Review Article

3D Printing Technology in Pharmaceutical Drug Delivery

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ABSTRACT

Three dimensional printing (3DP) enables the development of diverse geometries through computer aided design using different techniques and materials for desired applications such as pharmaceutical drug delivery system. The process of 3D printing was patented in 1986; however, the research in the field of 3DP did not become popular until the last decade. There has been an increasing research into the areas of 3DP for medical applications for fabricating prosthetics, bioprinting and pharmaceutics. 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 modelling. It is a valuable strategy to overcome some challenges of conventional pharmaceutical process. This technology will reform the pharmaceutical manufacturing style and formulation techniques. The present review focused on various techniques, applications of 3D printing in pharmaceutical technology.

Keywords: 3D printing, computer-aided design, manufacturing process, Novel drug delivery.

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INTRODUCTION

Three-dimensional printing (3DP) is a method to produce 3D objects from digital models by fusing or depositing materials in successive layers, which allows the fabrication of objects with various geometrics in a layer-by-layer process. The process is also called additive manufacturing, rapid prototyping, or solid free-form fabrication. 3DP technology has been available since the late 1980s and has been used in engineering and various non-medical manufacturing areas, including automotive, aerospace, and consumer goods industries, however, rapid advances in 3DP methods and the emergence of versatile biocompatible materials facilitate the pharmaceutical applications of 3DP technology in recent years[1]. Following the first medical applications of 3DP for the fabrication of custom prosthetics and dental implants, in the early 2000s, the 3DP technology has been since used to directly print medical devices having highly complex 3D architectures, and fabricate medical devices personalized to fit a patient's own anatomy. Furthermore, it has the potential to reduce the risk of failure at the later stages of new drug development process, as this technique can be deployed to fabricate more predictable drug screening platforms[2].

Due to its many inherent advantages over the conventional technologies, including the customization and personalization of medicines with individually adjusted doses, the ability to fabricate complex solid dosage forms with high accuracy and precision, on-demand manufacturing, and cost-effectiveness, the application of 3DP methods to the pharmaceutical manufacturing of drug products gains a great attention in recent years. For example, various drug delivery systems have been developed using 3DP technology, such as oral controlled released systems, microchips, implants, pills, immediate release (IR) tablets, and multiphase release dosage forms[3]. Given that personalized dosage forms are desirable to avoid unnecessary adverse effects, correct the dose regimen, and achieve personalized release profiles, the employment of rapidly evolving 3DP technologies also supports the fabrication of personalized drug delivery systems. In 2015, SPRITAM (Levetiracetam) is the first drug manufactured using 3D printing process by Aprecia Pharmaceuticals Company approved by the US Food and Drug Administration. SPRITAM (Levetiracetam) for oral use in epileptic seizure. The formulation rapidly disintegrated with a sip of liquid[4].

This review will introduce some 3DP technologies suitable for pharmaceutical manufacturing and also their applications to the development of dosage forms, indicating the feasibility of this technology in regular commercial production.

Advantages of 3D Printing Drug Delivery

1. High drug loading ability when compared to conventional dosage forms.
2. Accurate and precise dosing of potent drugs which are administered at small doses.

3. Reduces cost of production due to lesser material wastage.
4. Suitable drug delivery for difficult to formulate active ingredients like poor water solubility.
5. Narrow therapeutic window.
6. Medication can be tailored to a patient in particular based on genetic variations, ethnic differences, age, gender and environment.
7. In case of multi drug therapy with multiple dosing regimen, treatment can be customized to improve patient adherence.
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[5].

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 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[6].

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.

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[7].

Then a new layer of material is applied on top and the process is repeated until the object is completed (Figure 1).

