Available online on www.ijpqa.com
International Journal of Pharmaceutical Quality Assurance 2018; 9(3); 267-270
doi: 10.25258/ijpqa.v9i3.13658
ISSN 0975 9506

Research Article

3D Printing: An Emerging Technology in Pharmaceuticals

Sharma S*, Saxena V

Ram Eesh Institute of Vocational and Technical Education, 3 Knowledge Park-I, Greater Noida, U.P. India 201310

Received: 7th Aug, 18; Revised: 31st Aug, 18, Accepted: 14th Sep, 18; Available Online: 25th Sep, 2018

ABSTRACT

Three-dimensional (3D) Printed medicines can be defined as the potential tools/medicines to achieve personalized treatments adapted to the specific requirements of each patient, taking into account their age, weight, comorbidities, pharmacogenetic, and pharmacokinetic characteristics. The aim of this review is to give an overview of 3D printing in pharmaceuticals, highlighting their advantages, disadvantages and applications. 3D printing technologies will emerge as boon to the pharmaceuticals and humanity.

Keywords: 3D printing, Personalized Medicines, Drug Delivery, Additive layer fabrication, Customized Medicines.

INTRODUCTION

An Introduction to 3D-Printing Technology: Three Dimensional Printing (3D) Printing is also known as Additive layer fabrication or Additive Manufacturing because it involves precisely adding layer on top of layer to build a 3D object[1,2]. It has capability to produce sophisticated structures in click. 3D printing brought an evolution of the field of printing. The process consists of two stages:

The direct transfer from software data to printed structures: First the design is made by in CAD (Computer Aided Design) file using a 3D-modeling program, such as SolidWorks® or AutoCad®, and then the areas are printed through a compilation of two dimensional slices representing the 3D object to consequently print layer by layer until the object is completed.

Repeatedly positioning the print head in all three axes in space in order to print the whole object layer by layer: The second stage of the manufacturing process can also be subdivided in two basic steps- Coating and Fusing. Throughout these steps, the material is laid over a surface and by the action of a source of energy the layers are created. The source of energy and the raw materials vary depending on the used technology[3].

Following techniques of additive manufacturing are mostly used in the 3D printing of medicines. The main differences between them being the way layers are deposited and the materials used[4].

Printing-based inkjet systems: The two main modes of inkjet printing are continuous inkjet (CIJ) mode and drop-on-demand (DOD) mode. In both the methods, the liquid goes through an orifice or nozzle. In former method the flow is continuous and breaks into a stream of droplets, charged and deflected using plates onto the substrate during printing. Rest of the droplets is collected by catcher for recycling. The method is fast, useful for markings and bar coding.In the later widely used method, drop is only generated as needed by thermal or piezoelectric actuation and it produces products of high resolution. As compared to CIJ, this printer is prone to drying of ink at the nozzle during downtime[5].

Nozzle-based deposition systems: In this process drug and polymer are mixed prior to 3D printing and passed through a nozzle that ultimately turn up into three dimensional product.

Laser-based writing systems: This is more popular technique as the laser beams are focused and directed very accurately. It is of two types Stereolithography (SLA) and Selective Laser Sintering (SLS). In the former 3D objects are produced in layer by layer fashion by photopolymerizing a photosensitive material with an ultraviolet (UV) laser. It is basically described as a system for making solid objects by successively curing thin layers of a photo-polymer using UV light. The later technique employs a high-power laser to sinter layers of material in powder form. The laser beam heats the powder to melting point and causes the powder particles to melt together to form a solid mass. Subsequent layers are built directly on top of the earlier layers, with new layers of powder deposited on the top of the already sintered layers using a roller[6].

FDA and the Revolutionary 3D Technology

With the development of Spritam-A revolutionary antiepileptic, first US-FDA approved drug has opened gateway to a promising 3D technology in pharmacy. It has marked beginning of a new era which was even difficult to imagine a few years back[6].

FDA experts are striving for understanding of the science involved in 3D printing of drugs and devices at its Center for Devices and Radiological Health (CDRH) and the Center for Drug Evaluation and Research (CDER). Though there is no unique regulatory pathway for the approval of 3D drugs, but there are existing approval pathways that are flexible enough to address new technologies, small batches, orphan/expedited review, and personalized medicines. In anticipation of possible unique

**Author for Correspondence: shalinisharma23@yahoo.com*

challenges, FDA is working with drug makers in a new way to help the industry adopt scientifically sound, novel technologies to produce quality medicines that are consistently safe and effective. This will be a large step towards avoiding drug shortages[7,8].

