INTERNATIONAL RESEARCH JOURNAL OF PHARMACY
www.irjponline.com
ISSN 2230 – 8407

Review Article

3D PRINTING IN PHARMACEUTICAL TECHNOLOGY: A REVIEW

L. Srinivas *, M. Jaswitha, V. Manikanta, B. Bhavya, B. Deva Himavant
GITAM Institute of Pharmacy, GITAM Deemed to be University, Rushikonda, Visakhapatnam, India
*Corresponding Author Email: srinivas.lankalapalli@gitam.edu

Article Received on: 09/11/18 Approved for publication: 08/01/19

DOI: 10.7897/2230-8407.100234

ABSTRACT

Three-dimensional (3D) printing is an additive manufacturing method, where successive layers of material are deposited or solidified to form a 3D structure. It uses computer aided drafting technology and programming to produce 3D object by layering material on to a substrate. A variety of 3D printing technologies have been developed to fabricate novel solid dosage forms, which are among the most renowned and distinct products today. The present review focussed on briefing various techniques, applications of 3D printing in pharmaceutical technology.

Keywords: 3D printing technology, Zip dose, Thermal-Inkjet printing, fused deposition.

INTRODUCTION

Three-dimensional (3D) printing is unique technology which uses computer aided drafting technology and programming to produce three dimensional objects by layering material onto a substrate [1]. It is a process of making three dimensional solid objects from a digital file.[2] Hence the process is called as additive manufacturing (AM), rapid prototyping (RP) or solid freeform technology (SFF).

Nowadays, 3DP could be extended throughout the drug development process, ranging from preclinical development and clinical trials, to frontline medical care.[3] When compared to the manufacturing process of conventional pharmaceutical product, it has a lot of advantages like high production rates due to its fast operating systems; ability to achieve high drug-loading with much desired precision and accuracy especially for potent drugs that are applied in small doses; reduction of material wastage which can save in the cost of production and amenability to broad types of pharmaceutical active ingredients including poorly water-soluble, peptides and proteins, as well as drug with narrow therapeutic windows[4]. Different types of drug delivery systems such as oral controlled release systems, micro pills, microchip, drug implants, fast dissolving tablets and multiphase release dosage forms have been developed using three-dimensional (3D) printing technology.[5] Hence, it is expected that three-dimensional (3D) printing technology could offer new approaches for developing novel pharmaceutical dosage forms.

TECHNIQUES IN 3D PRINTING

3D printing includes a wide variety of manufacturing techniques, which are based on digitally-controlled depositing of materials (layer-by-layer) to create freeform geometries.

Thermal Ink-Jet Printing

In thermal inkjet printing, the aqueous ink fluid is converted to vapour form through heat and expands to push the ink drop out of a nozzle.[6] It is used in the preparation of drug-loaded biodegradable microspheres, drug-loaded liposomes [7], patterning microelectrode arrays coating and loading drug eluting stents.[8] It is also an efficient and practical method of producing films of biologics without compromising protein activity. (Table 1)(Fig 1)

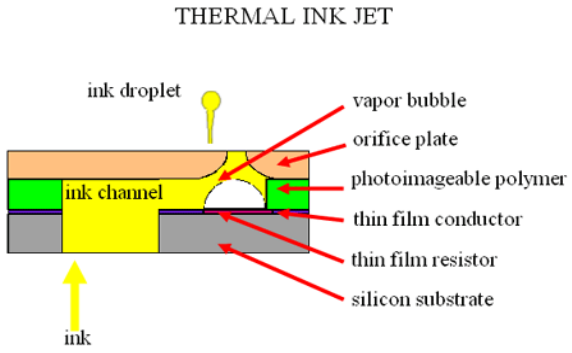

Fig 1: Thermal inkjet technique in 3D printing [9]

Table 1: Some of the drugs prepared by thermal inkjet printing

Sl.no	Drug	Dosage form	Application	Reference
1	Prednisolone	Tablet	Anti-inflammatory or Immunosuppressant	6
2	Salbutamol sulphate	Solution	Bronchodilators	10
3	Felodipine	Solid dispersion	Antihypertensive	11
4	Folic acid	Nano suspension	Anemia	12
5	Carbamazepine	Cocrystals	Antiepileptic drug	13
6	Terbutaline sulphate	Solution	Bronchodilator	14

Inkjet printing

In this technique, the Ink is deposited onto a substrate either in the form of Continuous Inkjet printing (CIJ) or Drop on Demand (DoD) printing, hence it provides a high resolution printing capability[15] (Table 2).Inkjet printing is also called as 'mask-less' or 'tool-less' approach because the formation of desired structure mainly depends upon the movement of inkjet nozzle or movement of the substrate for an accurate and reproducible formation. It has a low processing cost, rapid processing rates, generation of minimal waste, it gives CAD information in a 'direct write' manner and it process material over large areas with minimal contamination .[16] (Fig2)

