THE 3D PRINTING TECHNOLOGY IN PHARMACEUTICAL APPLICATIONS

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Abstract

Although 3D printing (3DP) has long been an integral part of industries such as aviation and automotive, its use in healthcare, especially the pharmaceutical industry, is relatively new and currently receiving close attention. Due to the rapid development of this field, it is necessary to summarize the latest development in this field after two years. In this article, we reviewed the three major areas in pharmaceutical application. The 3DP could support formulation development because it can produce rapid product iterations for testing, such as excipient compatibility and drug release.

Keywords: 3D printing technology, 3D drug product, Drug Delivery System 3D Printing, medical devices

Introduction:

Three-dimensional printing (3DP) is one of the prospective innovative technologies in the pharmaceutical area. During the last decade, it has magnificence role in production of various drug delivery system and excipient, which used in numerous manufacturing techniques. There are many methods used in the production of 3DP formulas, which represent on the outer layers of the item by using particular software to design the required dimensions (1).

At the current time, 3DP is considered one of interesting technique with broad and developing zone in the pharmaceutical industry, food manufacturing, art, and computer science. The principle of 3DP technology is performed by depositing the material using a nozzle or printing head device to produce models of three-dimensional objects from the predesigned that prepares pieces of depositing materials layer-by-layer combination to get the 3D materials. (2) For the manufacturing of viable tablets in a unique medication administration method, 3D printing is used. These tablets are made in such a way that they can pass regulatory tests and meet the same high requirements as conventional tablets. (3)

Three-Dimensional Printing technology is a unique rapid prototyping approach that creates solid objects by depositing many layers in sequential order. 3D printing's introduction and implementation have sparked massive innovation various sectors, including tissue engineering, aerospace, architecture, and biomedical research. Based on its versatility and diversity, it appears that 3D printing technology

will lead a fresh approach to the next industrial revolution. With advancements in science and technology, 3D printing technology has matured to the point where anyone can use open-source program with low-coat materials. (4, 5)

There are various types of drug delivery systems for instance oral controlled release systems, micro pills, implants, fast dissolving tablets and multiphase release dosage forms have been developed using three dimensional printing technology (6) . This type of printing is a layer-by-layer technique; that can turn a digital file into a 3D medicinal product. The 3D printing technology is unrivaled in terms of flexibility, speed, and the capacity to produce high-quality pharmaceutical products. (7)

