Indo Global Journal of Pharmaceutical Sciences, 2021; 11(1): 70-75

INDO GLOBAL JOURNAL OF PHARMACEUTICAL SCIENCES
ISSN 2249- 1023

Novel Approach for Producing Pharmaceuticals in Layer by Layer Fashion: Additive Manufacturing

Lakshmi Usha Ayalasomayajula[*1], Kishore Pathivada [1], Radha Rani Earle [1], A.V.S. Ksheera Bhavani [2]

[1] *Department of Pharmaceutics, Maharajah's College of Pharmacy, Phool Baugh, Vizianagaram, AP, India -535002*

[2] *Department of Pharmaceutics, Sri Venkateswara College Of Pharmacy, Etcherla, Srikakulam, AP, India -535002*

Address for Correspondence: Lakshmi Usha Ayalasomayajula, alakshmiusha@gmail.com

Received: 28.03.2020
Accepted: 18.08.2020
Published: 30.03.2021
Keywords
3D printing, Additive manufacturing, Unit operations, Computer aided design.

ABSTRACT: A novel approach for producing pharmaceuticals from digital designs, in a layer-by-layer fashion is 3D printing. It has been acclaimed as a disruptive technology having the potential to make a paradigm shift in the conventional manufacturing of pharmaceuticals products which involves various unit operations like milling, mixing, granulation, drying and compression. It results in final products of different qualities. The quality of the product is influenced by loading of the drug, release of the drug, stability of the drug and stability of pharmaceutical dosage form. FDA approved 3D printed drug is creating a novel era in pharmaceutical manufacturing. To overcome some of the challenges associated with conventional pharmaceutical unit operations, 3D printing is gaining more attention in the manufacture of pharmaceuticals in the future. 3D printing is capable of overcoming the difficulties relating to the drug delivery of peptides, potent drugs, water-soluble drugs, and the release of multi-drugs. On the other hand we can prepare patient specific or patient tailored medications on patient demand thus making safe administration of drug without any side effects or adverse drug effects. Nevertheless,certain limitations are there in terms of regulatory aspects hindering the launch of 3DP products into the market.

Cite this article as: Ayalasomayajula, L.U.; Pathivada, K.; Earle, R.R.; Bhavani, A.V.S.K. Novel Approach for Producing Pharmaceuticals in Layer by Layer Fashion: Additive Manufacturing. Indo Global J. Pharm. Sci., 2021; 11(1): 70-75. **DOI**: http://doi.org/10.35652/IGJPS.2021.111010 .

INTRODUCTION

3D printing (3DP) is a computer-aided design with unique technology of proto-typing layer-by-layer, fabricating 3D objects in the form of digital designs to achieve unmatched suppleness, time conservation and extraordinary manufacturing capability of pharmaceutical dosage forms. It works by depositing, binding and polymerization through layering until the desired object is completed, thereby, applying a brilliant combination of chemistry, robotics and optics principles. 3D printing is also termed as Additive manufacturing (AM) or Solids of free-form (SFF). [1]

In personalized pharmacotherapy pharmacists can fabricate and dispense the personalized dosage instantly to the patients. Currently, the focus is to develop a patient-specific or tailored drug dosing system rather than using the conventional dosage forms, because an individualized dosage form will diminish all potential adverse effects. At present, dose modifications in solid drug delivery is achieved by dispensing multiple low dose tablets or by cutting up the larger sized tablets into smaller portions. Reportedly, over 3000 compounding pharmacies in the United States, dispensed more than 30 million prescriptions annually to provide customized drugs for specific patients. [2]

Although a number of advancements in drug delivery systems and formulations are being discovered, the oral route is still preferred, due to its simplicity and convenience. The advancement of 3D printing technology in the field of pharmaceuticals has brought about a drastic change in the manufacturing process and expected to be used as a large-scale industry in the future. The innovation of 3DP technology recently bequeathedvery first 3D printed orodispersible tablet SPRITAM®(Levetiracetam) by Aprecia Pharmaceuticals and was approved by the US Food and Drug Administration (FDA) in 2015. This drug was indicated as an additional therapy for three prevalent types of seizures that were

myoclonic and primary generalized tonic clonic and partial onset in adults and children with epilepsy. [3,4]

