approach will be utilized in many ways such as fabricate and engineering various novel dosage forms, achieving optimized drug release profiles, developing new excipients, avoiding incompatibilities between multiple drugs, drug dosage forms, supporting delivery, limiting degradation of biological molecules or helping to research cures. 3D printing could add a whole new dimension of possibilities to personalized medicines. On-demand printing of drug products can be implemented for drugs with limited shelf life or for a patient-specific medication, offering, and an alternative to traditional compounding pharmacies. In the future, it may lead to innovation in garage biology. As the technology is still so new, there's a lack of regulation, safety, and security concerns of 3D. So these problems can be overcome in the early future.

VII. PATENTS:

Patent bears technical, legal,and commercial information in general, thus is an important and strategic information resource for users. Therefore, it is necessary to study the development of 3D printing technology from the perspective of patent retrieval and analysis. In addition, this research perspective can also shed light on technological development, the adjustment of enterprises' R&D direction, and the change of market competition pattern to some extent. As the result of in-depth analysis on 3D printing technology, we construct a retrieving term for 3D printing patents using Innography software: (abstract, claims, title) ("three-dimension printOR "3D print OR "rapid prototypeOR "additive manufact OR "digit manufact OR "fused deposit manufact OR "direct metal laser sinter OR "selective laser sinterOR"selective heat sinter OR "stereo lithograph*"OR "digital light process OR "electron beam freeform fabricatOR "laminated objected manufact. In total, 10121 3D printing patents have been found worldwide[.6]

The overall R&D situation and the popularity of 3D printing technology in different nations and areas can be reflected by the statistics of patent applications digging out through global patent retrieval. The top-ranking offices with regard to 3D printing patent applications include the United States Patent and Trademark Office (3509 patent applications), the State Intellectual Property Office (hereinafter SIPO) of the P.R.C (2023 patent applications), European Patent Office (958 patent applications), Japan Patent Office (805 patent applications), Korean Patent Office (342 patent applications), German Patent and Trade Mark Office (256 patent applications) and soon.Generally speaking, patent infringement situations and lawsuits are also more likely to happen in nations where 3D printing R&D is more frequentlyconducted.

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Study shows that the United States ranks first in 3D printing patent applications for more than 10 years and its number of applications have stayed above 150 each year since 2003. The applications in World Intellectual Property Office (hereinafter WIPO) and China have increased dramatically in recent years. In 2013, the number of applications in SIPO soared to 350, hitting a historical record. The situation indicates a trend of globalization in the area of 3D printing patent application and it also suggests that China, as a global manufacturing powerhouse, hasgreat potential in developing and using 3D printingtechnology.[6]

Title of patent	Inventor	Description	Patent number	Country
Apparatus and methods for 3D printing	David Rusella Andres Hemandez Andrew Berlin	The invention relates to apparatus and methods for producing three-dimensional objects and auxiliary systems used in conjunction with the aforementioned apparatus and methods.	**7291002B2** US7291002B2	United state
Methods of reinforced cementitious construction by high-speed extrusion printing and apparatus using same	Brian C. Giles	Method of apparatus automated reinforced concentrated	US10688683B2	United state
Process for making controlled release medical implant products	Robert.w. Admas Wyane .c. Pollock	A method making implant device for releasing self-contained drug on a controlled	US100010501B2	United State
Gas flow in three-dimensional Printing	Richard joseph ROMANO, joe TRALONGO,	The present disclosures provide three-dimensional printing processes apparatus system for treating gas borne debris	US10661341B2	United state
Multilayer fiber reinforcement design 3D printing	Gregory Thomas Mark, Rick Bryan woodrfull,David steven	Embodiesment of the invention provide 3d orinter comprising an anistropic head that solidifies along toolpaths	US10603841B2	United state
3d printers and feedstocks for 3d printers	SatyabrataRaychaudhari ,Yongan Yan	The Discoloures related in general to three dimensional printers having a 3D object by using feedstock comparising a metal polymer	US20210178470A1	United state
The method of the prepration and 3D printing of the active functional additive prepration for 3D printing preceramic polymer	Zach Eckltobias Schulder john Martinkenneth Kanter	The present invention provides can be used for 3d printing and pyrolysis to produce resin formulation of cremic matrix composites	CN109996773A	China