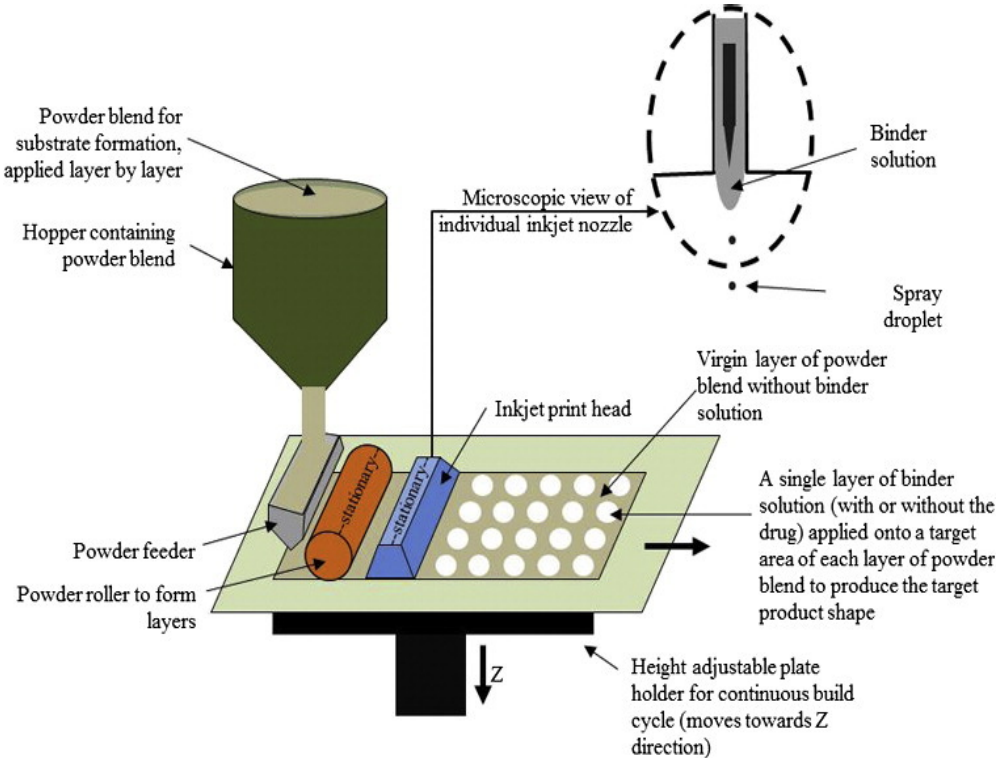

Fig 2: inkjet printing in 3D printing[17]

Table 2: Inkjet printing for pharmaceutical applications

Sl.no	Drug	Dosage form	Application	Reference
1	Felodipine	Microdots	Antihypertensive	18
2	Polyvinyl pyrrolidone (PVP)	Microdots	Excipients	18
3	Insulin	Microneedle	Antihyperglycemia	19
4	5-Fluorouracil, curcumin and cisplatin	Microneedle	Anticancer agents	20
5	Paclitaxel	Microparticles	Anticancer agents	21
6	Fluorescein 5-isothiocyanate	Microparticles	Fluorescence	21
7	Loperamide	Tablets or capsules	Inflammatory bowel disease.	22
8	Caffeine	Tablets or capsules	CNS stimulant	22
9	Paracetamol	Tablets	Analgesics	23
10	Atenolol	Tablets ,sprays	Antihypertensive	24
11	Influenza vaccine	Microneedles	Against influenza viruses	25
12	Voriconazole and Itraconazole	Microneedles	Antifungal agent	26
13	Piroxicam	Capsules	Nonsteroidal anti-inflammatory	27
14	Lysozyme and Ribonuclease-A	Films	Antibacterial and Antiviral	28
15	Erythropoietin	Uncoated rubber stopper syringes	Anemia	29
14	Rifampicin	Implants , Nanoparticles	Antibiotic	30
15	Levofloxacin	Implant	Antibiotic	31
16	Folic Acid	Nanosuspension	Anemia	32
17	Nitroglycerin	Injection	Angina	33
18	Fenofibrate	Tablets	Anti Hypertriglyceridemia and Anti Hypercholesterolemia	34
19	Rapamycin	Tablets	Immunosuppressant	34
20	Ketoprofen	Tablet	Nonsteroidal anti-inflammatory	35
21	Rasagiline mesylate	Oral dosage	Antiparkinson agent	36

Fused deposition modelling (FDM)

Fused deposition modelling (FDM) is commonly used technique in 3D printing, in which the materials are soften or melt by heat to create objects during printing[37] (Fig 3),Hence there are several dosage forms listed in Table 3. FDM 3D printing helps in manufacturing delayed release printlets without an outer enteric coating, and also provides personalised dose medicines.[38]

FDM 3D printing however, indicates several limitations of the system such as lack of suitable polymers[39], slow and often incomplete drug release because the drug remain trapped in the polymers[40,41] and the miscibility of the drug and additives with the polymers used was not evaluated[42]