Developing personalized dosage forms has proven to be competitively cost-efficient in the long run. The complex geometries could be easily fabricated to develop multiple functional pharmaceutical products in a single tablet having diverse drug release kinetics. It provides a great possibility for personalization, e.g. drug eluting implants adjusted to a patient's anatomical and physiological variations. Furthermore, maintaining the steady-state of drugs with a narrow therapeutic index requiring therapeutic drug monitoring e.g., Digoxin, Vancomycin, etc., in the terms of expediency, the rapid prototyping nature of AM is comparatively easy. 3D printing technology provides enhanced porosity to the tablets by layering both the active and inactive components, using aqueous fluid to bind the powder multi-layers together. This makes the pills easy to dissolve as it comes in contact with the liquid medium. It also becomes easy to swallow the higher doses of medicament in comparison to conventional tablets.

STEPS INVOLVED IN A 3D PRINTED DOSAGE FORM

- Design of a pharmaceutical product in three dimensions with computer-aided design.
- Conversion of design to a machine-readable format to describe the external surface of the 3D dosage form.
- The computer program then slices this surface into several distinct printable layers and transfers that layer-by-layer to the machine. [5]

ADVANTAGES AND LIMITATIONS OF 3DP IN PHARMACEUTICAL DRUG DELIVERY

Compared to conventional pharmaceutical product manufacturing process, 3DP deals with a lot of interesting characteristics like:

a. Low-cost production
b. High production rates due to its fast operating systems
c. Ability to customize products
d. Rapid production of prototypes
e. Ability to achieve high drug-loading with much-desired precision and accuracy especially for potent drugs that are applied in a small dose
f. Reduces wastage of materials
g. Safety, efficacy, and accessibility of pharmaceuticals can be enhanced
h. Compliance to wide types of active pharmaceutical ingredients including poorly water-soluble, peptides and proteins, as well as drugs with a narrow therapeutic window. [6]