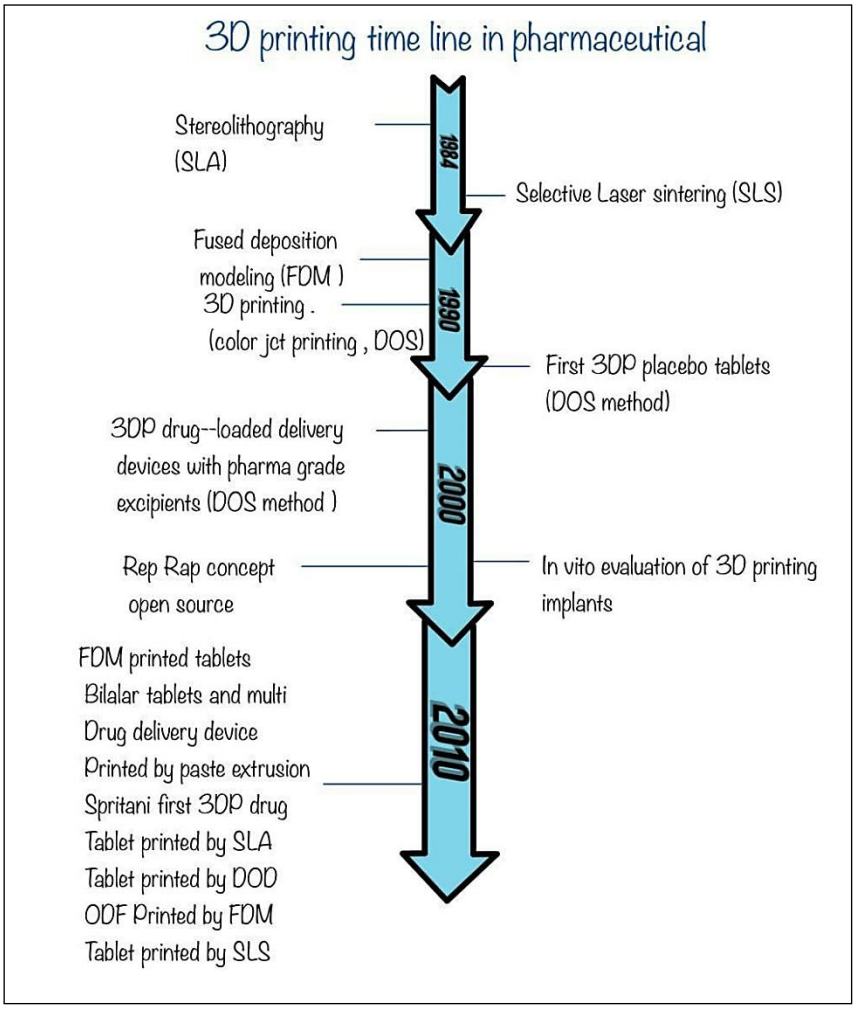

Figure 1: The Evolution of 3D printing technology in pharmaceutical field

History

Hideo Kodama of Nagoya Municipal Industrial Research Institute pioneered Additive Manufacturing Fabricating Methods of 3D plastic model using photo hardening polymer; the UV exposure zone is controlled by a scanning fiber transmitter. Another technique is called the Prototype device developed

by Check Hull of Three Dimension Systems Corporation; the principle of this type is known as Stereolithography in 1984. (2)

Since many other approaches and methods for developing 3D printing techniques have been invented, one of the current and new use of the 3DP in the treatment of COVID-19 in 2021, where 3DP can be used for improving the designs for mask fitting and looking, even though there is still no specific antiviral or treatment for COVID-19, a number of antiviral drugs are used in the treatment protocol, so it may be possible to produce. (8, 9)

Advantages of 3D printing (10, 11, 12)

- Reduces production costs by reducing material waste. (10)
- Low therapeutic index can minimize material wattage for long term use.
- Treatment is used for patient's special needs that relies on genetic differences, age, gender and others environmental factors. (11)
- Treatment is tailored to promote patient acceptance during multi-drug therapy with numerous dose regimens. (12)

Disadvantages of 3D printing

- These are very expensive
- One of the major drawbacks of this technology is that it is a size-limited technology, which means that massive items are still impossible to create with a 3D printer. (13)
- Although 3D printers can deal with a wide range of raw materials, when compared to the vast range of raw materials used in traditional production, it is insufficient.
- Cyber-threat, one of the most serious problems with 3D printing is the rapid increase in the production of counterfeit medications. Furthermore, hackers are now using 3D printers to make counterfeit drugs faster than traditional manufacturing methods. (14)
- Pharmaceutical businesses cannot possibly control the efficiency of every 3D printing operation due to product liability concerns. Furthermore, they must examine the potential for product responsibility. (15)

Types of 3D printing

- **Selective laser sintering (SLS)**

Additive Manufacturing (AM) is a process in which the quality of printed structures is determined by a variety of characteristics such as powder qualities such as shape, size, roughness, density and porosity of the particles (15). In addition to the distribution and thermal characteristics which affects the

flowability of powder (16).

The powdered material is fuses by cross-sections scanning that generated from 3D digital design; for instance, the scanned data on the surface of the powder; as the final part density is obtained by using peak laser power instead of laser duration. In this technique the pulsed laser is used following scanned cross-section, powdered bed is decreased by one layer thickness, followed by another layer of a material is placed on the top, this process is repeated to complete the final part. (17) As shown in Figure (2).

