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3D PRINTING IN PHARMACEUTICAL PRODUCT

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ABSTRACT .

Three-dimensional printing is a revolutionary technique that uses computer aided design software and programming to create three dimensional objects by placing material on a substrate. 3D printing is an additive layer manufacturing techniques, where consecutive layers of material are deposited or solidified to form a 3D structure. The 3D PRINTING technology has caught the attention of medical devices industry and pharmaceutical industry due to its applications on various platform in health care industry. Even though this technology exists for a long time it is of public interest highly now due to the approval of 3-D printed tablet and other medical devices and also with the advent of USFDA's guidance on technical considerations specific to devices using additive manufacturing which encompasses 3-dimensional (3D) printing has triggered many thoughts about this technology which needs to be considered for successful delivery of intended product. This technology will reform the pharmaceutical manufacturing style and formulation techniques.

Keywords- Revolutionary technique, 3D printing, medical device, Tablet ,revolutionary,3D structure,3D dimensional

INTRODUCTION

Three-dimensional printing is matchless method which uses computer aided drafting technology and programming to make three dimensional objects by layering material onto a substrates(1).Now a days, 3D printing could be extended throughout the drug development process, ranging from preclinical development and clinical trials to frontline medical care(2). Different types of drug delivery systems for instance oral controlled release systems, micro pills, microchip, drug implants, fast dissolving tablets and multiphase release dosage forms have been developed using three-dimensional (3D) printing technology(3). Three-Dimensional Printing technology is a novel technique for rapid prototyping, which constructs solid objects by deposition of several layers in sequence. It seems that 3D printing technology will lead a new approach of the next industrial revolution based on its versatility and diversity3D printing technology has enabled unprecedented flexibility in the design and manufacturing of complex objects, which can be utilized in personalized and programmable medicine.(4)

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.(5)

HISTORY

3D Printing posed as a possible platform for personalized medicine in the 1990s. There are major achievements in 3D printed medical device, FDA's Centre for Device and Radiological Health (CDRH) has reviewed and cleared 3DP medical devices (6). 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. The process was repeated until the final desired structure was obtained. This first happened in the early 90's at the Massachuset Institute Technology invented and patented by Sachs et al (7). In 1989, Scott Crump, filed a patent on another 3D printing technology: fused deposition modelling, 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 (8, 9). Inkjet printing was the method used to manufacture Spritam (levetiracetam) tablets for oral use, the first 3D printed drug approved by the Food and Drug Administration (FDA) in 2016 by Aprecia Pharmaceuticals (8). 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 advanced manufacturing technologies, including 3Dprinting, using risk-based approaches.

ADVANTAGE OF 3D PRINTING IN THE PHARMACEUTICAL FIELD

1. Enhanced productivity: 3D printing works more quickly in contrast to traditional methods especially when it comes to fabrication of items like prosthetics and implants with an additional benefit of better resolution, repeatability, more accuracy, and reliability [10]. . 2. Customization and personalization: One of the pioneer benefits of this technology is the liberty of fabrication of customized medical equipment and products. Customized implants, prosthetics, surgical tools, fixtures can be a great boon to patients as well as physicians [10].

3. Increased cost efficiency: Objects produced by 3D printing are of low cost. It is an advantage for small-scale production units or for companies that produce highly complex products or parts because almost all ingredients are inexpensive [11, 12]. By eradicating the use of unnecessary resources, manufacturing cost can also be reduced. For instance, 20-mg tablets could be potentially formulated as 1-mg tablets as per need [13]. 4. 3DP allows controlled size of droplets, complex drug release profiles, strength of dosage and multi-dosing [14, 15, 16].

DISADVANTAGE OF 3D PRINTING

1. In inkjet printing, proper flow of ink can only be achieved with ink that has precise viscosity [17].

2. Ink formulation material should have the property of self-binding but should not bind to other printer elements. In some formulation when the ink does not possess adequate self-binding property or it binds with other elements of printer then the resultant formulation does not have required hardness [18].

3. Rate of drug release may get affected due to binding of ink with other printer materials [19].

3D PRINTING PROCEDURE

1. First, a virtual 3D design of an object using digital design software like On shape, Solid works, Creo parametric, Autocad, Autodesk etc. is created [20, 21, 22].
2. This digital model is then converted to (.STL) digital file format which stands for standard tessellation language or stereo lithography [20].
3. Triangulated facets give information regarding the surface of the 3D model that is present in the (.STL) file [20].
4. The (.STL) file is converted into G file by slicing the design into a series of 2D horizontal cross-sections by the help of specialized slicer software, which is installed in the 3D printer
5. Now the print head is moved in the x-y axis to create the base of the 3D object.
6. The print head is now allowed to move in the z-axis, thereby depositing the layers sequentially of the desired material, hence creating a complete 3D object [20, 23]. Maximum numbers of 3D printing technologies are compatible with (.STL) file format. Some errors might occur during the conversion of the 3D model to .STL digital file; therefore, software like Magic's (Materialise) can be employed to correct the errors during conversion. File formats other than .STL like additive manufacturing file format (AMF) and 3D manufacturing format (3MF) are used as .STL does not have information regarding the type of material, its colour, texture, properties, and other features [24].

