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3D PRINTING IN PHARMACEUTICAL TECHNOLOGY - A REVIEW

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Abstract:

Growing demand for customized pharmaceutics and medical devices makes the impact of additive manufacturing increased rapidly in recent years. 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 technique, where consecutive layers of material are deposited or solidified to form a 3D structure. The 3D printing has become one of the most revolutionary and powerful tool serving as a technology of precise manufacturing of individually developed dosage forms, tissue engineering and disease modeling. The current achievements include multifunctional drug delivery systems with accelerated release characteristic, adjustable and personalized dosage forms, implants and phantoms corresponding to specific patient anatomy as well as cell based materials for regenerative medicine. The 3D printing process desires to be espoused by pharmaceutical sector and capable of exploring the marvels fetched by the approach.

Key words: *Three-dimensional printing, Structure, Pharmaceutics, Medical devices, Tissue engineering.*

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INTRODUCTION:

Three-dimensional printing technology is a novel rapid prototyping technique in which solid objects are constructed by depositing several layers in sequence. The rapid prototyping involves the construction of physical models using computer-aided design in three dimensions. It is also known as additive manufacturing and solid free form fabrication. 3D printing technology has enabled unprecedented flexibility in the design and manufacturing of complex objects, which can be utilized in personalized and programmable medicine.

Drug delivery is the technology and formulation developed to efficiently transport a pharmacologically active compound in the body to achieve therapeutic efficiency in a safe manner. The efficiency and safety of a pharmaceutical product can be improved by controlling the release profile which in turn modulates the pharmacokinetics of a drug. The inter-species variability is an obstacle frequently faced in the clinical scenario. Customized medicine and dosing receives increasing attention because of the high chances of undesirable side effects. The probability of adverse reactions is higher in the pediatric and geriatric populations when the bulk manufacturing of pharmaceuticals concentrates on the average population. 3D printing can play a significant role in multiple active ingredient dosage forms, where the formulation can be as a single blend or multi layer printed tablets with sustained release properties. This reduces the frequency and number of dosage form units consumed by the patient on a daily routine. 3D printing technology has high potential in individualized dosage form concept called the polypill concept. This brings about the possibility of all the drugs required for the therapy into a single dosage form unit.

HISTORY:

3D Printing is a platform for personalized medicine from the beginning of 1990. There are major successes in 3D printed medical device, FDA's Center for Device and Radiological Health (CDRH) has revised and cleared 3DP medical devices. The first 3D printing method used in pharmaceutics was attained by inkjet printing, a binder solution onto a powder bed, therefore the particles bind together. The technique was repeated until the final desired structure was obtained. This first happened in the early 90's at the Massachusetts Institute Technology developed and patented by Sachs *et al*. In 1989 Scott Crump filed a patent on another 3D printing technology, fused deposition modeling, to harden the surface where extruded polymer filaments heated into a semi-liquid state and extruded through a heated nozzle and deposited onto a build platform as layer by layer. Inkjet printing was the technique used to manufacture Spritam tablets (levetiracetam) for oral use, the first 3D printed drug approved by the Food and Drug Administration (FDA) in 2016 by Aprecia Pharmaceuticals. 3D printing is most advanced technique in the fields such as automobiles, aerospace, biomedical, tissue engineering and now in the pharmaceutical industry (initial phase). FDA motivates the development of advanced manufacturing technologies such as 3D-printing and by means of risk-based approaches.

ADVANTAGES OF 3D PRINTED DRUG DELIVERY:

- Accurate and Precise dosing of potent drugs which are administered at small doses for activity.
- Reduced production cost due to less wastage of materials High drug loading capability compared to conventional dosage forms.
- Suitable drug delivery for difficult to formulate active ingredients like poor water solubility and narrow therapeutic windows drugs.
- Medication can be tailored to a patient in particular based on age, gender, genetic variations, ethnic differences and environment.
- In case of multi drug therapy with multiple dosing regimen, treatment can be customized to improve patient adherence.
- As immediate and controlled release layers can be incorporated owed to flexible designs, manufacturing method of dosage form and it helps in pick out the best therapeutic regimen for an individual.
- Manufacture of small batch is feasible and the process can be completed in a single run.
- 3D printers capture minimal space and are affordable.