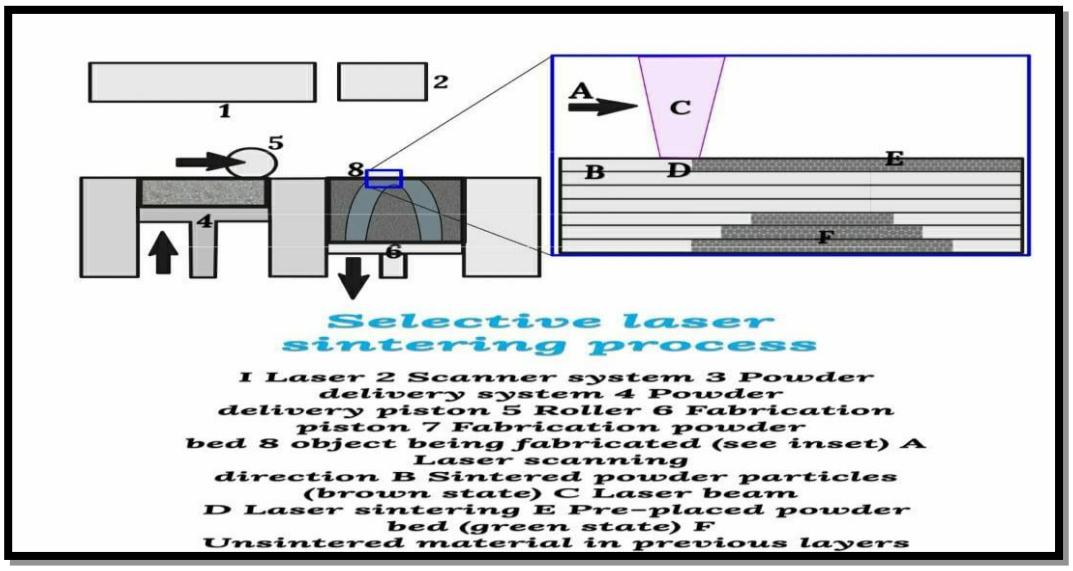

Figure 2: Selective laser sintering process

Fused Deposition Modeling

Rapid prototyping (RP) represents an advancement of the prototype process has gained a new edge. With recent advancements, at this time it is possible to produce other physical design in shorter period and more advanced geometry, this type of technique can be used to print final products in limited-series (18,19).

Above its melting point, the filament is melted inside the liquefier, and then pushed from the nozzle die as solid upstream filament. The polymer is placed beneath each layer of the object while the liquefier moving in before filling. This technique is considered as high-quality process with low-cost materials used and suitable investment (20) as shown in figure 3.

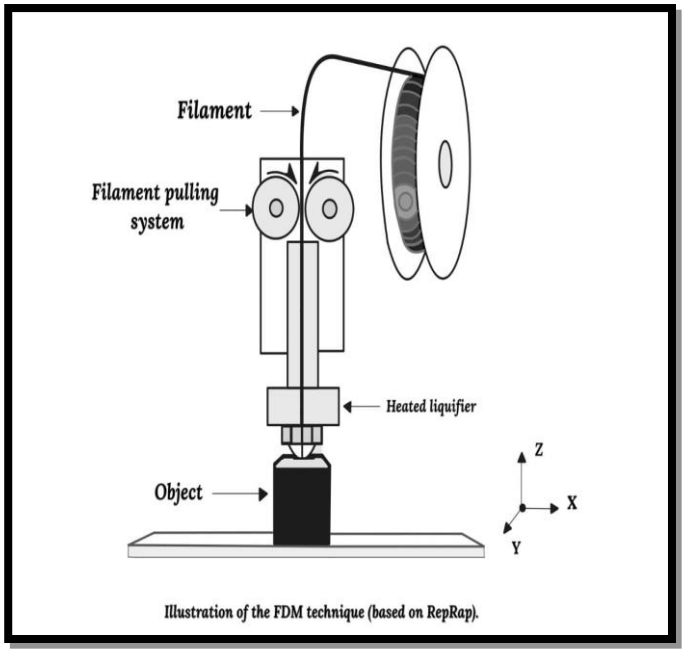

Figure 3: Illustration f the FDM technique

Hot melt extrusion technique (HME)