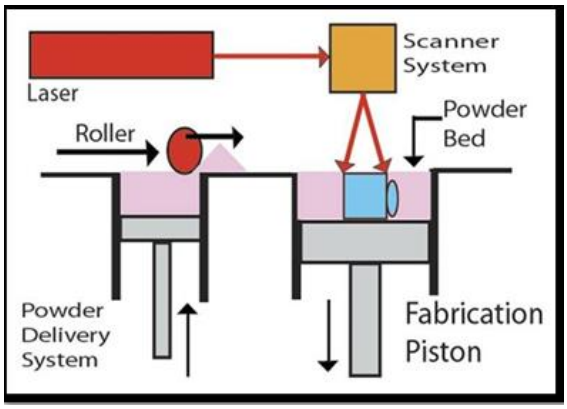

Figure 1: Selective Laser Sintering Technique in 3D Printing

2. Fused Deposition Modelling:

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. 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[8].

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. 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[9]. (Figure 2).

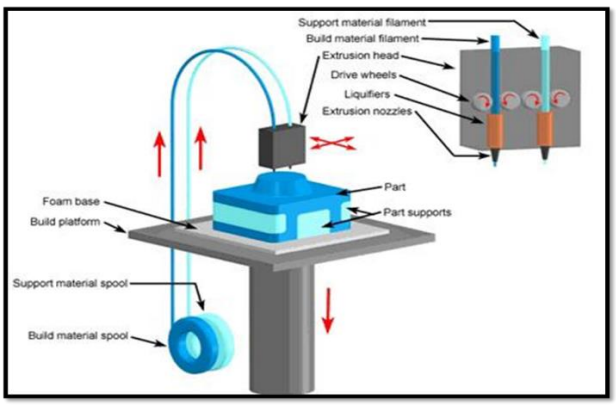

Figure 2: Fused Disposition Modelling

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[10].

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[11].

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[12].

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 (Figure 3).

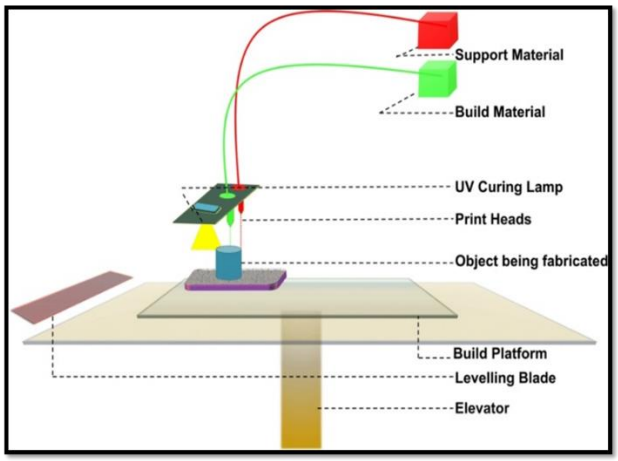

Figure 3: Inkjet Printing in 3D printing

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. 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[13].

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[14] (Figure 4).

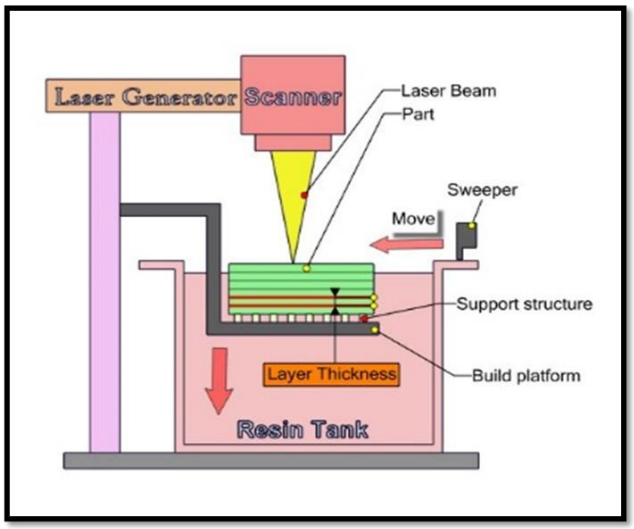

Figure 4: Stereo Lithography in 3D printing

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[15].