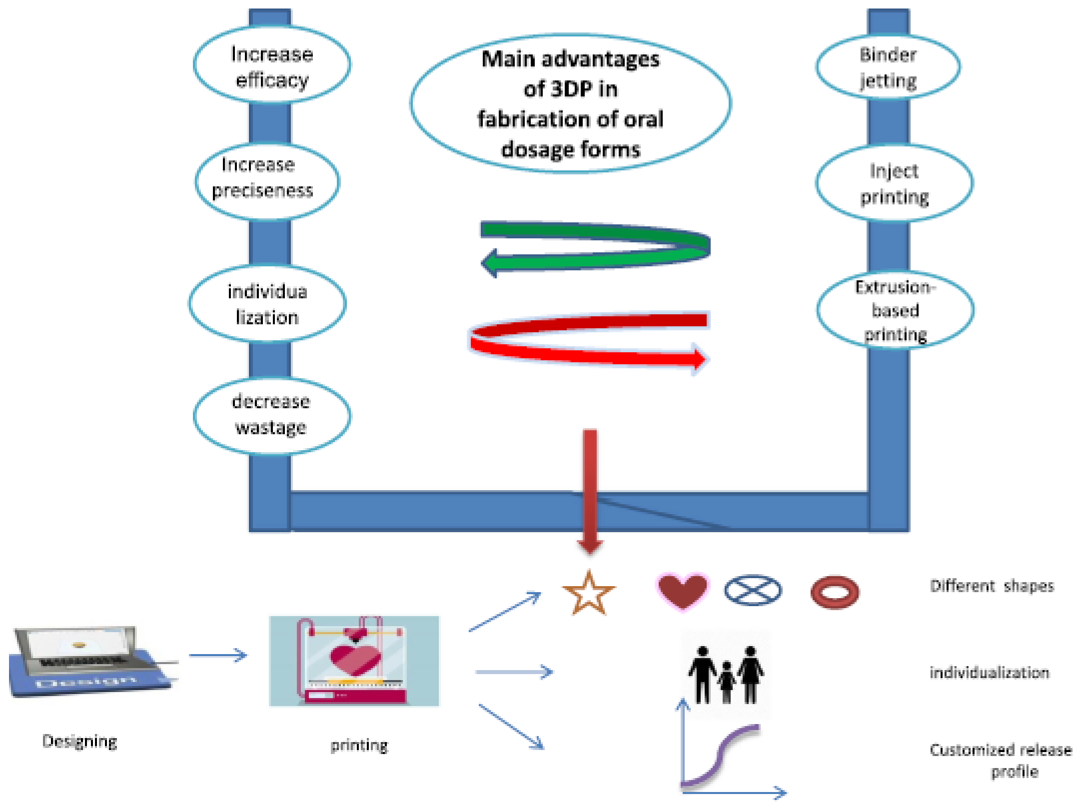

Fig. 1: Main advantages of 3D printing technology in the pharmaceutical applications.

DISADVANTAGES:

- Problems related to nozzle are a major challenge as stopping of the print head which affects the final products structure.
- Possibility of modifying the final structure on to mechanical stress, storage condition adaptions and ink formulations effects.
- Printer related parameters and these effects on printing quality and printercost.

3D TECHNOLOGY ADOPTION IN THE PHARMACEUTICS:

There are a number of technical trends for fabricating 3D printing products which can be used in the pharmaceutical industry and correspond to different applications and materials. These various methods vary in their function and productivity, where the key difference between them is the way a layer deposits on another layer. In addition, speed, accuracy, quality, and material properties are the major criteria which should be considered in selecting a suitable method for 3D printing. The main characteristic of a 3D medical product such as drug load and its release rate can be precisely modified by printing parameters such as manipulating the numbers of printed layers for a given area or changing the entire area of printing.