This technique is invented to produce lead pipes by the end of the 18th century, in this process is used in the rubber, plastic, sheets and food. (12,22) In addition, this technology (HME), figure 4, is useful in pharmaceutical manufacturing because of its reliable means in the developing of wide range of drug delivery systems. (23) The principle of this process is pumping the raw materials at high predetermined temperature and pressure through heated barrel to produce a suitable shape and density products (24).

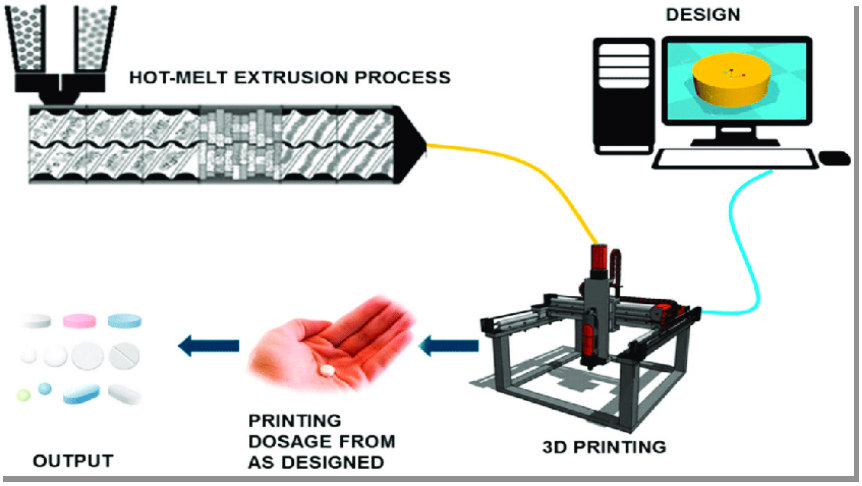

Figure 4: Hot Melt Extrusion process

Considering the many different advantages of 3D printing its use has been useful in fabricating many different drugs of different dosage forms some of which are illustrated in Table (1) below (25).

Table 1: Fabrication of dosage forms by 3D Printing technology

S.no	Drug	Dosage form	Technique used
1	Paracetamol	Oro-dispersible tablets	Selective laser sintering
2	Domperidone	Tablet	Fused deposition model
3	Theophylline	Tablet, Capsule	
4	Budesonide	Controlled release tablet	
5	Prednisolone	Extended release tablet	
6	Captopril	Intermediate release tablets	
7	Enalapril maleate	Tablet	
8	Hydrochlorothiazide	Tablet	
9	Nitrofurantoin	Catheter, Implant	
10	Hydroxyapatite	Implant	
11	Rifampicin	Compartmentalized shells	Hot melt extrusion technique
12	Paracetamol	3D-printed cube, pyramid, cylinder, sphere and torus	
13	Indomethacin	Subcutaneous rods	
14	Polymer Polyvinyl Alcohol (PVA), Mannitol and Hydrochlorothiazide, Polylactic Acid (PLA)	Three-compartment hollow cylinder	

The Three Dimension printing technologies

Each technique works according to various modes which requires a sufficient material to solidify and to produce a final item. (25) (As shown in Figure (5).

