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3D Printing of Medicines: A Review

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Abstract

3D Printing is an expeditious space of investigation in the pharmaceutical field, due to its flexibility and feasibility. This is an additive process of stacking materials in layers to form a solid object by means of a 3D Printer. Fabrication of the product has been done with the instruction based on a CAD file. The 3DP technologies developed includes Selective Laser Sintering, Stereolithography, Fused Deposition Modelling, Thermal Inkjet printing, Zip dose technology etc. and this article will discuss each technique in detail. Aprecia's Spritam is the first FDA approved 3D printed medicine, developed by means of Zip dose technology. The ultimate advantage by the adaptation of this technology is due to its potential ability for dose tailoring and personalization. Though the technology is much accessible, this is overdone with numerous regulations.

Keywords: 3D Printing, Computer aided design, Dose tailoring.

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Introduction

3D Printing technology is a contemporary expeditious prototyping technique by which materials, which can be powder, filaments, pellets, granules etc [1]. Stacked by consecutive layers using a 3D Printer. This technology also known to be "Additive manufacturing", "Rapid prototyping" [2] and "Solid free-form technology" [3]. A 3D printer is a machine that forms physical 3D model from a digital data, using computer-aided design (CAD) file [1]. A 3D scanner or 3D printing application is employed for developing CAD file that results in producing three dimensional digital copy of an object. International Standard Organization (ISO) defines 3DP as "fabrication of objects through deposition of a material using a print head, nozzle, or any other printing technology" [4]. Additive manufacturing is Achieved by instantaneous prototyping, used to fabricate a tangible assembly of medicine using 3D CAD data by combining a series of processes. Here, 3D printer receives instructions in CAD file and build an object by moving print head across x-y-z plane.

3D Printing Technologies

Before selecting a 3D printer to be operated, we should consider all the material parameters which is to be used in addition the way by which layers are bonded. The main approaches to consolidate materials are mechanical, photochemical and thermal transformation. Most common 3DP technologies are Selective Laser Sintering (SLS), Stereolithography (SLA), Thermal Inkjet Printing (TIJ), Fused Deposition Modeling (FDM), etc.

Thermal Inkjet Printing

This technique utilizes deposition of ink droplets, which constitutes the materials to be deposited over a substrate by employing electromagnetic or thermal technology. Here the print heads are heated, generates tiny air bubbles that will collapse and prompt pulses that produce ink out of nozzle, of volume 10-150 picoliters. Droplet size can be adjusted by varying applied

temperature, frequency of pulse and viscosity of ink. Altering the number of layers printed in a particular area will help in changing dose of the medicament and can thereby achieve dose accuracy. This technology has an advantage of combining doses and modification of drug release.

Characteristics of the material influences the process, particle size should be <1μm, in order to avoid clogging up of print head; viscosity should be <20 cP and a surface tension need to be in between 30-70 mN/m for efficient flow. Thus we can incorporate low therapeutic doses, even in microgram range [5].

Stereolithographic Printing

This technique involves photopolymerization to form a 3D object. Curing of photosensitive material (photo-polymerization) is made possible by ultraviolet (UV) light or by the use of a digital light projection (DLP) technique. The process is mediated by digital mirroring device that initiates a chemical reaction in the photopolymer, results in the gelation of exposed area. The process continues until object formed. The layer formed as the unreacted functional group on solidified structure in one layer polymerizes with the illuminated resin in subsequent layer, ensuring adhesion [6, 7].

Selective Laser Sintering (SLS)

In this process, the substrate used for printing is powdered materials. Laser draws object shape in the powder and fuse it together. A new layer of powder stacked over it and process continues until a complete object formed. Detailed and intricate structure can be generated using this technology. Sintered materials form the final product, at the same time un-sintered materials left as a supporting structure. This technique is not widely applied in pharmaceutical products, due to the utilization of higher energy from the laser beam that increases the possibility of degradation [1, 4 ,6].