Advantages of 3D-Printing in Healthcare: Following are the advantages of this revolutionary technology

Personalized Medication or Patient Specific medication:[4,2,9]

This aspect leads to the following advantages

Ability to stratify patient population and segregate them in more precise manner

Suitable for patients who respond to drugs in different ways

Based on age, race and gender of patients

Delivers optimal medication dose

Deliver combinations of drugs to treat multiple ailments

Ideal for targeted and controlled release of drugs

High drug loading which is difficult to achieve with conventional technology

Clearer understanding of drug performance

Instantaneous release of drug

Versatile Technology: The versatility of the techniques clearly indicates the advantages associated with improving controlled release, targeted release, and delivery of poorly water soluble drugs without compromising quality and efficacy of the dosage form. Inspite of the complexity of human anatomy, technology is able to create complex shapes and geometry in order to deliver drug in a different way[10,11,12]

Fewer Side Effects: Inter individual variability is an increasingly global problem when treating patients from different backgrounds with diverse customs, metabolism, and necessities. Dose adjustment is frequently based on empirical methods, and therefore, the chance of undesirable side effects to occur is high. Personalized medication will leads to fewer side effects[13].

Consumer acceptance: Tailor made medicines will be widely accepted by humans. For pediatrics it may prove to be ultra beneficial as the drug design may be customized as per child's acceptance and demand[14].

Suitable for Orphan Drugs: Orphan drugs are medicinal products intended for diagnosis, prevention or treatment of life-threatening or very serious diseases or disorders that are rare. Cycle Pharmaceutical founded by James Harrison is involved in manufacture of orphan drugs. The company has signed a deal with Aprecia Pharmaceuticals**,** a company specialized in the 3D Printing (3DP) of drugs to explore the possibilities offered to patients with rare diseases. Research on these possibilities can drastically improve their quality of life and raise the interest of the healthcare industry[15].

New Organ Development: Patients needing organ replacement are dependent on the availability of organs from living or deceased donors. They are given immunosuppressive drugs during and after the treatment. This causes numerous side effects and added cost to the therapy. Development of 3-D printed biological tissues for organ replacement hopes to offer a revolutionary solution provided nerves, blood vessels and lymphatic vessels are integrated and are compatible with the host system to create transplantable organs such as kidneys, lungs, hearts or livers[16].

Bioprinted cells for drug testing: Introduction of new drug to market involves a lot of money and time. Out of identified new drugs, only about 10% qualifies for the regulatory approval. Due to physiological differences between trial animals and human subjects, some drugs fail to show efficacy in humans despite showing promising results in animals. Complex human models reproducing human liver, kidney or heart muscles created using 3D printing technology are suitable for testing and identifying novel pharmaceutical molecules. These models are currently being used by multinational companies for research purpose. FDA is also considering this alternative for drug safety and assessment along with trusted animal studies[16].

Reduces dependence on animal testing: Restrictions are imposed by regulatory agencies on the use of animals for drug and cosmetic testing. Technology is now available and has enabled a reduction in the number of research animals. Human-based 3D models of skin are widely used. Microphysiological Systems (MPS) consisting of interacting organs-on-chips or tissue-engineered 3D organ constructs can simulate the structure and function of native tissues in vitro. These constructs are made with immortalize cell lines, primary cells from animals or humans or from human embryonic stem cells. Each construct is designed to replicate the structure and function of human organ or organ region in compatible cellular microenvironment. It has the potential to replace/ alternate conventional testing. It should dramatically reduce animal testing numbers, as it can replace the need to test on animal subjects[17]

Useful in Pharmaceutical Product Packaging: Product packaging is another field where 3D printing has been used and is found to be economical and helpful in modifications in product packing especially for older people's convenience. We just need a CAD blueprint to prepare a part instead of using number of traditional techniques like injection molding, thermoforming and blow molding etc.[18]

Aid surgical training and practices: as the technology is having easy access to digital (CT Scan/MRI) anatomical data in hospitals and dental practices[17]

Improve R& D productivity: CDER/OPQ's Office of Testing and Research (OTR)'s Division of Product Quality Research (DPQR) has established a manufacturing science research program. The goal of this program is to enable innovation and advancement and to understand the risk and benefits of novel technologies, including process analytical technologies and 3D printing, to support FDA's regulation of pharmaceutical quality. They are also working on understanding of the relationship between material properties and process parameters on product quality for 3D-printed drug products. Academic researchers are investigating 3DP for printing living cells and organs[7].