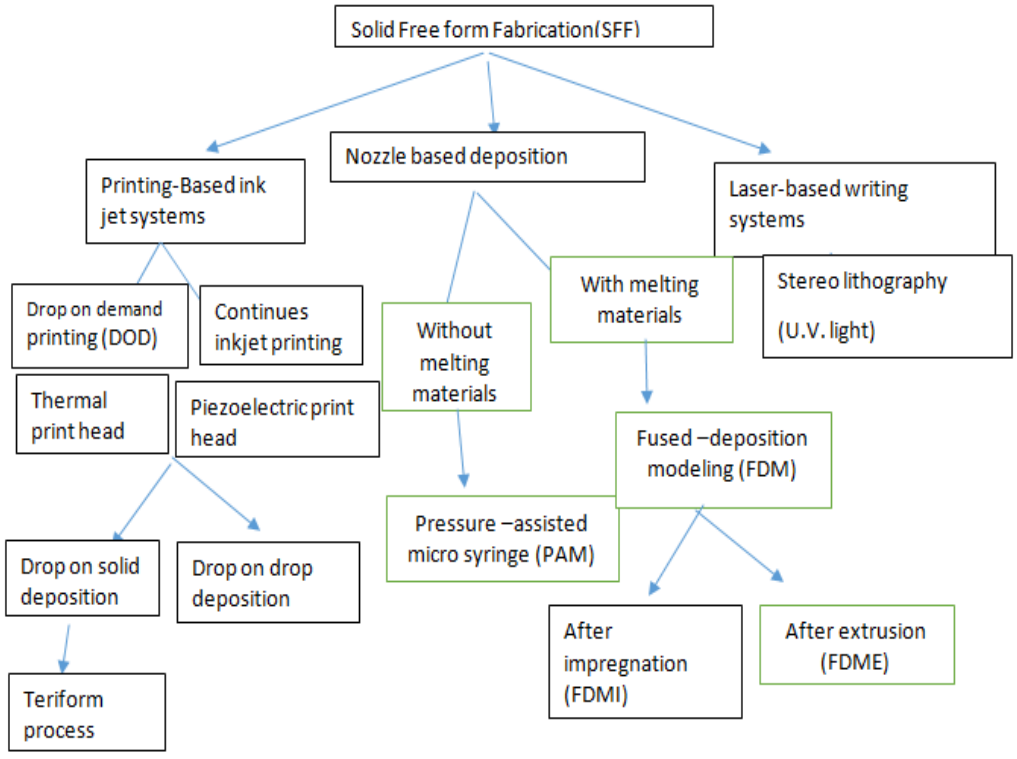

Fig. 1. 3D Printing Technologies for Manufacture of Dosage Forms

CURRENT 3D PRINTING METHODS

Figure 1 illustrates various 3D printing methods which are described as below.

INKJET PRINTING

This approach to personalize pharmaceuticals originate from the same technique of computer-operated inkjet printing. It was adapted for pharmaceutical applications by the replacement of the ink with pharmaceutical solutions containing drugs and normal paper with edible sheets known as substrates. [7]

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 designed in a ratio such that it has the 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. Printing-based inkjet systems is based on two techniques: Continuous Inkjet Printing (CIJ) and Drop-On-Demand (DOD) printing. In continuous inkjet printing, the liquid ink is directed through an orifice of 50-80 µm 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[8]. These parameters are controlled by creating an electrostatic field. 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.

The drop-on-demand technique (**Figure 2**) contains multiple heads (100–1000) and can use two types of translators, a thermal head or a piezoelectric crystal. The thermal head is restricted only to volatile liquids, whereas the piezoelectric crystal can be used for a several liquids. Besides, the thermal head reaches temperatures of up to 300 ºC, which implies that the use of solvents of high vapor pressure could cause the degradation of bioactive compounds. This factor limits the use of thermal print heads for pharmaceutical applications. The piezoelectric crystal changes rapidly, but this can generate a sudden variation of volume. Both of the heads are capable of producing droplets of between 10 and 50 µm, corresponding to a volume of between 1 to 70 pL. The ability to operate at room temperature, with less volatile and more biocompatible liquids, makes piezoelectric printing technology more suitable for the development of drug delivery devices. [9]

The DOD technique has 2 subtypes: Drop-On-Drop Deposition and Drop-On-Solid Deposition (powder bed fusion). Inkjet drug printing offers a significant advantage of accurate control of dose combination and pattern of drug release. Inkjet 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 70mN/m for efficient flow. [10]

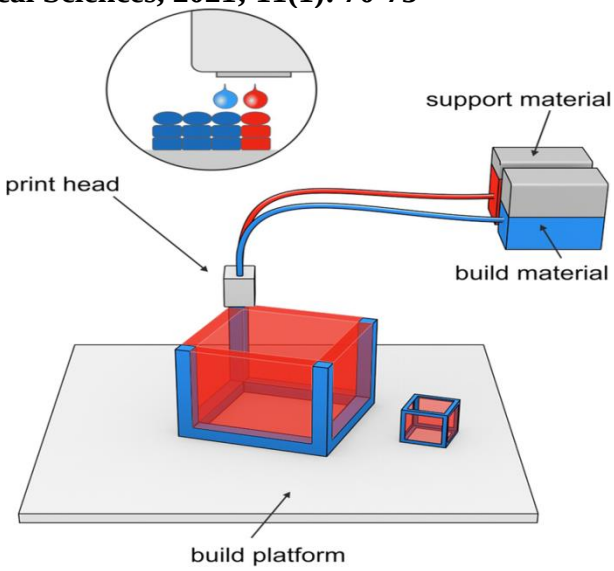

Fig. 2. Drop-On-Demand deposition technology

Formulating higher doses through this technology is difficultas it takes longer drying time for multiple layer printing in a particular area. Increasing surface area to sort this problem would in turn increase the size of the dosage form.