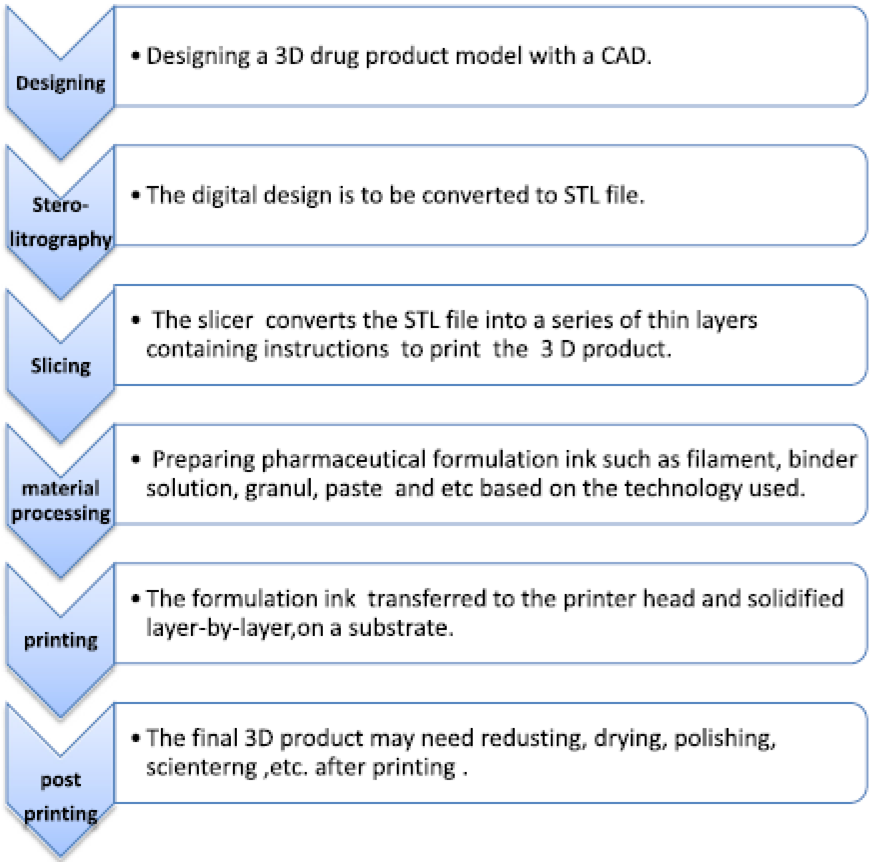

Fig 2: A schematic representation of different processing steps involved in fabrication of 3D printing objects.

TECHNIQUES IN 3D PRINTING:

There are numerous varieties of manufacturing practices intricate in 3D printing, which are grounded on digitally organized depositing of materials (layer-by-layer) to create free form geometries.

Inkjet Printing:

Inkjet printing known as 'mask-less' or 'tool-less' approach for its desired structure formation mainly depends upon the inkjet nozzle movement or substrate movement for an accurate and reproducible formation. In this methodology, the Ink is deposited onto a substrate either in the form of Continuous Inkjet printing / Drop on demand printing. Hence it provides a capability of high-resolution printing. It has a low cost, rate of processing in printing and generation of low level of wastes. It gives CAD information in a 'direct write' manner and process material over large areas with minimal contamination.

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 design in a ratio such that it has a 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.

Fused Deposition Modelling 3D Printing:

Fused deposition modelling (FDM) is commonly used method in 3D printing, the materials are softer or melt by heat to create objects during printing**.** This is the extruding a thermoplastic filament through high temperature nozzle into semi-solid fused state filament in 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 the filament is usually achieved through incubation in organic solvents and poor drug loading may limit its use to low-dosed drugs.

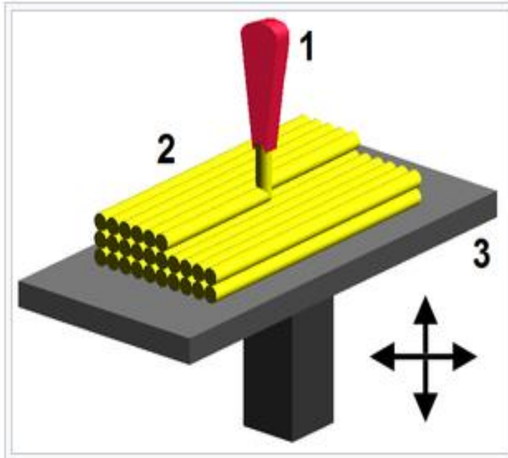

Fig 3: Fused deposition modelling: 1-Nozzle ejecting molten material, 2-Deposited material (modeled part), 3-Controlled movable table
Source*: https://en.wikipedia.org/wiki/Fused_deposition_modeling*

With this technology, objects can be built with production-grade thermoplastics. Objects are built by heating a thermoplastic filament to its melting point and extruding the thermoplastic layer by layer. Special techniques can be used to create complex structures. For example, the printer can extrude a second material that will serve as support material for the object being formed during the printing process. This support material can later be removed or dissolved.

Stereolithography (SLA)
Stereolithography makes use of a liquid plastic as the source material and this liquid plastic is transformed into a 3D object layer by layer. Liquid resin is placed in a vat that has a transparent bottom. A UV (UltraViolet) laser traces a pattern on the liquid resin from the bottom of the vat to cure and solidify a layer of the resin. The solidified structure is progressively dragged up by a lifting platform while the laser forms a different pattern for each layer to create the desired shape of the 3D object.

