Review Article

Review on Applications of 3D Printing in Pharmaceuticals

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ABSTRACT

Three-dimensional printing technologies is a new quick prototyping method in which solid objects are constructing 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. It is a valuable strategy to overcome some challenges of conventional pharmaceutical processes. This technology will reform the pharmaceutical manufacturing style and formulation techniques. Here we present an overview of three-dimensional printing in the progress of new drug dosage form and applications in pharmaceutical and biomedical studies.

Keywords: 3D printing, technology, manufacturing process.

INTRODUCTION

3D Printing also known as additive manufacturing refers to a various processes used to synthesize a three dimensional object. In 3D Printing successive layers of material are formed under computer control to create an object[1].

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: fabrication of objects through the deposition of a material using a print head, nozzle, or another printer technology. In this technique 3D model are used for preparing the parts in the process of joining materials layer by layer[2]. In novel drug delivery system 3D printing are used for viable tablet production. These tablets are manufactured in such a way that that are capable of satisfying regulatory tests and matching the standards of commercial tablets[3].

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 aerospace industry, architecture, tissue engineer, biomedical research and pharmacy. It seems that 3D printing technology will lead a new approach of the next industrial revolution based on its versatility and diversity. Along with development and progress in science and technology, the 3D printing technology gets mature enough so that anyone can apply it with open-source software at a relative lower material cost[4]. 3D printing technology has enabled unprecedented flexibility in the design and manufacturing of complex objects, which can be utilized in personalized and programmable medicine[5].

When compared to the manufacturing process of conventional pharmaceutical product, it has a lot of advantages like-

1. High production rates due to its fast operating systems;
2. High drug loading can be achieved with precision and accuracy especially in case of potent drug in small dose;
3. Cost of production and amenability to broad types of pharmaceutical active ingredient including poorly water soluble, peptides and proteins as well as drug with narrow therapeutic windows can ultimately reduce material watage.[6]

Different types of drug delivery systems such as oral controlled release systems, micro pills, microchip, drug implants, fast dissolving tablets and multiphase release dosage forms have been developed using three-dimensional printing technology[7]. The 3D Printing is a layer-by-layer process having capability to produce 3D drug products from digital file. The 3D Printing technology is unparalleled, flexible, rapid and with exceptional manufacturing capability of pharmaceutical drug products of desired quality[8].

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 fiber transmitter or mask pattern.

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 Stereolithography. The Umbrella term additive manufacturing gained wider currency in the decade of the 2000's[2].

The first 3D printing technique used in pharmaceutics was achieved by inkjet printing a binder solution onto a powder bed, binding therefore the particles together thanks 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).

FDA approved Spritam as the first 3D printed drug and in summers of 2016 Aprecia Pharmaceuticals released it in the market.[9] Inkjet printing now a day has become the most used method for 3D printing.

In the previous decade, in 1989, Scott Crump, filed a patent on another 3D printing technology: Fused deposition modeling (FDM), where extruded polymer filaments heated into a semi-liquid state were extruded through a heated nozzle and deposited onto a build platform layer by layer to harden[6,9]. Since there are many others methods have been developed for 3D printing techniques.

After the start of the 21st century, machines of 3D printing sale out very rapidly and there price has been dropped gradually[10].

Advantages [11,12]

1. Accurate and precise dosing of potent drugs which are administered at small doses.
2. Reduces 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 case of multi drug therapy with multiple dosing regimen, 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 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.

Disadvantages [12]

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 in order to print different types of objects and the printers that can manufacture in color are costlier than those that print monochrome objects.
3. As with all new technologies, manufacturing jobs will decrease. This disadvantage can have a large impact to the economies of third world countries especially China, that 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 rang of raw materials used in traditional manufacturing. More research is required to devise methods to enable 3D printed products to be more durable and robust.

TYPES OF 3D PRINTING

1. Selective Laser Sintering

Selective laser sintering is a quick manufacturing process based on the use of powder coated metal additives, a process generally used for rapid prototyping. For scanning and aligning particles in predetermined sizes and shapes of the layers a continuous laser beam are 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 stereo-lithography. After scanning the first layer, the scanning of second layer continues which is placed over the first, repeating the process from the bottom to the top until the product is complete[13].

To fuse small particles 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 thickness.

Then a new layer of material is applied on top and the process is repeated until the object is completed[13].