Selective laser sintering (SLS)

It is a technique (**Figure 3**), which is further derived from Drop-On-Solid Deposition Technique. Laser radiations are utilized in this technique to fuse the layered powder particles instead of using liquid ink. SLS is a typical procedure for 3Dprinting of metals. The final product is made up of sintered materials while the un-sintered materials share as the supporting structure and need post-printing processing to be removed. SLS has been well established in tissue engineering. It has not been employed in pharmaceutical manufacturing till now, probably due to a high energy laser beam causing possible decomposition of drug and other excipients [11].

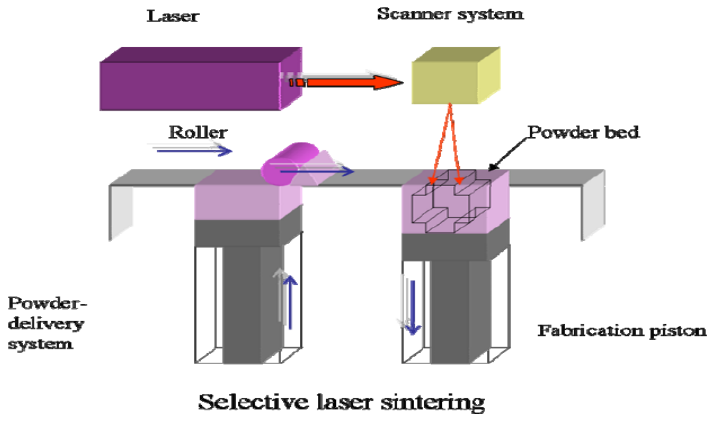

Fig.3. Selective laser sintering (SLS) technology

NOZZLE-BASED DEPOSITION SYSTEMS

Nozzle-based deposition systems (**Figure 4**) includes the mixing of drugs and polymers and other solid elements before 3D printing. The mixture is passed through a nozzle so that it comes out as layer by layer, a three-dimensional product. There are two types of printings according to the type of material used: Fused Deposition Modelling, which uses melted components, and Pressure-Assisted Micro syringes, which does not require the use of melted materials. [12, 13]

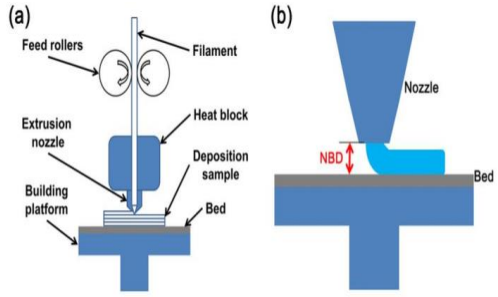

Fig.4. Nozzle based Extrusion System

Fused Deposition Modeling

This (**Figure 5**) involves extruding a thermoplastic filament through a high-temperature nozzle into semi-solid fused state filament in a layer by layer fashion. The object is formed by layers of melted or softened thermoplastic filament extruded from the printer's head at specific directions as dictated by computer software. The material is heated to just above its softening point which is then extruded through a nozzle, and deposited layer by layer, solidifying in a second. This is why it is also called Fused Filament Fabrication Drug loading in which the filament is usually achieved through incubation in organic solvents. [14]

This type of 3D printing relays on the thermoplastic polymers likepolyvinyl alcohol (PVA), polylactic acid (PLA) or acrylonitrilebutadiene styrene (ABS). It is reported that acrylonitrile butadienestyrene is non-biodegradable polymer and not appropriate for3D printing of pharmaceuticals. [15]