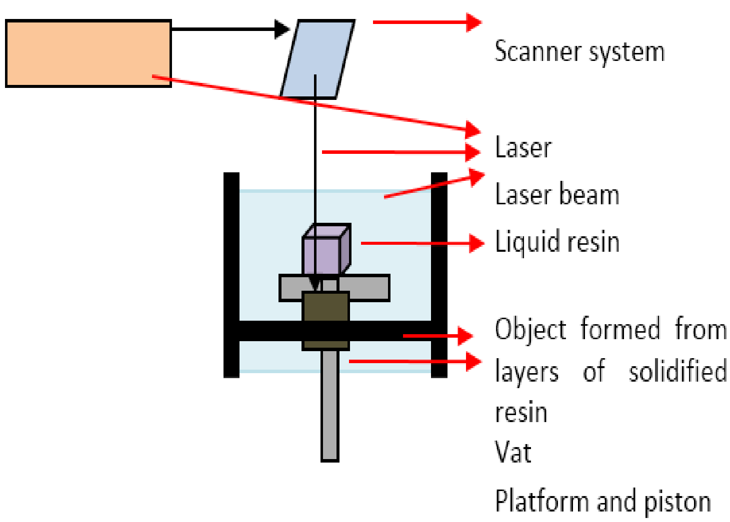

Fig 4:Schematic representation of Stereolithography

Digital Light Processing (DLP):
3D printing DLP technology is very similar to Stereolithography but differs in that it uses a different light source and makes use of a liquid crystal display panel. This technology makes use of more conventional light sources and the light is controlled using micro mirrors to control the light incident on the surface of the object being printed. The liquid crystal display panel works as a photomask. This mechanism allows for a large amount of light to be projected onto the surface to be cured, thereby allowing the resin to harden quickly.

Selective Laser Sintering (SLS)
SLS has some similarities with Stereolithography. However, SLS makes use of powdered material that is placed in a vat. For each layer, a layer of powdered material is placed on top of the previous layer using a roller and then the powdered material is laser sintered according to a certain pattern for building up the object to be created. Interestingly, the portion of the powdered material that is not sintered can be used to provide the support structure and this material can be removed after the object is formed for re-use.

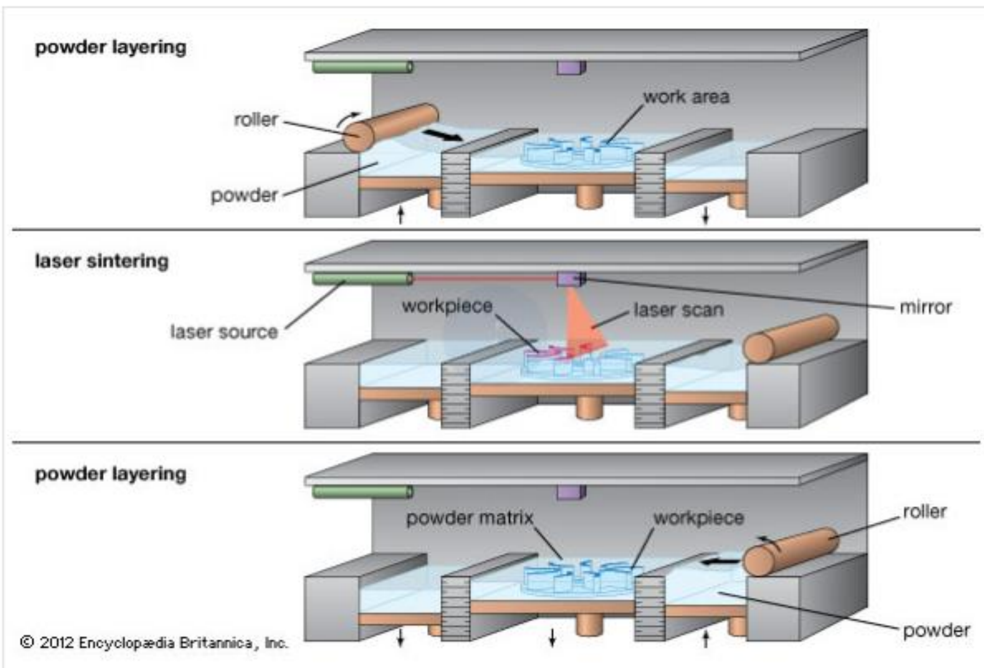

Fig 5: Selective Laser Sintering Process

Selective Laser Melting (SLM):
The SLM process is very similar to the SLS process. However, unlike the SLS process where the powdered material is sintered the SLM process involves fully melting the powdered material.