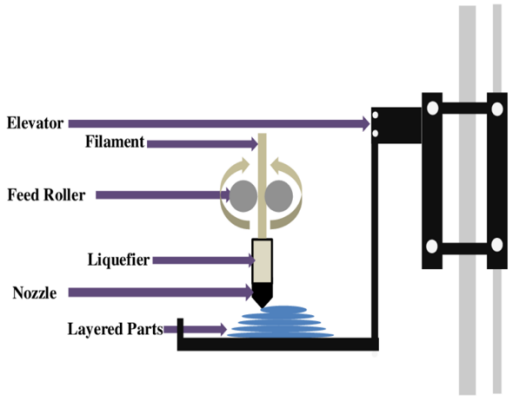

Fig 3: Fused deposition models in 3D printing[42]

Table 3: Some of the Pharmaceutical dosage forms by Fused deposition models

Sl .no	Drug name	Dosage Form	Use	Reference
1.	Domperidone	Tablet	Nausea, vomiting	43
2.	Ibuprofen	Tablet	NSAID	44
3.	Aminosalicylate	Tablet	Antibiotic	45
4.	Metformin, Glimepiride	Tablet	Antidiabetic	46
5.	Disopyramide	Tablet	Antiarrhythmic	47
6.	Theophylline	Tablet, Capsule	Lung diseases	47
7.	Paracetamol	Tablet	Antipyretic	48
8.	Budesonide	Controlled release tablet	Ulcerative colitis	49
9.	Diclofenac sodium	Tablet	NSAID	49
10.	Prednisolone	Extended release tablet	Immunosuppressant	50
11.	Enalapril maleate	Tablet	Antihypertensive	51
12.	Hydrochlorothiazide	Tablet	Diuretic	51
13.	Acetaminophen	Oral pulsatile capsule, Tablet MR	Antipyretic	52
14.	Captopril	Intermediate release tablets	Hypertension,CHF	52
15.	Budesonide	Capsule	Ulcerative colitis	52
16.	Nitrofurantoin	Catheter, Implant	Urinary tract infections	53
17.	Hydroxyapatite	Implant	Carrier	53
18.	Dye	Implant CR	Excipients	54
19.	Gentamicin sulphate, Methotrexate	General Device	Antibiotic and Anticancer	55
20.	Furosemide	Capsules IR, MR	Congestive heart failure	56
21.	Pravastatin	Tablet (IR, SR)	Lower "bad" cholesterol	57
22.	Atenolol, Ramipril		Anti -hypertensive	
23.	Aspirin		Nonsteroidal anti-inflammatory drug	
24.	Hydrochlorothiazide		Anti-hypotensive	
25.	Fluorescein	Tablet	Corneal ulcers and Herpetic corneal infections.	58
26.	5-aminosalicylic acid and 4-aminosalicylic acid	Tablet (MR)	Antibiotic	59
27.	Indomethacin	T-shaped (IU, SC rods)	Nonsteroidal anti-inflammatory	60
28.	5-Aminosalicylic acid	Tablets (IR)	Antibiotic	61
29.	Captopril		Anti -hypertensive	
30.	Prednisolone		Immunosuppressive drug	

Zip dose

Zip dose is the world's first and only FDA-validated, commercial-scale 3DP in new therapeutic areas for drug manufacturers. (Fig 4) It has a unique digitally coded layering and zero-compression processes, which is used for formulating a tablet with high dose and rapid disintegration .Hence it helps in overcoming a difficulty in swallowing.[62] Spritam® (Antiepilipsey drug) is an orodispersible tablet, marketed by Aprecia Pharmaceuticals based on powder bed fusion by layer-by-layer production system. In which it consists of the active ingredient, excipients and a binder liquid to produce a matrix tablet. [63]