Powder Based 3D Printing

This technology is in use from 1980s and is developed by Massachusetts Institute of Technology (MIT). In this technique, thin layers of powder are distributed which is then combined by applying liquid binder drops from an inkjet/piezoelectric printer head. Post-printing processes are done to remove excess powder arise during printing, which attributes to the wastage of materials. PB 3DP contributes highly porous structures makes it of poor mechanical strength and high friability. However, this technology has been adapted in the industry due to its easiness [6].

Fused Deposition Modelling

This technique is also known as Fused Filament Fabrication, is inexpensive, in addition common. Inside the print head, substrate is heated over melting point and allowed to extrude through nozzle [7] and deposited layer after layer. Thermoplastic polymers such as PVA and PLA have been used as drug carriers and drug loaded into it by incubation in saturated drug organic solution. To enhance polymer range to be adopted into the production, we will combine FDM with Hot Melt Extrusion. Production of tablets in different shapes (cube, spherical, cylindrical, pyramid) can be made possible with this technique. FDM utilizes a high temperature~220℃, which may leads to the degradation of many drugs is one among its limitations. Generally, this technique obtains extended release products [6, 1].

Semi-Solid Extrusion (EXT) Printing

The technique involves semisolid substrate material deposition through a syringe headed tool. Semi-solids, such as pastes or gels mixed in combination with the polymer and solvent to form a mixture of right viscosity, enable it for printing. Since the material has been used in gel or paste form, there may be chances of shrinking or deformation of product after drying process [4].

ZIP Dose

Zip dose technology is the first FDA validated 3DP technique regulated in the drug manufacturing area. The first FDA approved 3D printed medicine is Aprecia's Spritam, an oral dosage form of Levetiracetam which is an anti-epileptic drug in 2015 formulated using this technology. By this technology, we can load upto 1000mg of active drug. Zip dose technology relies upon the layer by layer powder bed fusion system, where a layer of active pharmaceutical ingredient is fused with that of excipients and subsequently a binder liquid [8].

Regulations in 3D Printing

Legal rights, to protect both consumer and manufacturer are of primary concern in this rapidly growing scenario. Potential effects of 3D Printing is studied by FDA's Office of Science and Engineering Laboratories (OSEL), Laboratory for Solid Mechanics and FDAs Functional Perfomance and Device Use Laboratory. Approximate of about 85 medical devices and implantables developed through 3D printing technology have gained clearance from FDA [2, 6].

Dose Tailoring and Personalization

3DP is a highly flexible, simple and accessible technique. We can alter the dose and dosage form according to

patient's needs. This application is most important in case of pediatric and geriatric doses.

"Polypill" as the name suggests, is a single tablet that include multiple drug, advantageous for those who take medication for multiple drug therapy. This has been benefitted in cardiovascular protection and in the treatment of hypertension [2, 9].

Khalid et. al., introduced this technology where he incorporated active ingredients of varying release characteristics into single system. Atenolol, Ramipril and Pravastatin were printed in an sustained release compartments separated with a permeable membrane of Hydrophobic Cellulose Acetate with a top layer formed by Aspirin and Hydrochlorothiazide. This combination is a potential treatment for the diabetics who is suffering from Hypertension [10].

Constraints of 3D Printing

Most 3D printing technologies are based on nozzle technique to construct layer after other to form a solid object. This directs to a challenge in maintaining consistent flow as print head break off. Also chances of clogging up of nozzle head, binder migration and improper feeding may affect the formulation characteristics.

The very first step to the printing of medicines is the selection of raw materials. While selecting, we have to consider whether it is printable, its physical and chemical properties, thermal conductivity, melting point etc. therefore, the choice of material are important [4].

Several machines work on high temperature that imparts the disintegration of materials even before manufacturing. Surface imperfections can be observed with many formulations due to accumulation of plastic beads and powder layer over other [2].

Post processing treatments like unsticking objects from build platform and brushing of excess powder may leads to product wastage and affect its appearance and final characteristics.

Since all of these processes are computer designed, there are risks of cyber hacks. The blueprints and the CAD data can be accessed and there will be large outflow of fake manufacturing. This will be a threatening situation to both consumers and manufacturers [3].

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