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Support ink for 3D printing	Deel, Dust, Tobias , N golo	A method for producing a three producing 3d article proving an article ink compromising the first solid particle	JP6625529B2	Japan
Method for Additive manufacturing a 3D printed object	Wang ZhiguangheMeilling pan Licheng Fu yinzhichenchonghuanzhangruigen	A 3d printed an article in layers comprising printing and depositing one or more layers of slurry with 3 d printer	TWI611892B	Taiwan
System and method of 3-dimensional structure additive manufacturing	Simon Travis Amhad Mohammad	System includes at least one printing head for recipient and distribution of materials	RU2643138C2	Russia
Kit for the production of 3 dimensional objects by using of electromagnetic radiation	Eugene Giller, JamesF. Bredt, Thomas Davidson	A kit for 3-dimensional printing the kit comparising a fluid which is adapted to carry an absorbed comparising	EP2001656B1	European Patent office
Fine powder recoater for 3D printer	Anthony S.Durgan Andrew	The present invention relates to powder layer 3-dimensional printer recoater for fine powder	KR101971847B1	Sothkorea
3D printing system and equipment assembly	Mahendra Earl patel Amit s Patel	A step of forming one or more powder layers on the receptacle in the cavity	JP6903659B2	Japan
Mid part in process inspection for 3D printing	Gregory Thomas Mark	According to one aspect,embodiesment herein provide a method for in-process inspection of a 3 D printing part with a 3 d printer	US11014305B2	United state
A kind of 3D printing system for supporting cloud service	Wang zhongfeiJinQingxian	A kind of 3D printing system for supporting cloud service platform the 3D printer support cloud service and user operate the terminal module	CN105291440B	China
Consummate 3D printing	Benjamin Buller Errell Milstein tassoRapastomas Blasius BrezosikiKimonSimeonidis Sherman	Present disclose the various instrument and system 3D printing the disclosures provide a 3-dimensional method of printing	CN108698126A	china
Slicing and or texturing for 3D printing	Mahendra Earl patel Amit S Patel Thomas Jay Braadbury Thomas G west	A method for slicing a 3-dimensional model to print the corresponding object by a 3D printer where in the slicing is done having a Z-axis	JP6306616B2	japan
Twin stage 3D printer	Li Dongxum	One twin stage 3D printer includes one framework one extrusion device with a nozzle is used to extrude the raw material	CN105992689B	China

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Conductive liquid three dimensional printer	Scotter Vader Zachary Vader	A printer produces objects from liquid conductive material is disclosed in one embodiment	US 10040119B2	United state
Metal filament of 3D printer	Landscaping	The metal filament 650 is injected into a nozzle 610 formed in the induction heating coil 620 and meted from extruded to form a metal alloy	KR101764058B1	South Korea
Method and system for controlled Rotational 3d printing	MenchikGuy James Carlson Andrew Bennhard Hedlund Jonthan	A system For Three Dimensional printing comprising a rotary tray configured to rotate about a vertical axis an inkjet printing head having a plurality of separated nozzles	IL282005D0	Israel
Calibration and Alignment of 3d printing deposition heads	Michael A.Bell, Kyle Dumont	A 3-dimensional printer includes a frame a first device coupled to the frame a dispensing system having acartridge holder with a sensor mounted at a location	US10406801B2	United state
High speed Flexibe 3d freefrom techniques	Che ChihSao	A novel rapid 3d prototype manufacturing technology which is characterized by breaking through the current horizontal lamination mode and adopting the elastic direction lamination method	TW1611909B	Taiwan
3D printing surgical repair system	Philipp lang Daniel Steines	Various embodiments of methods of making one or more components of surgical repair system including embodiment oneor more compound	US20170249440A1	United state
3d printing Apparatus and 3d image forming method	MotoyanagiYoshimune	A first print image forming means for forming the first image on one side of the thermally expandable sheet on which heat expansion layer is formed	JP5915673B2	Japan

VIII. CONCLUSION:

3D printing has become useful for the pharmaceutical sector, leading to personalized medicine focusing 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 has been a significant barrier. Regarding the establishment of guidelines, laws, quality systems, and safety as well as the 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. 3D printing technology can make complex formations as cost and time-efficient. It may improve its applications in Pharmaceutical Research and Biotechnological fields. 3D printing involves a wide technical range in the pharmaceutical field with novel drug delivery systems, generation of new excipients, improvements of drug compatibility, and customized dosage forms. In the future 3D printing can be regulated and followed by pharmaceutical

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