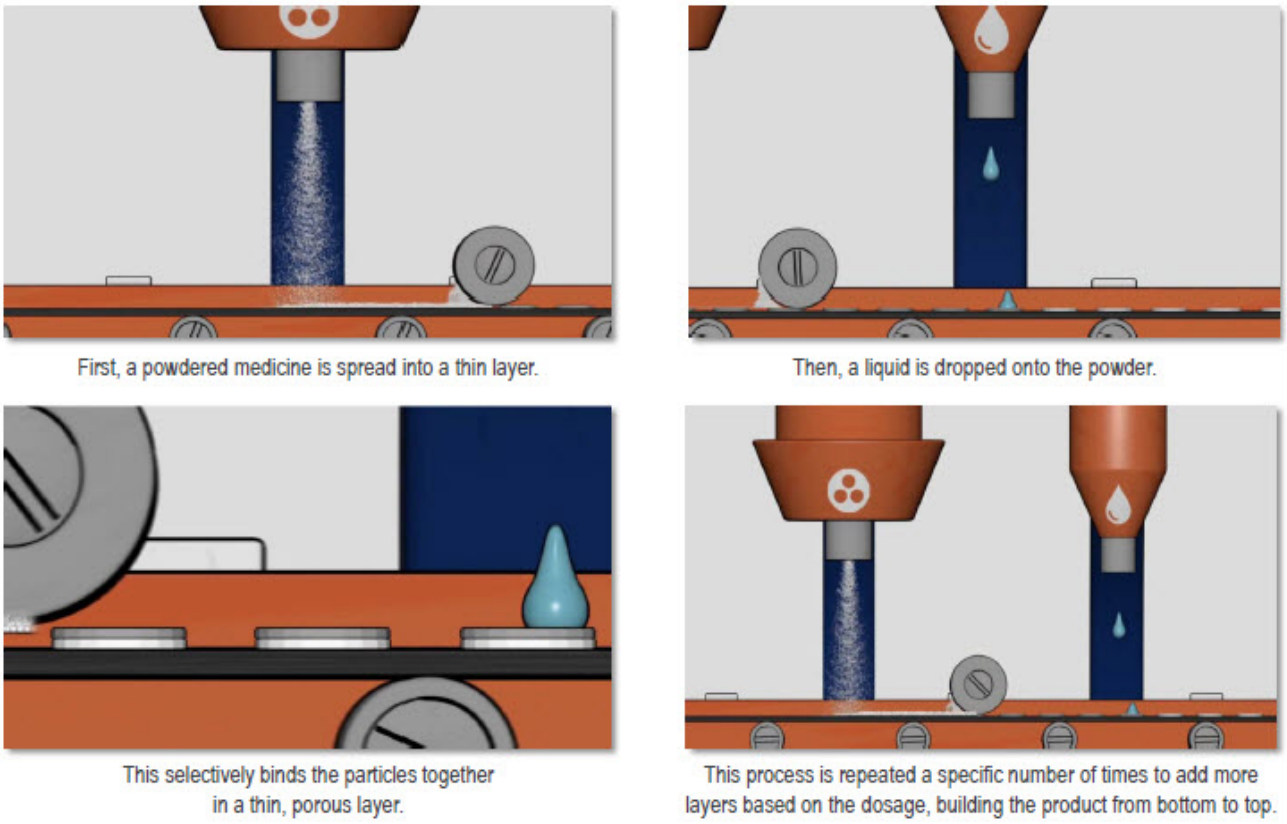

Fig 4: Zip dose technique in 3 D printing[64]

Extrusion 3D printing

In this technique the material is extruded from the automated nozzle on to the substrate and it does not require any higher support material. It is only used to fabricate tablet containing Guaifenesin as expectorant. The materials that can be extruded are molten polymers, suspensions, semisolids, pastes. [65, 66] (Table 4)

Table 4: Different dosage forms prepared by Extrusion 3D Printing

Sl.no	Drug	Dosage	Application	Reference
1	Captopril	Tablet	Anti-hypertensive	67
2	Glipizide	Tablet	Anti-diabetic	
3	Nifedepine	Tablet	Anti-hypertensive	
4	Dexamethazone	Drug encapsulated film of PLGA and PVA	Arthritis	68
5	Aspirin	Multi- active solid dosage form (polypill)	Anti -inflammatory	67
6	Atenolol		Angina	
7	Hydrochlorothiazide, Ramipril		Anti-hypertensive	
8	Pravastatin		Cardio vascular disease	
9	Prednisolone	Tablet	Immunosuppressive drug	69
10	Polydimethylsiloxane (PDMS)		Surfactant	

3D printer

The 3D printer is a valuable tool which is used to create customised medications with tailored release profiles and the medication is changed as per the patients comfort. (Table 5)(Fig 5)

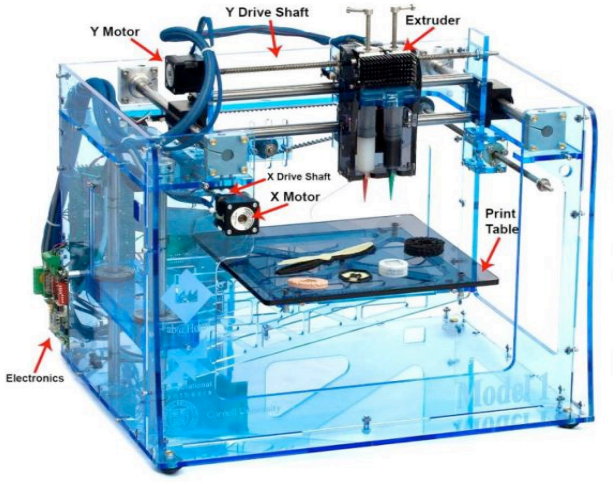

Fig 5: 3D printer used in 3 D Printing[70]

Table 5: Different drugs prepared by 3D printer method are

Sl.no	Drug	Dosage form	Application	Reference
1	Rifampicin, Isoniazid	Multi-drug implant	Antibiotic	71
2	Saline solution	Microfluidic pump	Electrolyte	72
3	Paracetamol	Fast-disintegrating tablets	Analgesics	73
4	Acetaminophen	Capsule-shaped solid Devices, fast disintegrating tablet	Analgesics	74
5	Caffeine	Capsule-shaped solid Devices	CNS stimulant	74
6	5-Fluorouracil	Biodegradable patch	Anti-cancer	75
7	Tetracycline, Vancomycin, Ofloxacin	Microporous bioceramics	Antibiotic	76
8	Chlorpheniramine maleate	Tablet	Antihistamine	77
9	Diclofenac sodium	Oral pulsatile tablet	Nonsteroidal anti-inflammatory drug	77
10	Fluorescein	Complex oral dosage forms	Corneal ulcers and Herpetic corneal infections.	78
11	Nitrofurantoin	Biofilm disk	Urinary tract infections	79
12	Polycaprolactone	Biodegradable patch	Manufacture of speciality Polyurethanes	79