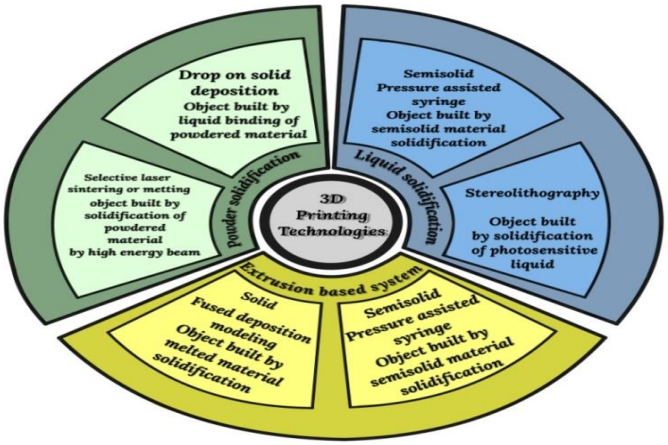

Figure 5: Three-dimensional printing methods applied for drug formulation

In addition to the variety of these methods, the preparation of such products there are some additional stages to be considered:

1. Using computer-aided design tools create a 3D model and optimize the shape to meet printer specifications. (24)
2. The model should be exported into a recognized file format, as in (STL) that contains a geometry in 3D design from each vertex position data, which includes additional data like color texture and geometrical polygonal surfaces. (24)
3. Entering the given file into software to create the printed layers which has a significant impact on the quality of the final product and time consumed in this technique. (25)
4. The solidification of the material layers is designated for a particular 3D procedure.

Applications of 3D printing

Since long time this technique is used in many medical areas; especially when used in dental implant and prosthetics medicine. Nowadays 3D printing can be categorized into several classes according to the applied dosage form.

Tissues and Organs Bio-Printing

The 3D-printing has been used in organ printing technology to form layer by layer cell creation, cell-laden biomaterials which produces 3D tissue-like structures, heart- valve, knee meniscus, spinal-disk, in addition to other design of bones, cartilage and an artificial ear by utilizing this printing technique. (26)

Dosage Forms and Drug Delivery System 3D Printing

In pharmaceutical industry, there are many different techniques used and one of these methods is 3D-Printing technology in the research and development in addition to the manufacturing area because of the accurate droplet size and predetermined dosage, perfect reproducibility and loading drug capacity that have crucial effect on the drug release profiles. (27,28)

The use of 3D printing used to standardize complex medication manufacturing procedures, making them easier and more viable. 3D printing technology also has an important role in the development of Personalized-Medicine II. (29) Some of these applications are shown in Table (2).

Table 2: Selective examples of pharmaceutical dosage forms fabricated by 3DP (29, 30)

Dosage form	**3DP method**	**API (Active pharmaceutical ingredient)**
Tablets	Inkjet system	Acetaminophen Chlorpheniramine maleate pseudoephedrine HCl
	Laser assisted system	4-Aminosalicyclic acid, paracetamol
	Fused deposition	5-Aminosalicylic acid, 4-aminosalicylic acid 5-Amino salicylic acid, theophylline, prednisolone
Implant		5-Fluorouracil Isoniazid and rifampicin Levofloxacin
Microneedles		Dacarbazine Diclofenac Insulin

Challenges

To enhance the performance of such technology, and to obtain an effective dosage form as 3D-Printing products and to widen the range of application to develop patent drug delivery systems, in spite of facing various challenges especially in the estimation and optimization methods (31), improving of device performance and in the selection of suitable additives all these factors, and many crucial issues to be considered during the optimization process to obtain the high quality products like rate of printing, velocity of line printing head, time interval, printing passes and the distance between the powder layers and nozzle. (32,33)

Conclusion

In the current study, shows that the concept of 3D Printing of drug formulation has direct impact to improve patient's compliance, therapeutic effectiveness, lowering the adverse effects and to be used as drug-delivery system. In addition, FDA approval of 3D-technology in drug manufacturing has an exceptionally development in the research area such as topical and oro-mucosal dosage forms. When this technology has been approved by US FDA, to be used in the pharmaceutical area started to improve by techniques and materials used. In 2015, approval is granted. However, before 3DP becomes the new standard, there are a few issues to be considered, in order to prepare for challenges, regulations and guidelines must be created. It is bound to happen. Pharmacists' unmet needs and pharmaceuticals' unfulfilled requirements. The private sector will band together to become the driving force behind this. In this field, new technologies will find various uses.