2. Fused Deposition Modeling

Fused Deposition Modeling Printers are much more common and inexpensive than the Selective Laser Sintering type. Fused deposition modeling printer uses a print head similar to an inkjet printer[14]. However, instead of ink, beads of heated plastic are released from the print head as it moves, building the object in thin layers. Continuously the process is repeated, to shape each layer precise control the amount and location of each Since the material is heated to fuse or bonds to the layers below[15].

As each layer of plastic cools, it hardens, gradually creating the solid object as the layers build. Depending on the complexity and cost of a Fused Deposition Modeling printer, it may have enhanced features such as multiple Print heads. Fused Deposition Modeling printers can use a variety of plastics[14]. In fact, 3D Fused Deposition Modeling printed parts are often made from the same thermoplastics that are used in traditional injection

molding or machining, so they have similar stability, durability, and mechanical properties[15].

3. 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[16].

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 design in a ratio such that it has a 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[17].

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 µm 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 guard" to minimize the electrostatic repulsion between them. The electrostatic field created directs the charged droplets to the substrate[18].

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[17,18].

4. Stereo Lithography

Charles Hull discovered this technique in 1988 as a first printing technique of 3D system. During the printing process photopolymer material like resin or acrylate was used which can cured by UV laser[19]. It is rapid and popular prototyping technology which can produce highly accurate and detailed polymer parts. Stereo lithography builds objects one layer at a time by tracing a laser beam on the surface of a vat of liquid photopolymer, inside of which is a movable stage to support the part being built. Wherever the laser beam strikes the surface of the liquid the photopolymer quickly solidifies. The platform is lowered by a distance equal to the layer thickness (typically 0.003-0.002 inch), and a resultant layer is formed on top of the previously completed layers. Thus three dimensional object out of many layers formed completely due to the self-adhesive property of material causes each succeeding layer to bond to the earlier one. Objects which have overhangs or undercuts must be supported during the fabrication process by support structures. These are either manually or automatically designed with a computer program developed for rapid prototyping. Once complete, the part is elevated above the vat and drained. Excess polymer is swabbed or rinsed away from the surfaces. In several cases, a final cure is given by placing the part in a UV oven. After the final cure, supports are cut off the part and surfaces are polished, sanded or otherwise finished[20].

5. Hot melt extrusion

Hot melt extrusion is the process of melting polymer and drug at high temperature and the pressure is applied in the instrument continuously for blending[21].

It is a continuous manufacturing process that includes several operations such as feeding, heating, mixing and shaping[22]. In recent years, it has proved that Hot Melt Extrusion has the ability to improve the solubility and bioavailability of poorly soluble drugs[23].

6. Extrusion 3D Printing

In this technique the material is extruded from the automated nozzle on to the substrate and it does not require any higher support material. It is only used to fabricate tablet containing Guaifenesin as expectorant. The materials that can be extruded are molten polymers, suspensions, semisolids, pastes[24,25].

Table 1: Fabrication of dosage forms by 3D Printing technology

S.no	Drug	Dosage form	Technique used
1.	Paracetamol [26,29]	Oro-dispersible tablets	Selective laser sintering, Fused deposition model
2.	Domperidone [27]	Tablet	Fused deposition model
3.	Theophylline [28]	Tablet, Capsule	Fused deposition model
4.	Budesonide [30]	Controlled release tablet	Fused deposition model
5.	Prednisolone [31]	Extended release tablet	Fused deposition model
6.	Captopril [32]	Intermediate release tablets	Fused deposition model
7.	Enalapril maleate [33]	Tablet	Fused deposition model
8.	Hydrochlorothiazide [33]	Tablet	Fused deposition model
9.	Nitrofurantoin [34]	Catheter, Implant	Fused deposition model
10.	Hydroxyapatite [34]	Implant	Fused deposition model