Hot melt extrusion (HME)

Hot melt extrusion (HME) is the process of melting polymer and drug at high temperature and the pressure is applied in the instrument continuously for blending [80] (Fig 6).It is a continuous manufacturing process that includes several operations such as feeding, heating, mixing and shaping.[81] In recent years, it has proved that HME has the ability to improve the solubility and bioavailability of poorly soluble drugs [82]. (Table 6)

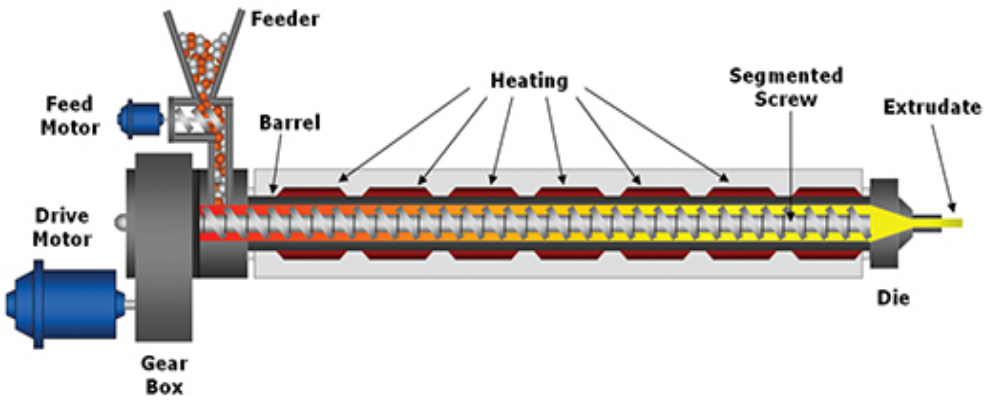

Fig 6: Hot melt extrusion technique in 3D printing[83]

Table 6: some of the drugs prepared by Hot melt extrusion technique are

Sl .no	Drug	Dosage form	Application	Reference
1	Paracetamol	3D-printed—cube, pyramid, cylinder, sphere and torus	Analgesic	84
2	Domperidone	Tablet	Parkinson's disease	85
3	Hydroxypropyl cellulose		Keratoconjunctivitis	
4	Rifampicin	Compartmentalized shells	Antibiotic	86
5	Isoniazid		Tuberculosis (TB) infections	
6	Indomethacin	Subcutaneous rods	Nonsteroidal anti-inflammatory	86
7	Ethylene Vinyl Acetate (Eva) Copolymers		Adhesive, sealants and coatings.	
8	Polymer Polyvinyl Alcohol (PVA), Mannitol and Hydrochlorothiazide (Hctz), Polylactic Acid (PLA)	Three-compartment hollow cylinder	Polymers	87
9	Indomethacin	T-shaped prototypes of intrauterine system (IUS)	Nonsteroidal anti-inflammatory	88
10	Ethylene Vinyl Acetate (Eva) Copolymers		Hot melt adhesives	

Stereolithography

Stereolithography is the technique in which a computer controlled laser beam is used to solidify the liquid polymer or resin, thereby creating a 3D structure[89] (Fig 7).SLA has some advantages over other types of 3DP, mainly it's remarkable resolution and the avoidance of thermal processes can be detrimental for certain drug molecules.[90] Some of the drugs prepared by Stereolithography are given in Table 7.

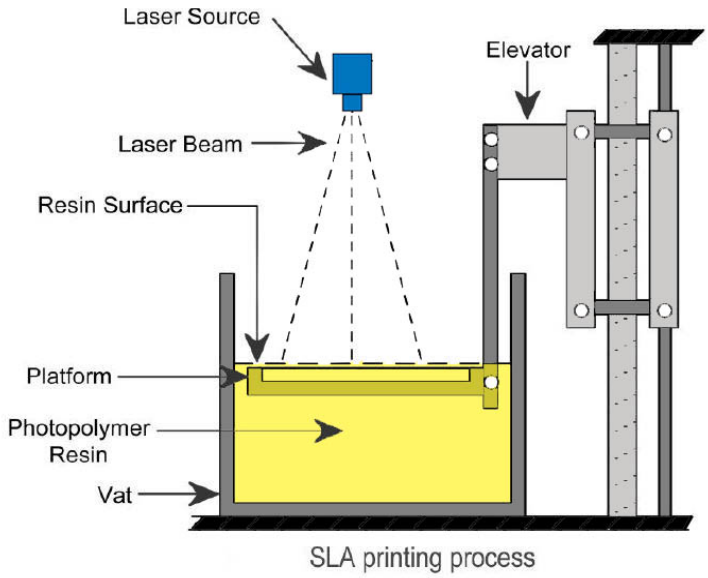

Fig 7: Stereolithography in 3D printing[91]