It is a continuous manufacturing process that includes several operations such as feeding, heating, mixing and shaping. In recent years, it has proved that Hot Melt Extrusion has the ability to improve the solubility and bioavailability of poorly soluble drugs[16].

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[17].

MARKETED EXAMPLES OF 3D PRINTING TECHNOLOGY

Table 1 shows some 3DP technologies and pharmaceutical formulations for drug delivery.

3DP Technology	Dosage Forms	Active Ingredients
Fused Deposition Modelling (FDM)	Tablet	5-aminosalicylic acid (5-ASA, mesalazine) and 4-aminosalicylic acid (4-ASA)
3DP extrusion-based printing	Tablet	Captopril with Nifedipine and Glipizide
3DP machine	Multi-drug implant	Rifampicin and Isoniazid
Desktop 3D printer	Tablet	Guaifenesin
3DP technology	Tablet	Acetaminophen
Inkjet 3DP	Nanosuspension	Folic Acid
Inkjet 3DP	Implant	Levofloxacin
Thermal Inkjet (TIJ) Printing	Solid dosage forms	Prednisolone
3D Extrusion Printing	Encapsulated within a polymer (PLGA) poly(vinyl alcohol) (PVA)	Dexamethasone- 21-phosphate disodium salt
Thermal Inkjet (TIJ) Printing	Solution	Salbutamol sulphate
Inkjet 3DP	Nanoparticles	Rifampicin
FDM	Tablet	Hydrochlorothiazide
(FDM) and Hot Melt Extrusion (HME)	Tablet	Domperidone, hydroxypropyl cellulose (HPC)
FDM	Tablet	Nitrofurantoin, polylactic acid and hydroxypropyl methylcellulose
3D printed	Biodegradable patch	poly(lactide-co-glycolide), polycaprolactone, and 5-fluorouracil

APPLICATIONS

1. **Rapid prototyping:** Used to create a real scale model of an object in short lead time, using CAD software.
2. **In the healthcare sector:** Tools can be prepared for surgery and are made to measure the patient's body.
3. **Reconstituting bones and body parts in forensic pathology:** Fingerprint examination, accident reconstruction, structural, and industrial accidents.
4. **Drug testing:** Ability to fabricate complex geometries to achieve various drugs releasing kinetics.
5. **Personalized dosing:** It uses digitally controlled devices for formulating active pharmaceutical ingredient (API) and excipients.
6. **Unique dosage forms:** Capable of producing various 3D drug products and various customized dosage forms.
7. **Complex drug release profile:** To fabricate fully customizable tablets that can deliver drugs with any type of releasing profiles.
8. **Low cost of production:** It can decrease production time, costs, and allow testing of new product designs[18].

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[19].

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[20].

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. 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[21].

FUTURE PROSPECTS

New possibilities in 3D printing may open up whole new opportunities for pharmaceutical research and bio-

technology applications. In near future 3D printing approach will be utilized in many ways such as fabricate and engineer various novel dosage forms, achieve optimized drug release profiles, develop new excipients, avoid incompatibilities between multiple drugs, drug dosage forms, supporting delivery, limit degradation of biological molecules or helping to research cures. 3D printing could add a whole new dimension of possibilities to personalized medicine. In its most simplistic form, the idea of experts and researchers is to produce personalized 3D printed oral tablets. On demand printing of drug products can be implemented for drugs with limited shelf life or for patient specific medications, offering an alternative to traditional compounding pharmacies. In future it may lead to the innovation in garage biology. As the technology is still so new, there's a lack of regulation, safety and security concerns of 3D printing. So these problems can be overcome in nearby future[22].

CONCLUSION

3D printing has become a useful and potential tool for the pharmaceutical sector, leading to personalized medicine focused on the patients needs. 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 revolutionize the pharmaceutical manufacturing style and formulation techniques.

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