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3D PRINTING TECHNOLOGY IN PHARMACEUTICAL INDUSTRY

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ABSTRACT

3D printing technology is a novel technology. It is a process used to create 3D objects by deposition of layer upon layer of different shapes obtained from a virtual design of the objects using computer aided design. The process of layer deposition is an additive process. Each layer is a thinly cut cross section of the finished product. It is useful for medication with narrow therapeutic indices. In case of long-term illnesses like HIV where people are required to take 20 tablets a day, producing a polypill of all the APIs of these tablets using 3D printing technology may provide effective treatment. 3D printing technology can be used for targeted drug release. It intends to revolutionize the field of drug manufacturing and the surgical process.

KEYWORDS: Computer aided design, Polypill, 3D printing, Novel drug design.

INTRODUCTION

3D printing aims to provide tailor made tablets as per patient need. It takes into consideration the pharmacogenomics with the information about their diet, lifestyle, and environment. Since the current pharmaceutical companies fail to comply these growing needs of the patients, a novel technology like 3D printing proves useful.

This ensures a move over manufacture of tablets with predetermined dosage amount. A paradigm shift in manufacture of medicines is required. The new technology should not only be able to generate such medicines, but it should do so in short period of time, must be economically viable, occupy minimal space and have operational training requirements. In 2015, the U.S. Food and Drug Administration agency (FDA) granted the approval of Spritam (levetiracetam), the first 3D printed tablet for the treatment of epileptic seizure.[1]

MATERIAL AND METHODS

Types of 3D printers

1) Laser based writing

It is based on the principle of photopolymerization, in which free radicals are released after the interaction between photo initiator and UV light.[2,3,4]

a) Selective laser sintering 3D printing.

This is a lesser used technique as the possibility of chemical degradation of the material is high. Instead of resin, powder bed is spread as thin layers and radiation is used to fuse them and sinter the bed layer by layer.[5]

b) Stereolithographic 3D printing

This technique involves the use of photopolymerization to produce a 3D printed object. Scanning a focused UV laser over the photopolymerizable liquid in a layer by layer fashion, induces a chemical reaction is that causes gelation of the exposed area. Layer upon layer repetition of this process produces an entire object. The layers stick together as the unreacted functional group on the solidified structure polymerizes with the illuminated resin in the next layer producing adhesion of layers. Thickness of the cured layers depends upon the energy of UV light and to which resin is exposed. The resin used must be FDA approved for human use and must have the ability to solidify upon exposure to UV.[6,7]

2) Thermal inkjet printing

These printers use thermal, electromagnetic, piezoelectric technology to deposit tiny droplets of “ink” onto the substrate in accordance with the digitalized instructions fed to the printer. The ink is ejected from the nozzle using heat or mechanical compression.[8]

3) Fused deposition modeling

These are the most common and inexpensive type of printers. They are somewhat similar to the thermal inkjet printer. But instead of ink they use beads of heated plastic onto the substrate. These beads of heated plastic cools, hardens and eventually forms a solid object.[9]

4) Power bed inkjet 3D printing

This involves two chief droplet forming techniques:

1. Continuous jet printing (CJ)
2. Drop on demand (DOD)

CJ printing involves release of charged droplets in continuous stream through a nozzle under pressure. These droplets are directed towards the substrate with the help of electrostatic plates.

DOD printing is more precise than CJ printing because it produces droplets which are dispensed only when required, this results in less wastage. Hence the name. The volume can be as low as 1-300pL and frequency up to 10000Hz.

DOD printheads operate on two mechanisms

1. Thermal

The heat generated due to the embedded resistors on account of induction of electric current, causes formation of bubble within the volatile material used this results in the mobilization of small amount of material out of the nozzle causing droplet formation. This involves use of high vapor pressure solvents and can cause degradation of heat labile bioactive compounds.

2. Piezoelectric trigger

Piezoelectric materials are those which expand and contract when electric current is induced. This periodic pressure difference generated during this process leads to the mobilization of liquid out of the nozzle in the form of droplets.[10]

This method is preferred over thermal inkjet printers as they can be used for volatile and thermo labile substances.

The 3D printing of tablets helps produce customized product and patient centric medicine. It can be primarily used in the development of pediatric and geriatric medicines.[11] However, a major problem that one might face during manufacturing of 3D printed tablets is the biocompatibility of the printing material and other ingredients in the tablet. Also, another disadvantage is increased defects during manufacturing of polypills that contain more than one API. Incorporation of amorphous drugs can be easier.[12] It involves melting of API and a polymer or heating of the drug solution to evaporate the solvent. The use of individualized pharmacotherapy is based on age, body weight, lifestyle of the patient, medical history, etc. 3D printers can be installed in hospital pharmacies as well as community pharmacies that would raise the level of pharmaceutical compounding. The geometric shape, size, dimensions of the 3D printed tablet must also be taken into consideration as it affects the dissolution rate of the tablet. The geometric shape that has the biggest surface area\volume ratio has the fastest dissolution rate.