Electronic Beam Melting (EBM):
This technology is also much like SLM. However, it makes use of an electron beam instead of a high-powered laser. The electron beam fully melts a metal powder to form the desired object. The process is slower and more expensive than for SLM with a greater limitation on the available materials.

Laminated Object Manufacturing (LOM):
This is a rapid prototyping system. In this process, layers of material coated with adhesive are fused together with heat and pressure and then cut into shape using a laser cutter or knife. More specifically, a foil coated with adhesive is overlaid on the previous layer and a heated roller heats the adhesive for adhesion between the two layers. Layers can be made of paper, plastic or metal laminates. The process can include post-processing steps that include machining and drilling. This is a fast and inexpensive method of 3D printing. With the use of an adhesion process, no chemical process is necessary and relatively large parts can be made.

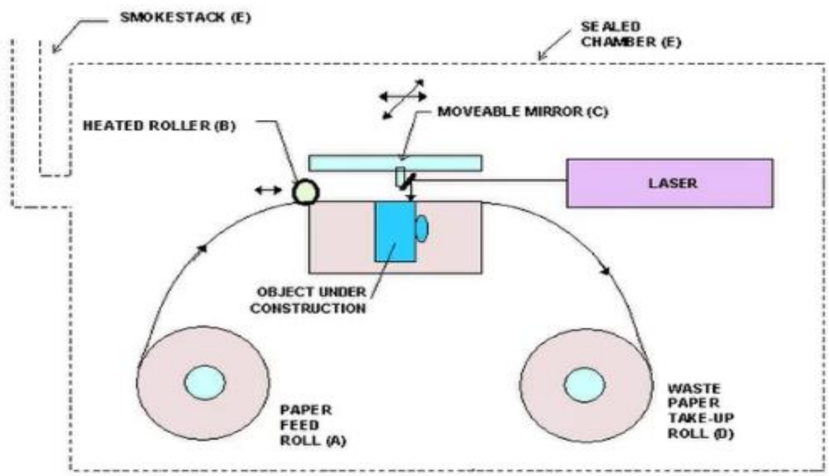

Fig 6: Laminating Object Manufacturing
Source: http://www.livescience.com/40310-laminated-object-manufacturing.html

Hot melt extrusion (HME):
Hot melt extrusion (HME) is the method of melting polymer and drug at elevated temperature and the pressure is employed in the instrument sequentially for blending. It is a continuous manufacturing technique that involves feeding, heating, mixing and shaping. In recent years, it has proved that hot melt extrusion capable to optimize the solubility and bioavailability of moderately soluble drugs.

APPLICATIONS OF 3D PRINTING:

- Potential use in improving process, modifying performance for industrial design, aerospace, medical engineering, tissue engineering, architecture, pharmaceuticals.
- In Healthcare industry to create dental implants.
- On fabricating an organized release multi-drug implant for bone tuberculosis remedy.
- It mostly targets on the two potential sites to rise pharmaceutical product development to unexplored areas, manufacturing sophisticated structures for the delivery and personalized medicine.
- Helps in Organ printing, biomaterials and cell-laden materials.

Use of 3D printing in personalized/ precision medicine:
3D printing offers the completely new opportunity for the development and preparation of personalized medicines at both the pharmacy and industrial scale. Introducing 3D printers to pharmacies and hospitals would allow physicians, nurses and pharmacists to form a dose and delivery system based on the patients body size, age, lifestyle, and sex. This would make medicine personal to the patient, and also save money and resources.

Aprecia Pharmaceuticals is the only company with an approved 3D printed pharmaceutical, Spritam for the treatment of epilepsy.

Use of 3D Printing to fight the Covid-19 pandemic:
The rapid proliferation of Covid-19 has been putting great strain on healthcare systems across the world, with demand for critical medical equipment and supplies mounting. Major manufacturers to individuals, have responded to thye Covid-19 crises by supporting the production of vital medical equipment for hospitals. 3D Systems, Carbon, and Renishaw have begun designing and manufacturing open-source PPE for healthcare workers worldwide.