3. TYPES OF 3D PRINTING TECHNOLOGY

1 Fused deposition modelling (FDM)- The process involves the selection of the desired polymer, which is melted and forced through a movable heated nozzle. Along the entire 3 axis (i.e., x-y-z), the polymer is laid down layer by layer, which on solidification gives the exact shape as was designed by computer aided design models. Multiple dosage forms like implants, zero-order release tablets etc. that include polymer as a part of their formulation can be made by this method [25, 26–28].

2 Thermal inkjet (TIJ) printing- It involves the heating of ink fluid by the help of micro-resistor, thereby creating a bubble of vapor that nucleates and upon expansion forces the ink to drop out of the nozzle. Dispensing of extemporaneous preparation/solution of drug onto 3D scaffolds is an area where this technique can be employed [29, 30].

3. Inkjet printing It is a powder-based 3D printing that utilizes powder as a substrate on which layer by layer different combinations of active ingredients and ink is sprayed which is of varying droplet size that eventually solidifies into solid dosage form [25, 26, 31–35].

4 .Direct-wise It encompasses a pattern-generating device that moves as per the guidance of computer-controlled translational stage so that layers after layers are put on in order to achieve a 3D microstructure [42].

5. Zip dose- This technology provides a personalized dose in additional to the delivery of a high drug-load with high disintegration and dissolution levels by manufacturing highly porous material [32].

6 .Vat photo polymerization -It is light-induced polymerization where materials like photopolymers, radiation-curable resins, and liquid are collected in vats, which are successively cured into layers, one layer at a time by irradiating with a light source, thereby providing a 2D patterned layer. This involves techniques such as stereo lithography (SLA), digital light processing (DLP), and continuous direct light

processing (CDLP). Depending on the orientation of light source and the surface where polymerization of the photoactive resin occurs, SLA can be divided into two different configurations: 1. Bath configuration (free surface approach) 2. Bat configuration (constrained surface approach) [2].

Limitations and Challenges of 3d Printing Dosage Forms There are a couple of challenges that 3D printing faces which has to be overcome before it is adopted as a widely used manufacturing technique for personalized dosage forms. Process Challenges

Raw material physicochemical selection: characteristics, thermal conductivity, Print fluid characteristics and viscoelastic property has to be carefully scrutinized along with safety of the raw materials for human

use Nozzle. Mechanisms :during 3D printing, nozzle mechanism is used to form the layers of the dosage form. As the printer head stops and restarts during the sequenced layer formation, consistent flow of the printing material is necessary. The common problems faced at this level are clogging of the nozzles in printer head, scraping, binder migration and bleeding and improper powder feeding (36). Powder based 3D printing: confined or special area is required to perform the printing as powder spillage is critical and can pose as an occupational hazard (37)Surface imperfections in finished product: due to stacking of plastic beads or large-sized powder on top of each other. Since the drying time required for the dosage form made with powder based and extrusion based techniques, there is more possibility of surface imperfections. Rate and method of drying can also affect surface imperfections (38 Mechanical resistance: friability is higher in 3D dosage forms especially in powder based technique. Production technology is important for good dosage form strength (39). The material choices, colours, and surface finishes currently available for 3D printing are relatively limited when compared to conventional tablet compression processes (39).Certain manufacturing process may not be appropriate for thermolabile drugs when printing at high temperatures (40).

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 through 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 (41) When a given printer is unable to print a given design, software controls should be employed

1. Variability in layer thickness has to be controlled by real – time layer thickness monitoring.
2. Improper layering due to environmental conditions should be dealt with controlling the temperature and humidity of the manufacturing areas .
3. naccurate position during printing can be avoided by monitoring print head height and print head speed.
4. Uneven layers can be avoided by checking powder water content and powder particle size distributions.
5. Print head clogging can be prevented by ensuring particle size distribution and monitoring inkjet flow.
6. Inconsistent agglomeration or binding can be due to variations in binder viscosity or binder surface tensions.

CONCLUSION

3D printing technology is a valuable and potential tool for the pharmaceutical sector, leading to personalized medicine focused on the patients' needs. It offers numerous advantages, such as increasing the cost efficiency and the manufacturing speed. 3D Printing technology will revolutionize the pharmaceutical manufacturing

style and formulation techniques. In the near future 3D printing approach will be utilized to fabricate and engineer various novel dosage forms. Although commercial production of such novel dosage forms is still challenging; developing personalized medication, optimized drug release from dosage form, compacting or avoiding drug-drug incompatibilities, protection of biomolecules during manufacture, construction of multiple drug dosage form and multiple release dosage forms will be taken to a new era through 3D printing technology.

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