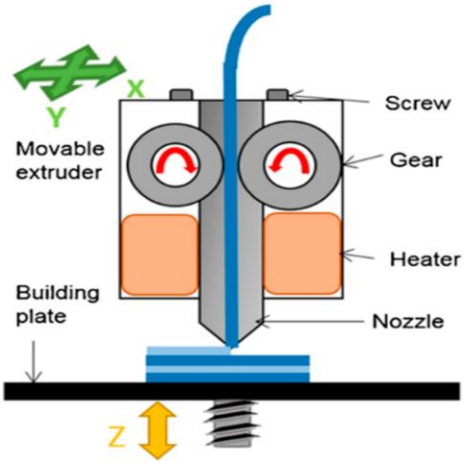

Fig. 5. Fused deposition modeling printing system

Advantages of Fluid Deposition modelling technique

Use of solvents could pose as health hazard and can degrade the active pharmaceutical ingredient as well

Use: Tissue printing substitutes or scaffolds of soft tissues.

LASER BASED WRITING SYSTEMS

Stereolithographic 3D Printing (SLA)

- Stereolithographic 3D printing (**Figure 6**) comprises exposing the liquid resins Obtains different release profiles of the printed dosage forms by modifying the infill percentage, the 3D model design, or the surface area of the formulation.
- This technique has advantage over powder-bed printing in terms of higher resolution.
- FDM permits to produce more composite scaffolds, with more accurate dosing. [16]

DISADVANTAGES

- Due to the high temperature of the process, thermosensitive drugs cannot be used for this technique.
- Limited options of thermoplastic materials are availablewhich have good melting and viscosity properties for extrusion.

Pressure-Assisted Microsyringe technology

In this technique, a syringe extruder is used for depositing viscous and semi-liquid material, layer by layer, with the help of a pressurized air piston. Rheological parameters mainly viscosity and the apparent elastic limit are the keystones that govern the reproducibility of this method. Gels or pastes are formed by mixing suitable solvent(s) with optimum ratios of polymers to attain a viscosity suitable for printing. [17,18]

Advantage

Flows continuously and works at room temperature.

Disadvantage

Polymers through ultraviolet light or any other high energy light favors polymerization reactions. Hence, it is also known as "Photo polymerization". So, for this technique, is limited to photosensitive or photopolymerizable materials primarily.
Stereolithography consists of a digital mirroring device, which induces a chemical reaction in the photopolymer resulting in the gelation of the particular exposed area. Unreacted functional groups attached to the solidified material in the first layer polymerizes with the illuminated resin in the next adjacent layer, first ensuring adhesion and thereafter, the formation of layers. Certain backing structures are used to link the different parts of the object to avoid its collapse during the printing process. The final product is further treated to enhance the mechanical integrity and to polish or remove the attached supports to the printed subject by post printing process. [20, 21]

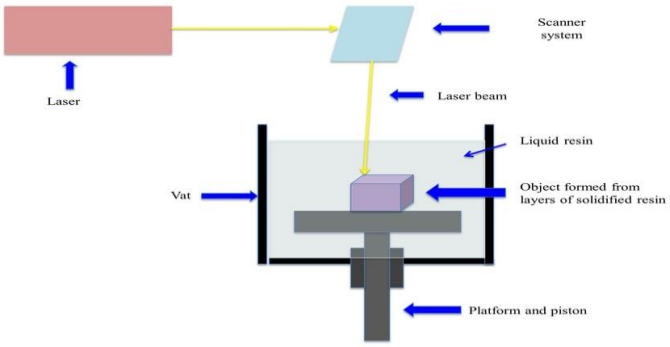

Fig. 6. Stereolithographic 3D printing (SLA) technology

CHALLENGES AND PERSPECTIVES

Advancement of technology in the pharmaceutical field is improving constantly and is providing possibilities to meet the needs of personalized drug therapy. The three-dimensional (3D) printing technology has endless potential in the fabrication of patient-specific drug delivery devices.3DP can successfully resolve the problems with the delivery of poorly water-soluble drugs, peptides, potent drugs, and the release of multi-drugs, etc. [22]