References

1. S.Swathi, N. jyothi, G. Nirmala jyothi, N. Lakshmi Prashanti; A review on 3D Printed tablets;Asian Journal of Pharmaceutical Technology & Innovation, 04(20), 2016, 34-39.
2. Witold Jamróz, Joanna Szafraniec, Mateusz Kurek, Renata Jachowicz;3D Printing in Pharmaceutical and Medical Applications-Recent Achievements and Challenges; Pharmaceutical research, 35, 2018,176.
3. Shaban A. Khaled, Jonathan C. Burley, Morgan R. Alexander, Clive J. Roberts; Desktop 3D printing of controlled release pharmaceutical bilayer tablets; International Journal of Pharmaceutics. 461, 2014, 105-111.
4. Li Q, Guan X, Cui M, Zhu Z, Chen K; Preparation and investigation of novel gastro-floating tablets with 3D extrusion-based printing; International Journal of Pharm, 535, 2018, 325-332.
5. Larush L, Kaner I, Fluksman A, Tamsud A, Pawar A A; 3D printing ofresponsive hydrogels for drug-delivery systems; Journal of 3d Printing in Medicine, 1(4), 2017.
6. Katstra W, Palazzolo R, Rowe C, Giritlioglu B, Teung P.; Oral dosage forms fabricated by three dimensional printing; Journal of Controlled Release, 66, 2000, 1-9.
7. Bansal M, Sharma V; 3D printing for future of pharmaceutical dosage form; Internationaljournal of applied pharmaceutics, 10(3), 2018, 1- 7.