Personalized medicine refers to the customization of the formulation depending upon genetic testing, proteomics and metabolomic analysis. The major advantage is to increase the effectiveness of the medicine in individual patient and achieve a large therapeutic index. 3D printing technology also helps in reducing the number of steps in the traditional manufacturing process.

It also can produce viable solid dosage forms in a complex geometric pattern. The major reason of designing a personalized medicine is for targeting the specific needs of the individual patients. Extrusion BASED 3D printing of tablets allows high drug loading. The mesh-like geometry allows faster drug release.

Evaluation parameters

1. Tablet’s shape and dimensions.
2. Weight variation.
3. Breaking force.
4. Friability.
5. Drug dissolution testing.
6. X-ray powder Diffraction.
7. Dimensions of 3D printed tablets.
8. Differential scanning calorimetery.

Zip dose technology

Zip dose technology is a technology developed by Aprecia Pharmaceuticals that helps in manufacturing of tablets with high drug loading capacity and instant oral-dispersible tablets. A disc shaped powdered bed is formed and the droplets of liquid are dropped from the nozzle. Due to this the mixing of the powder with liquid takes place at microscopic levels. Tablets with high drug loading capacity are produced as the technology squeezes the API and excipients into the tablet making more space to load a larger amount of dose. Also, tablets produced using zip dose technology disintegrate immediately upon contact with the tongue.[1]

Biomedical applications

The scope for customization that 3D printing allows makes it an indispensable tool in the biomedical engineering that provides patient specific implants that corresponds to the anatomy of the patient.[13]

- **Wound dressing**

Muwaffak put forth the idea of patient specific antimicrobial wound dressing made from Polycaprolactone incorporated with zinc, copper, and silver. The 3D models of nose and ears were obtained using hot melt extrusion of homogeneously loaded filaments. These dressings showed prolonged release of metals and bactericidal properties.

- **Implant and Prostheses**

The development of patient specific implants and prostheses can be completely revolutionized by the additive manufacturing as it can provide site specific mechanical and physical properties as well as spatial and temporal control of bioactive components. Herbert and coworkers demonstrated that 3D printing is an efficient technology of fabrication of prosthetic socket that patients after amputation find comfortable. Zuniga prepared low cost 3D printed hand for children upper-limb reductions.

- **Models for Surgical Planning and Training, Phantoms**

The use of 3D printed models enables accurate diagnosis, better evaluation, and assessment of the pathological changes in patient anatomy. One of the applications of the technology is the manufacturing of liver models. The growing demand for transplantations combined with the limited number of cadaveric livers increase the need of using the organs from healthy donors. The preoperative identification of the anatomy of the biliary tract and can increase the safety of both the donor and recipient. The colour coded vasculature was developed by Zein and his coworkers in 2013.[8]

- **Personalized Development of human organs using 3D printing**

With the increasing number of cases of organ failure and issues such as organ shortage, unavailability of suitable donors and high cost for organ transplantation procedures, 3D printing technology could be efficacious.[14]

The major issue with organ transplantation is life-long immunosuppression. This issue can be addressed with the help of 3D printing technology.

3D printing of human hollow organs like urethra, arteries, bile duct, etc. can be done by making use of detailed patient information obtained from medical imaging, 3D printing and suitable cell type.

However, there are certain issues associated with the application of 3D printing into clinical medicine such as vascularization, innervation, cost, and safety of the biomaterial used.

Another challenge faced would be preventing cell death during heating and printing of the scaffold.[11]

A lot of 3D printing medical devices have been cleared by the FDA's Center for Device and Radiological Health.[15]

The 3D printing can also help to plan the operation of resection of tumor in case of colorectal liver metastasis. But, the size of printer in this case is limited therefore the model was divided into 4 parts. The anatomy of the patient liver was obtained using CT scan and the contours, blood vessels and tumor were printed. The separate parts were then assembled and filled with silicone.[16]

Challenges in 3D printing

The technology is still in its infancy as the various important parameters remain unresolved. These challenges include the optimization of the process, improving the performance and selection of excipients, etc. Drop on demand printer heads show the problem of nozzle clogging. To achieve the quality 3D printed products the compatibility of excipients and binders need to be addressed. It is also mandatory to study the rheological properties of the binder polymers.[17]

CONCLUSION

The review shows that scope of 3d printing technology although wide has still got its own limitations. In the near future this technology has the potential to take the industry closer to the patient centric drug manufacturing and drug delivery. However, in order to achieve the aforementioned goal, it is also imperative to tackle the challenges that this technology faces, particularly the large-scale commercial operations. More and more scientists need to come forward and attempt to revolutionize this technology, so that it serves a useful purpose to the pharma industry.

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