Table 7: Drugs prepared by Stereolithography are

Sl.no	Drug name	Dosage form	Use	Reference
1	Paracetamol	Oral modified release tablets	Antipyretic	92
2	4-Aminosalicylic acid	Oral modified release tablets	Antibiotic	92
3	Salicylic acid	Anti-acne patch	Psoriasis	93

Selective laser sintering

SLS uses a laser to bind together the powder particles from a powder bed. During the printing process, the laser is directed to draw a specific pattern onto the surface of the powder bed thereby creating a 3D structure (Fig 8). For example Paracetamol is an Orodispersible tablets which was prepared by this technique. It is currently used for industrial manufacturing of plastic, metallic and ceramic objects. [94]

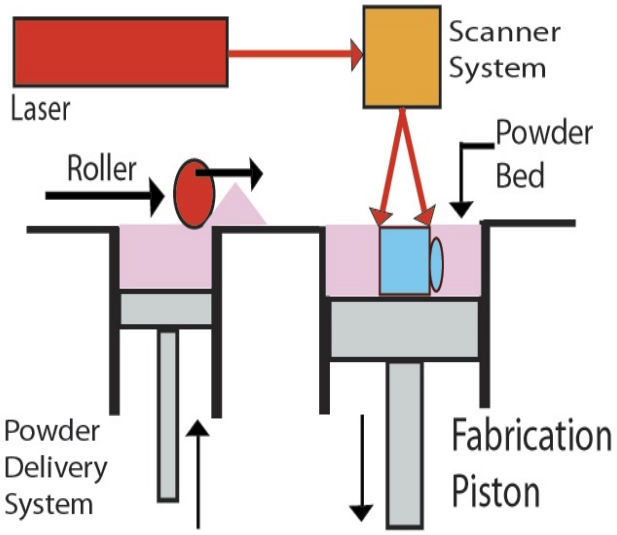

Fig 8: Selective laser sintering technique in 3D printing [95]

ADVANTAGES AND DISADVANTAGES

Use of 3DP has the advantage of adequate control on the spatial distribution of active pharmaceutical ingredients in the dosage form, which can help us to form a complex structure.[96] It also provides easy disintegration for patients who have difficulty in swallowing ,hence it increases the patient compliance.[97] There are basically 3 situations why this is on-demand in pharmacy because it includes printing directly on the implants or tissue scaffolds, printing "just in-time" in healthcare facilities or in other resource-constrained settings and printing low-stability drugs for immediate consumption. In all these scenarios, 3D printing technologies provide attractive solutions to explore on-demand pharmacy.[98]

Regarding possible disadvantages, there are several 3DP technologies based on the nozzle mechanism. Problems related to nozzle are a major challenge as stopping of the print head, which can affect the structure of the final product. Clogging in the case of powder printing is another hurdle. Other points of concern are the possibility of altering the final structure due to mechanical stress and storage condition alterations, the effect of ink formulations, printer related parameters and effect of these on quality of printing, cost of the printer. [99]

APPLICATION OF 3D PRINTING

3D printing applications are an enormous challenge, with potential use in a broad range of fields such as industrial design, aerospace, medical, tissue engineering, architecture, pharmaceutical and even food. [100]It mainly focus on two potential directions to bring the pharmaceutical product development to uncharted areas, one is the manufacturing of drug delivery systems with sophisticated structures and the other one is personalized medicine. It has expanded into the healthcare industry, where it's used to create dental implants. Now, there may be an opportunity to use it for personalized healthcare as well. It also fabricates a programmed release multi-drug implant for bone tuberculosis therapy. It also helps in Organ printing to produce cells, biomaterials, and cell-laden materials individually by layer by layer and directly creating 3D tissue like structure.

CHALLENGES IN 3D PRINTING TECHNOLOGY

Although 3D printing technology showed promising results in drug delivery applications, the technology is still under the developing stage. Hence it undergoes several challenges such as optimization process, improving performance of device for versatile use, selections of appropriate excipients, post treatment method, etc., to improve the performance of 3D printed products' and to expand the application range in novel drug delivery systems. Apart from the cost of developing new formulations or re-designing existing formulations through 3DP, the built-in flexibility may be a major source of liability from safety point of view. And to achieve quality 3DP products, many important parameters need to be optimized like printing rate, printing passes, line velocity of the print head, interval time between two printing layer, distance between the nozzles and the powder layer, etc.

FUTURE PROSPECTS

New possibilities in 3D printing may open up whole new opportunities for pharmaceutical research and bio-technology applications. In near future 3D printing approach will be utilized in many ways such as fabricate and engineer various novel dosage forms, achieve optimized drug release profiles, develop new excipients, avoid incompatibilities between multiple drugs, drug dosage forms, supporting delivery, limit degradation of biological molecules or helping to research cures. 3D printing could add a whole new dimension of possibilities to personalized medicine. In its most simplistic form, the idea of experts and researchers is to produce personalized 3D printed oral tablets. On demand printing of drug products can be implemented for drugs with limited shelf life or for patient specific medications, offering an alternative to traditional compounding pharmacies. In future it may lead to the innovation in garage biology. As the technology is still so new, there's a lack of regulation, safety and security concerns of 3D printing. So these problems can be overcome in nearby future

REFERENCES

1. Ursan I, Chiu L, Pierce A; Three-dimensional drug printing: a structured review. Journal of the American Pharmacists Association; 2013; P: 53.
2. Marzuka SK, Kulsum JU; 3D Printing: a new avenue in pharmaceuticals. World Journal of Pharmaceutical Research;2016; 5:1686-701.
3. 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.