However, selections of suitable binders, excipients and the pharmaco-technical properties of final products restrict the applications of 3DP in commercial market. Further advancement in process performance is required to overcome these drawbacks so that 3D printing technology can be successfully combined with a novel drug delivery system (NDDS). [23]

The main challenge to their exploitation for personalized pharmacologic therapy is likely to be related to the regulatory issues involved in the implementation of production models that may allow to efficiently change the therapeutic needs of individual patients into small batches of appropriate drug products to meet the quality requirements. [24]

Three-dimensional printing has become a useful and potential tool for the pharmaceutical sector. It focuses on patients' needs for personalized medicine. It also offers numerous advantages, such as increasing the cost efficiency and the manufacturing speed, since rapid prototyping (RP) can be done in a matter of minutes. However, there is still a significant barrier to ensure that 3D printed medicines have the same efficacy, safety, and stability as the conventionally manufactured pharmaceuticals. Regarding the establishment of guidelines, laws, quality systems and safety of use and consumption of 3D printed medicines, it is a great challenge for the regulatory authorities3. [25]

CONCLUSION

3D printing is gaining huge momentum in pharmaceutical industries despite the associated challenges. This advanced technology of 3D printing efficiently caters to the demand of patients for personalized medication. Certain unique systems, like personalized microneedle patch and drug-eluting implants, which were not possible with mass manufacturing, are now feasible by this novel technology. Apart from this, it also provides cost-effectiveness with high manufacturing speed, as rapid prototyping can be finished in minutes. It offers a great platform to bring dosage form manufacturing nearer to end-users with a more specifically adjusted dose to a patient in a safe and effective manner. Although 3D Printing technology is immensely promising for the fabrication of personalized drug delivery system, there are various technical and regulatory challenges for pharmaceutical applications which must be cleared for effective grounding of 3D printing technology. This technology opens the door to a new era of advanced drug delivery with built-in flexibility which is well suited for personalized/tailored medicine systems. It is anticipated that 3D printing would enable the development of mini dispenser and initiate the collaborative work between physician and pharmacist as for personalized therapy, the physician must understand the genetic sequence of the patient before starting any therapy followed by the pharmacist optimizing the drug excipients ratio of decided drug concentration.

AKNOWLEDGEMENT

We would like to thank the Almighty for giving us the strength to study the topic and write the review. We would also thank our family members for their continuous support and encouragement.

CONFLICTS OF INTREST

There are no conflicts of interest.

FUNDING SOURCE

There is no source of funding.

DATA AVAILABILITY

Not declared.

REFERENCES

1. Musarrat Hussianwarsi, Mohammad Yusuf, sabakhan, Majed Al, Robaian, Mariakhan, Haseem Alsaab; J. Current Pharmaceutical design, 24(2018) 1-8.
2.A. Eswarkumar, G. Chinna Devi, N. Sharada, kumar et al., IJPSR,2019; Vol.10(4):1575-1581.
3.Diogo Jose Horst; J. Arc Org Inorg Chem Sci 1(12)-2018.AOICS.MS.1D.000109
4.Witold Jamroz, Jonna Szafraniec, Mateusz Kurek, Renata Jachowicz; J. Pharm Res(2018)35;176
5.Preethy Ani Rose,Peter Christoper GV;J.AJPRD.2018;6(3):46-54.
6.Jassim-Jaboori A, Oyewumi M. 3D printing technology in pharmaceutical