11.	Furosemide [35]	Capsules (Intermediate Release, Mediate Release)	Fused deposition model
12.	Pravastatin [36]	Tablet (Intermediate Release, Sustained Release)	Fused deposition model
13.	Atenolol, Ramipril[36]	Tablet (Intermediate Release, Sustained Release)	Fused deposition model
14.	Insulin[37]	Microneedle	Inkjet printing
15.	Polyvinyl Pyrrolidone (PVP) [38]	Microdots	Inkjet printing
16.	Loperamide[39]	Tablets or capsules	Inkjet printing
17.	Caffeine[39]	Tablets or capsules	Inkjet printing
18.	Rifampicin[40]	Implants , Nanoparticles	Inkjet printing
19.	Levofloxacin[41]	Implant	Inkjet printing
20.	Folic Acid[42]	Nanosuspension	Inkjet printing
21.	Nitroglycerin[43]	injection	Inkjet printing
22.	Rapamycin[44]	Tablets	Inkjet printing
23.	4-Aminosalicylic acid[45]	Oral modified release tablets	Stereo Lithography
24.	Salicylic acid[46]	Anti-acne patch	Stereo Lithography
25.	Rifampicin[47]	Compartmentalized shells	Hot melt extrusion technique
26.	Paracetamol[48]	3D-printed cube, pyramid, cylinder, sphere and torus	Hot melt extrusion technique
27.	Indomethacin[47]	Subcutaneous rods	Hot melt extrusion technique
28.	Polymer Polyvinyl Alcohol (PVA), Mannitol and Hydrochlorothiazide, Polylactic Acid (PLA)[49]	Three-compartment hollow cylinder	Hot melt extrusion technique
29.	Ethylene Vinyl Acetate Copolymers[50]	T-shaped prototypes of intrauterine system (IUS)	Hot melt extrusion technique
30.	Captopril[51]	Tablet	Extrusion 3D Printing
31.	Nifedepine[51]	Tablet	Extrusion 3D Printing
32.	Dexamethazone[52]	Drug encapsulated film of Polylactic-co-glycolic acid (PLGA) and Poly Vinyl Alcohol (PVA)	Extrusion 3D Printing
33.	Hydrochlorothiazide, Ramipril[51]	Multi- active solid dosage form (polypill)	Extrusion 3D Printing
34.	Pravastatin[51]	Multi- active solid dosage form (polypill)	Extrusion 3D Printing
35.	Poly-di-methyl-siloxane (PDMS)[53]	Tablet	Extrusion 3D Printing

3D PRINTER MATERIALS [10]

Polymers used in 3D printing for medical purposes:

1. Acrylonitrile Butadiene Styrene

One of the most widely used material 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 higher temperature. Its glass transition temperature is about 105°C and temperature about 210 - 250°C is usually used for printing with acrylonitrile butadiene styrene materials.

2. Poly Lactic Acid

Poly lactic acid derived from corn and is biodegradable an 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 among other plastic materials. The other great feature of Poly lactic acid is its biocompatibility with a 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. Poly lactic acid glass transition temperature is between 60 – 65 ° C, so Poly lactic acid together with Acrylonitrile Butadiene Styrene could be some good options for any of 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 food industry for packaging. It is also used to pack CD discs 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 by using a heated bed during the printing. High Impact Polystyrene material that can also be used as support structure during the printing and then dissolved in a colorless liquid hydrocarbon Solution.

APPLICATIONS OF 3D PRINTING

3D Printing has been applied in medicine from long times when first it used to make dental implants and custom prosthetics[54,55].The current medical uses of 3D Printing can be organized into several broad categories: tissue and organ fabrication; creating prosthetics, implants, and anatomical models; and pharmaceutical research concerning drug discovery, delivery, and dosage forms[56].

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[57]. Researchers have used 3D printers to create a knee meniscus, heart valve, spinal disk, other types of cartilage and bone, and an artificial ear[54,58,59].

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[54,56,60]. This approach has been used to fabricate dental, spinal, and hip implants[60].

Anatomical Models

3D-printed neuro-anatomical models can be particularly helpful to neurosurgeons by providing a representation of some of the most complicated structures in the human body[56].

3D-Printed Dosage Forms and Drug Delivery Devices

In pharmaceutical industries various techniques have been used and the 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 profiles[61]. Complex drug manufacturing methods can also be standardized through use of 3D printing to make them simpler and more viable. 3D printing technology could be very important in the development of personalized medicine, too[60].

Unique Dosage Forms

The primary 3D printing technologies used for pharmaceutical production are inkjet-based or inkjet powder-based 3D printing[61]. These technologies offer the ability to create limitless dosage forms that are likely to challenge conventional drug fabrication[61].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[61].

CHALLENGES

It shows promising results in drug delivery applications. It 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 3D printed products' and to expand the application range in novel drug delivery systems [62].

To attain 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 layer, distance between the nozzles and the powder layer, etc[63,64.]

It is also important for post process after prototyping like drying (hot air heat, microwaves and infrared) methods, as it has major impact on the quality of the finished 3D Printed products[65-67]. 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[68,69].

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