4. Prasad LK, Smyth H; 3D printing technologies for drug delivery: A review; Drug Development Industrial Pharmacy; 2016; 42:1019–31.
5. Katstra W, Palazzolo R, Rowe C, Giritlioglu B, Teung P.; Oral dosage forms fabricated by three dimensional printing.; Journal of Controlled Release; 2000; 66,P-1-9.
6. Melendez PA, Kane KM, Ashvar CS, Albrecht M, Smith PA.;Thermal inkjet application in the preparation of oral dosage forms: dispensing of Prednisolone solutions and polymorphic characterization by solid-state spectroscopic techniques.; Journal of Pharmaceutical Sciences.; 2008; 97,P-2619–36.
7. Li TH, Stachowiak JC, Fletcher DA; Mixing solutions in inkjet formed vesicles; Methods Enzymol.; 2009; 465,P-75–94.
8. Tarcha PJ ,et al.;The application of ink-jet technology for the coating and loading of drug eluting stents.; Annals of Biomedical Engineering.; 2007;35,P-1791–9.
9. C.-H. Choi,L.-Y. Lin,C.-C. Cheng ,Chih-Hung Chang; Printed Oxide Thin Film Transistors: A Mini Review; ECS Journal of Solid State Science and Technology; (2015),4 (4), P-3044-3051
10. Buanz AB, Saunders MH, Basit AW, Gaisford S.; Preparation of personalized-dose Salbutamol sulphate oral films with thermal ink-jet printing.; Pharmaceutical research; 2011;28:2386-92.
11. Scoutaris N, Alexander MR, Gellert PR, Roberts CJ.; Inkjet printing as a novel medicine formulation technique.; Journal of Controlled Release ;2011;156:179-85.
12. Pardeike J, Strohmeier DM, Schrödl N, Voura C, Gruber M.; Nano suspensions as advanced printing ink for accurate dosing of poorly soluble drugs in personalized medicines.; International Journal of Pharmaceutics ;2011;420:93-100.
13. Patricia Van Arnum;Using Thermal Ink-Jet Printing Technology to Produce Pharmaceutical Cocrystals; Pharmaceutical Technology; May 02, 2013; Volume 37;Issue 5.
14. Sharma G[1], Mueannoom W, Buanz AB, Taylor KM, Gaisford S;In vitro characterisation of terbutaline sulphate particles prepared by thermal ink-jet spray freeze drying.; International Journal of Pharmaceutics. 2013; 447(1-2):165-70.
15. Maulvi FA, Shah JM, Solanki BS, Patel AS, Soni TG, Shah DO.; Application of 3D printing technology in the development of novel drug delivery systems.; International Journal of Drug Development and Research; 2017; 9:44-9.
16. M. Singh, et al.; Inkjet Printing—Process and Its Applications; Advanced Materials; 2010,P- 673-685
17. James Norman Rapti, D.Madurawe Christine, M.V.Moore Mansoor, A.Khan Akm Khairuzzaman ; A new chapter in pharmaceutical manufacturing: 3D-printed drug products.; Advanced Drug Delivery Reviews; 1 January 2017, Volume 108, P- 39-50
18. Scoutaris N, Alexander M, Gellert P, Roberts C. Inkjet printing as a novel medicine formulation technique. Journal of Controlled Release. Volume 156, Issue 2, 10 December 2011, P-179-185
19. Ross S, Scoutaris N, Lamprou D, Mallinson D, Douroumis D.; Inkjet printing of insulin microneedles for transdermal delivery.; Drug Delivery and Translational Research.; 2015 Aug;5(4):451-61.
20. Uddin MJ, Scoutaris N, Klepetsanis P, Chowdhry B, Prausnitz MR, Douroumis D.; Inkjet printing of transdermal microneedles for the delivery of anticancer agents.; International Journal of Pharmaceutics.;2015 Oct 30;494(2):593-602.
21. Lee BK, Yun YH, Choi JS, Choi YC, Kim JD, Cho YW. Fabrication of drug-loaded polymer microparticles with arbitrary geometries using a piezoelectric inkjet printing system; International Journal of Pharmaceutics.; 2012 May 10; 427(2):305-10.
22. Genina, N; Fors, D; Palo, M; Peltonen, J; Sandler, N.; Behavior of printable formulations of loperamide and caffeine on different substrates—Effect of print density in inkjet printing. International journal of pharmaceutics; 2013; Vol: 453, Issue: 2, Page: 488-97; ISSN: 1873-3476.
23. Sandler N, Maattanen A, Ihalainen P, et al. ;Inkjet printing of drug substances and use of porous substrates towards individualized - dosing.; Journal of Pharmaceutical Sciences, 2011, Volume 100, 3386 – 3395, Issue 8.
24. Alomari M, Mohamed F, Basit A, Gaisford S. ;Personalised dosing: Printing a dose of one's own medicine.; International Journal of Pharmaceutics; October 2015, Volume 494, P-568-577, Issue 2.
25. Allen. E, O'Mahoney C., Cronin M., et al.;Dissolvable microneedle fabrication using piezoelectric dispensing technology.; International Journal of Pharmaceutics; 16 March 2016; Volume 500 , P-1-10 ,Issues 1–2.
26. Boehm RD, Daniels J, Stafslien S, Nasir A, Lefebvre J, Narayan RJ.; Polyglycolic acid microneedles modified with inkjet-deposited antifungal coatings.;Biointerphases. 2015 Mar 2;10(1):011004
27. Raijada D, Genina N, Fors D, et al.; A Step Toward Development of Printable Dosage Forms for Poorly Soluble Drugs.; Journal of Pharmaceutical Sciences;2013 oct, Volume 102, 3694 - 3704, Issue 10.
28. Montenegro-Nicolini, M.Miranda, V. Morales, Inkjet Printing of Proteins: an Experimental Approach; Journal of The American Association of Pharmaceutical Scientists ;2017; 19: 234. 10.1208/s12248-016-9997-8.
29. K. Boven, S. Stryker, J. Knight, et al.; The increased incidence of pure red cell aplasia with an Eprex formulation in uncoated rubber stopper syringes; Kidney International, 2005,P-.2346-2353.
30. Gu, Y., Chen, X., Lee, J.H., Monteiro, D.A., Wang, H., Lee, W.Y.; Inkjet printed antibiotic- and calcium-eluting bioresorbable nanocomposite micropatterns for orthopedic implants; Acta Biomaterialia; 2012 , P-424-431.
31. 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: P-33-38.
32. Pardeike J,Strohmeier DM, Schrödl N, Voura C, Gruber M, et al.; Nanosuspensions as advanced printing ink for accurate dosing of poorly soluble drugs in personalized medicines.;International Journal of Pharmaceutics;2011, 420: P-93-100.
33. Daly R, Harrington TS, Martin GD, Hutchings IM.; Inkjet printing for pharmaceutics - A review of research and manufacturing; International Journal of Pharmaceutics.; 2015 Oct 30;494(2):554-567.
34. Tarcha PJ, Verlee D, Hui HW, Setesak J, Antohe B, Radulescu D, Wallace D.; The application of ink-jet technology for the coating and loading of drug-eluting stents.; Annals of Biomedical Engineering.;2007 Oct;35(10):1791-9.
35. Marizza, P., Keller, S.S., Mullertz, A., Boisen, A.;Polymer-filled microcontainers for oral delivery loaded using supercritical impregnation; Journal of Controlled Release; 2014 ;173, P-1-951
36. Genina, N; Jansen, E M; Breitenbach, A; et al.; Evaluation of different substrates for inkjet printing of rasagiline mesylate.; European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik e.V;2013,Vol:85,Issue:3 P-1075-83.
37. Yao xue xue bao ;3D printing via fused deposition modeling in pharmaceutics; Acta pharmaceutica Sinica ,November 2016,51(11):P-1659-1665 .
38. Alvaro Goyanes , Fabrizio Fina , Annalisa Martorana , Daniel Sedough , Simon Gaisford , Abdul W. Basit.; Development