8. Wang, J., Goyanes, A., Gaisford, S., Basit, A.W.; Stereolithographic (SLA) 3D printing of oral modified-release dosage forms; International Journal Pharm, 503, 2016, 207-212.
9. M.T. Vafea, E. Atalla, J. Georgakas, F. Shehadeh, E.K. Mylona, M. Kalligeros, et al. Emerging technologies for use in the study, diagnosis, and treatment of patients with COVID-19.
10. Ani jose preethy, christoper peter GV; 3d printing of pharmaceuticals-a potential technology in developing personalized medicine; Asian journal of pharmaceutical and development, 6(3),2018, 46-54.
11. Ghadge Snehal, Aloorkar Nagesh, Sudake Suresh; A Decisive overview on Three Dimensional Printing in Pharmaceuticals; Journal of Drug Delivery & Therapeutics, 9(3), 2019, 591-598.
12. Prasad LK,Smyth H; 3D printing technologies for drug delivery, A review; Drug Development Industrial Pharmacy, 42, 2016, 1019-31.
13. Ghadge Snehal, Aloorkar Nagesh, Sudake Suresh; A Decisive overview on Three Dimensional Printing in Pharmaceuticals; Journal of Drug Delivery & Therapeutics, 9(3), 2019, 591-598.
14. By Timothy Gosnear, Senior Vice President in Major Accounts, and Daniel Brettler, Life Science and Technology Practice Leader for Conner Strong & Buckelew Oct 31, 2016.
15. Leturia, M.; Benali, M.; Lagarde, S.; Ronga, I.; Saleh, K. (2014-02-01). "Characterization of flow properties of cohesive powders: A comparative study of traditional and new testing methods". Powder Technology. 253: 406–423. doi:10.1016/j.powtec.2013.11.045. ISSN 0032-5910.
16. Leu, Ming C.; Pattnaik, Shashwatashish; Hilmas, Gregory E. (March 2012). "Investigation of laser sintering for freeform fabrication of zirconium diboride parts". Virtual and Physical Prototyping. 7 (1): 25–36.
17. "Prasad K. D. V. Yarlagadda; S. Narayanan (February 2005). GCMM 2004: 1st International Conference on Manufacturing and Management. Alpha Science Int'l. pp. 73–. ISBN 978-81-7319-677-5. Retrieved 18 June 2011.
18. M. Too, K. Leong, C. Chua, Z. Du, S.F. Yang, C.M. Cheah, S.L.Ho,Investigation of 3D non-random porous structures by fused deposition modelling, Int. J. Adv.Manuf. Technol. 19 (2002) 217–223.
19. J. Kruth, M. Leu, T. Nakagawa, Progress in additive manufacturing and rapidprototyping, CIRP Ann. Technol. 47 (1998) 525–540.
20. S.H. Masood, W. Rattanawong,P. Iovenitti, Part build orientations based on volumetric error in fused deposition modelling, Int. J. Adv. Manuf. Technol. 16(2000) 162–168.
21. S. James, Encyclopedia of Pharmaceutical Technology, MarcelDekker, New York, NY, USA, 3rd edition, 2004.
22. G. P. Andrews and D. S. Jones, "Formulation and characterization of hot melt extruded dosage forms: challenges and opportunities," Cheminform, vol. 41, no. 43, 2010.
23. J. Breitenbach, "Melt extrusion: from process to drug Delivery technology," European Journal of Pharmaceutics and Biopharmaceutics, vol. 54, no. 2, pp.107–117, 2002.
24. G. P. Andrews, D. N. Margetson, D. S. Jones, M. S.McAllister, and O. A. Diak, "Hot-melt extrusion: an emerging drug delivery technology,"Pharmaceutical Technology Europe, vol. 21, no. 1, pp. 24–27, 2009.
25. Aditi Gujrati*, Alok Sharma, S.C. Mahajan Mahakal Institute of Pharmaceutical Studies, Ujjain Behind air strip, Datana, Dewas road, Ujjain (M.P.) India-456664
26. 3D Printing in Pharmaceutical and Medical Applications – Recent Achievements and Challenges Witold Jamróz 1 & Joanna Szafraniec 1 & Mateusz Kurek 1 & Renata Jachowicz1]Received: 29 March 2018 /Accepted: 30 June 2018 /Published online: 11 July 2018.
27. Gokhare Vinod G., Dr. Raut D. N., Dr. Shinde D. K.; A Review paper on 3D-Printing Aspects and Various Processes Used in the 3D-Printing; International Journal of Engineering Research & Technology, Vol. 6(6), 2017,2278-0181.
28. Cui X, Boland T, D'Lima DD, Lotz MK, Thermal inkjet printing in tissue engineering and regenerative medicine, Recent Pat Drug Delivery Formulation, 6(2), 2012, 149-155.

29. Gross BC, Erkal JL, Lockwood SY, Evaluation of 3D printing and its potential impact on biotechnology and the chemical sciences, Anal Chem. 86(7), 2014, 3240-3253.
30. Pharmaceutical applications of 3D printing technology: current understanding and future perspectives Byeong Ju Park1 · Ho Jae Choi1 · Sang Ji Moon1 · Seong Jun Kim1 · Rajiv Bajracharya1 · Jeong Youn Min1 · Hyo-Kyung Han1 Received: 19 June 2018 / Accepted: 26 October 2018 / Published online: 29 October 2018 © The Author(s) 2018, corrected publication 2019.
31. Gu D. Laser additive manufacturing of high-performance materials. Berlin: Springer; 2015. pp. 1–13.
32. Clark EA, Alexander MR, Irvine DJ, Roberts CJ, Wallace MJ, Sharpe S, Yoo J, Haguea RJM, Tucka CJ, Wildman RD. 3D printing of tablets using inkjet with UV photoinitiation. Int J Pharm. 2017;529(1–2):523–530.
33. Everett H. Merck, Aprecia, and FabRx on transitioning 3D printed pharmaceuticals from lab to clinic – 3D Printing Industry [Internet]. 3D Printing Industry. 2021