Applications of 3D-Printing in Healthcare [19,20,21,22,23]

Following are the areas where 3D printing is benefitting the health care segment

Fast dissolving Oral Films
Patient Specific Dental Implants
Invisalign Braces
Medical Devices
Tailored Orthopedics
Tailored products for maxillofacial / Craniomaxillofacal surgery
Orodispersible Tablet
Abuse Proof Tablets
Patient Specific Prosthetics
Hearing aids
Customized, solid-dosage drugs that can combine multiple types of drugs and different release rates

Challenges of 3D-Printing in Healthcare[24,25,26]

Investment of money and time: Application is projected as over simplified but it requires huge Investment of money and time

Proliferation of counterfeit medicines: There is a possibility of cyber risk as printers are more vulnerable to hackers than the traditional manufacturing process. Hackers may gain access to drugs blueprints. There is also a possibility of alteration to a drugs recipe or dose within a hospital or pharmacy where the drug is printed.

Large Scale Production: There are many complexities in implementation and it will take some more time to make technology suitable for large scale production. There are several drawbacks when using this technique and also the type of polymers readily available do not always possess the optimal properties for every drug. [4]

Safety and efficacy concerns: As compared to the traditional medicines which were subject to testing by regulatory bodies to produce safe and efficacious drugs, it is impossible to regulate every instance of 3-D printing.

Complexity of human structure: Due to intricate nature of vascular network, designing is very difficult. Body organs such as kidneys, livers and hearts are incredibly complex tissues. Each is made up of many different cell types, plus other components that give the organs their structure and allow them to function as we need them to. For 3D printed organs to work, they must mimic what happens naturally – both in terms of arrangement and serving a biological need. For example, a kidney must process and excrete waste in the form of urine. each cell type that makes up the different tissues of the human anatomy requires a unique mechanical environment. Each requires unique structural supports to function normally. As an example, bones are a resistant and brittle material, muscles of the heart are elastic, tough materials, and internal organs such as the liver are soft and compressible.

Factors which will further boost 3D- Printing Technology [1, 2, 27, 28]

Technological advancements and new scientific concepts e.g 3D bioprinting that involves adding cells to the printing technology. It requires appropriate temperature, humidity and sterile atmosphere to ensure that cells do not die.
Interdisciplinary Work: Pharmacy companies' needs to work closely with IT companies to understand the risk involved and top ensure proper functioning of printers.
Defined regulatory guidelines
Verified suppliers to ensure pure raw materials.

Some Milestones Achieved till yet

Aprecia's Spritam (levetiracetam) tablets for oral suspension used for the treatment of seizures in adults and children with certain types of epilepsy is the first 3D-printed drug approved by FDA in August 2015
RepRap, a 3D printer that is designed to be able to print replicas of itself is invented by Adrian Bowyer at Bath University, UK
Harvard university researchers have built the first fully 3D printed '*heart-on-a-chip'* by a completely automated digital manufacturing procedure. It can be quickly fabricated and customized to allow researchers to easily collect reliable data for short and long-term *in-vitro* studies.
Bioprinters uses human cells as ink. Like a 3D printer, it layers human cells and other biocompatible supporting materials to form three-dimensional tissues and organs

CONCLUSION

Patient focused 3D fabricated, personalized/ customized drug delivery system has shown sufficient promise in the field of medicine and pharmaceuticals. The technology holds immense potential in the field of organ development/ transplant and will reduce dependence on animal testing for new drug molecules. The technology is safe, versatile, customizable, biocompatible, reproducible and immensely beneficial to the mankind. However, issues related to large scale production, safety, efficacy and stability of drugs need to be addressed in the light of regulatory guidance to get the complete benefit of technology.

REFERENCES

1. Jassim-Jaboori AH, Oyewumi MO. 3D Printing Technology in Pharmaceutical Drug Delivery: Prospects and Challenges. Journal of Biomolecular Research & Therapeutics 2015; 4(4):1-3.
2. David KM. Future Medicine: The Impact of 3D Printing. Journal of Nanomaterials & Molecular Nanotechnology 2015; 4(3):1-3.
3. Wohlers T. Additive Manufacturing Advances. Manufacturing Engineering 2012; 148(4): 55–56.
4. Andrea AK, Marta GP, Dolores RS. Personalized 3D Printed Medicines: Which Techniques and Polymers Are More Successful? Bioengineering 2017; 4:79.
5. Yang G, Huseini SP, Brice B, Anson WK. Inkjet and inkjet-based 3D printing connecting fluid properties and printing performance. Rapid Prototyping Journal 2017; 23(3):562–576.
6. Wang J, Goyanes A, Gaisford S, Basit AW. Stereolithographic (SLA) 3D printing of oral modified-release dosage forms. International Journal of Pharmaceutics 2016; 503:207–212.
7. Markarian J. FDA and the Emerging Technology of 3D Printing. Pharmaceutical Technology 2016; 40: 8
8. FDA, *Draft Guidance for Industry: Advancement of Emerging Technology Applications to Modernize the Pharmaceutical Manufacturing Base* (Rockville, MD, Dec. 2015).
9. Goyanes A, Buanz AB, Hatton GB, Gaisford S, Basit AW. 3D printing of modified-release aminosalicylate