drug delivery: prospects and challenges. J Biomol ResTher 2015; 4: 1-3.
7.Fina F, Goyanes A, Gaisford S, Basit AW. Selective laser sintering(SLS) 3D printing of medicines. Int J Pharm 2017; 529(1-2): 285-93
8. Li Q, Guan X, Cui M, Zhu Z, Chen K, et al. (2018) Preparation and investigation of novel gastro-floating tablets with 3D extrusion-based printing Int J of Pharm 535: 325-332.
9. Asmat Majeed, Syed Naiem Raza and Nisar Ahmad Khan, Majeed et al. IJPSR, 2019; Vol. (3)10: 1025-1036.
10. Pamela Robles-Martinez , Xiaoyan Xu , Sarah J. Trenfield, Atheer Awad, Alvaro Goyanes , Richard Telford , Abdul W. Basit and Simon Gaisford. J.Pharmaceutics2019, 11, 274.
11.Fina F, Goyanes A, Gaisford S, Basit AW. Selective laser sintering(SLS) 3D printing of medicines. Int J Pharm. 2017;529(1–2):285
12.Andrew Kjar and Yu Huang.J.Pharmaceutics2019, 11, 390.
13.Bandyopadhyay A, Bose S, Das S. 3D printing of biomaterials. MRS Bull 2015; 40: 108-15.
14.Pere CPP, Economidou SN, Lall G, Ziraud C, Boateng JS, Alexander BD, et al. 3D printed microneedles for insulin skin delivery. Int J Pharm. 2018;544:425–32.
15. Zhang J, Feng X, Patil H, Tiwari RV, Repka MA. Coupling 3D printing with hot-melt extrusion to produce controlled-release tablets. Int J Pharm. 2017;519(1–2):186–97.
16. Goyanes A, Scarpa M, Kamlow M, Gaisford S, Basit AW, Orlu M. Patient acceptability of 3D printed medicines. Int J Pharm.2017;530(1–2):71–8.
17. Marks M, Alexander A, Matsumoto J, Matsumoto J, Morris J, Petersen R, et al. Creating thre dimensional models of Alzheimer's disease. 3D Print Med. 2017;3(13):1–11.
18. Gladman AS, Matsumoto EA, Nuzzo RG, Mahadevan L, Lewis JA. Biomimetic 4D printing. Nat Mat. 2016;15:413–8.
19.Ligon SC, Liska R, Stampfl J, Gurr M and Mülhaupt R. Polymers for 3D printing and customized additive manufacturing. ChemRev 2017; 117(15): 10212-10290
20.Skowyra J, Pietrzak K and Alhnan MA. Fabrication of extended-release patient-tailored prednisolone tablets via fused deposition modeling (FDM) 3D printing. European Journal of Pharmaceutical Sciences 2015; 68: 11-7.
21.Skowyra J, Pietrzak K and Alhnan MA. Fabrication of extended-release patient-tailored prednisolone tablets via fused deposition modeling (FDM) 3D printing. European Journal of Pharmaceutical Sciences 2015; 68: 11-7.
22.Yu DG, Yang XL, Huang WD, Liu J and Wang YG. Tablets with material gradients fabricated by three-dimensional printing. Journal of Pharmaceutical Sciences 2007; 96: 2446-2456.
23. Kumar AE, Devi GC and Sharada N. A review on novel approach to pharmaceutical drug delivery: 3D printing. Int J Pharm Sci & Res 2019; 10(4): 1575-81.
24. Katstra WE, Palazzolo RD, Rowe CW, Giritlioglu B, Teung P,Cima MJ. Oral dosage forms fabricated by three dimensional printing. J Control Release 2000; 66(1): 1-9.
25. Goyanes A, Robles Martinez P, Buanz A, Basit AW, Gaisford S. Effect of geometry on drug release from 3D printed tablets. Int J Pharm 2015; 494(2): 657-63.

Indo Global Journal of Pharmaceutical Sciences(ISSN 2249 1023; CODEN- IGJPAI; NLM ID: 101610675) indexed and abstracted in CrossRef (DOI Enabling), CNKI, EMBASE (Elsevier), National Library of Medicine (NLM) Catalog (NCBI), ResearchGate, Publons (Clarivate Analytics), CAS (ACS), Index Copernicus, Google Scholar and many more. For further details, visit http://iglobaljournal.com