CONCLUSION:
3D printing has become a useful and potential tool for the pharmaceutical sector, leading to personalized medicine focused on the patients' needs. 3D Printing technology is emerging as a new horizon for advanced drug delivery with built-in flexibility that is well suited for personalized/customized medication. 3D printing technology can make complex formations as cost and time efficient. It may improve its applications in Pharmaceutical Research and Biotechnological fields. It involves wide technical range in pharmaceutical field with novel drug delivery system, generation of new excipients, improvements of drug compatibility and customized dosage forms. In future 3D printing can be regulated

and followed by pharmaceutical and all other sectors with needed level of safety and security concerns.

REFERENCES:

1. Scoutaris N, Ross S, Douroumis D (2016) Current trends on medical and pharmaceutical applications of inkjet printing technology. Pharm Res 33(8): 1799–1816.
2. Zhang J, Vo AQ, Feng X (2018) Pharmaceutical additive manufacturing: a novel tool for complex and personalized drug delivery systems. AAPS PharmSciTech 19:3388–3402.
3. Awad A, Trenfield SJ, Gaisford S (2018) 3D printed medicines: a new branch of digital healthcare. Int J Pharm 548(1):586–596.
4. Konta AA, Garcia-Pina M, Serrano DR (2017) Personalised 3D printed medicines: which techniques and polymers are more successful? Bioengineering (Basel, Switzerland) 4 (4).
5. Shafiee A, Atala A (2016) Printing technologies for medical applications. Trends Mol Med 22(3):254–265.
6. Hsiao WK, Lorber B, Reitsamer H (2018) 3D printing of oral drugs: a new reality or hype? Expert Opin Drug Deliv 15:1–4
7. C. L. Ventola, (2014) "Medical applications for 3D printing: current and projected uses," Pharmacy and theraerapeutics, 39(10), 704–711.
8. D. B. Jones, R. Sung, C. Weinberg, T. Korelitz, and R. Andrews (2016) "'three-dimensional modeling may improve surgical education and clinical practice," Surgical Innovation, 23(2):189–195.
9. Sachs EM, Haggerty JS, Cima MJ, Williams PA(1993) Three dimensional printing techniques. In: US Patent US 5,204,055.
10. Jamroz W, Koterbicka J, Kurek M, Czech A, Jachowicz R(2017) Application of 3D printing in pharmaceutical technology. Farm Pol.;73(9):542–548.
11. Zema L, Melocchi A, Maroni A (2017) Three-dimensional printing of medicinal products and the challenge of personalized therapy. J Pharm Sci 106:1697–1705.
12. Rahman Z, F. Barakh Ali S, Ozkan T (2018) Additive manufacturing with 3D printing: progress from bench to bedside, vol 20. doi:10.1208/s12248-018-0225-6.
13. Ameeduzzafar RM, Abbas Bukhari SN (2019) 3D printing technology in design of pharmaceutical products. Curr Pharm Des.
14. Rayna T, Striukova L (2016) From rapid prototyping to home fabrication: how 3D printing is changing business model innovation. Technol. Forecast. Soc. Change 102:214–224.
15. Long J, Gholizadeh H, Lu J (2017) Application of fused deposition modeling (FDM) method of 3D printing in drug delivery. Curr Pharm Des 23(3):433– 439.
16. Preis M, Breitkreutz J, Sandler N (2015) Perspective: concepts of printing technologies for oral film formulations. International Journal of Pharmaceutics 494(2):578–584.
17. Chai X, Chai H, Wang X (2017) Fused deposition modeling (FDM) 3D printed tablets for intragastric floating delivery of domperidone. Scientific Reports 7:2829.
18. Sadia M, Arafat B, Ahmed W (2018) Channelled tablets: an innovative approach to accelerating drug release from 3D printed tablets. J Control Release 269:355–363.
19. Wen H, He B, Wang H (2019) Structure-based gastro-retentive and controlled-release drug delivery with novel 3D printing. AAPS PharmSciTech 20:68.
20. Preis M, Oblom H (2017) 3D-printed drugs for children-are we ready yet? AAPS PharmSciTech 18(2):303–308.
21. Zhang J, Yang W, Vo AQ (2017) Hydroxypropyl methylcellulose-based controlled release dosage by melt extrusion and 3D printing: structure and drug release correlation. Carbohydr Polym 177:49–57.
22. Tian P, Yang F, Xu Y (2018) Oral disintegrating patient-tailored tablets of warfarin sodium produced by 3D printing. Drug Dev Ind Pharm 44:1918–1923.