(4-ASA and 5-ASA) tablets. European Journal of Pharmaceutics and Biopharmaceutics 2015; 89:157-162.
10. Tails M, Wallace GG. 3-dimensional (3D) fabricated polymer based drug delivery systems. Journal of Controlled Release 2014; 193:27-34.
11. Khaled SA, Burley JC, Alexander MR, Roberts CJ. Desktop 3D printing of controlled release pharmaceutical bilayer tablets. International Journal of Pharmaceutics 2014; 461:105-111.
12. Khaled SA, Burley JC, Alexander MR, Yang J, Roberts CJ. 3D printing of five-in-one dose combination polypill with defined immediate and sustained release profiles. Journal of Controlled Release 2015; 217:308-314.
13. Skowyra J, Pietrzak K, Alhnan MA. Fabrication of extended-release patient-tailored prednisolone tablets via fused deposition modeling (FDM) 3D printing. European Journal of Pharmaceutical Sciences 2015; 68:11-17.
14. Yu DG, Zhu LM, Branford-White CJ, Yang XL. Three-dimensional printing in pharmaceutics: promises and problems. Journal of Pharmaceutical Sciences 2008; 97: 3666-3690.
15. Pardeike J, Strohmeier DM, Schrödl N, Voura C, Gruber M. Nanosuspensions as advanced printing ink for accurate dosing of poorly soluble drugs in personalized medicines. International Journal of Pharmaceutics 2011; 420:93-100.
16. Vermeulen N. 3D Bioprint Me -A Socioethical View of Bioprinting Human Organs and Tissues. Journal of Medical Ethics 2017; 43:618–624.
17. Liaw CY, Guvendiren M. Current and emerging applications of 3D printing in medicine. Biofabrication 2017; 9:1-18.
18. Ursan ID, Chiu L, Pierce A. Three-dimensional drug printing: a structured review. Journal of the American Pharmacists Association 2013; 53:136-144.
19. Maulvi FA, Shah MJ, Solanki BS, Patel AS, Soni TG. Application of 3D Printing Technology in the Development of Novel Drug Delivery Systems. International Journal of Drug Development and Research 2017; 9:44-49.
20. Huang W, Zheng Q, Sun W, Xu H, Yang X. Levofloxacin implants with predefined microstructure fabricated by three-dimensional printing technique. International Journal of Pharmaceutics 2007; 339:33-38.
21. Katstra W, Palazzolo R, Rowe C, Giritlioglu B, Teung P. Oral dosage forms fabricated by Three Dimensional Printing™. Journal of Controlled Release 2000; 66:1-9.
22. Mok SW, Nizak R, Fu SC, Ho KWK, Qin L. From the printer: Potential of three-dimensional printing for orthopaedic applications. Journal of Orthopaedic Translation 2016; 6:42-49.
23. Preis M, Breitkreutz J, Sandler N. Perspective concepts of printing technologies for oral film formulations. International Journal of Pharmaceutics 2015; 494:578-584.
24. Pardeike J, Strohmeier DM, Schrödl N, Voura C, Gruber M. Nanosuspensions as advanced printing ink for accurate dosing of poorly soluble drugs in personalized medicines. International Journal of Pharmaceutics 2011; 420: 93-100.
25. Ventola CL. Medical applications for 3D printing: current and projected uses. Pharmacy and Therapeutics 2014; 39:704-711.
26. Goyanes A, Det-Amornrat U, Wang J, Basit AW, Gaisford S. 3D scanning and 3D printing as innovative technologies for fabricating personalized topical drug delivery systems. Journal of Controlled Release 2016; 234:41-48.
27. Dimitrov D, Schreve K, De Beer N. Advances in three dimensional printing-states of the art and future perspectives. Rapid Prototyping Journal 2006; 12:136-147.
28. Gross BC, Erkal JL, Lockwood SY, Chen C, Spence DM. Evaluation of 3D printing and its potential impact on biotechnology and the chemical sciences. Analytical Chemistry 2014; 86:3240-3253.