of modified release 3D printed tablets (printlets) with pharmaceutical excipients using additive manufacturing.; International Journal of Pharmaceutics.;15 July 2017, Volume 527, Issues 1–2, P-21-30.
39. M.A. Alhnan, T.C. Okwuosa, M. Sadia, K.-W. Wan, W. Ahmed, B. Arafat.; Emergence of 3D printed dosage forms: opportunities and challenges; Pharmaceutical Research; 2016;33 (8) ;P-1817-1832.
40. S.H. Lim, S.M.Y. Chia, L. Kang,et.al;Three-dimensional printing of carbamazepine sustained-release scaffold ; Journal of Pharmaceutical Sciences; 2016,105 (7) , P. 2155-2163.
41. A. Goyanes, H. Chang, D. Sedough, et al.;Fabrication of controlled-release budesonide tablets via desktop (FDM) 3D printing;International journal of Pharmaceutics; 2015; 496 (2) ,P- 414-420
42. S.G. Gumaste, S.S. Gupta, A.T.M. Serajuddin;Investigation of polymer-surfactant and polymer-drug-surfactant miscibility for solid dispersion;American Association of Pharmaceutical Scientists; 2016, 18 (5) , P- 1131-1143.
43. Xuyu Chai1, et.al;Fused Deposition Modeling (FDM) 3D Printed Tablets for Intragastric Floating Delivery of Domperidone; National Center for Biotechnology Information; 6 june 2017, 7: 2829.
44. Yan Yang, Huihui Wang, Haichao Li, ZhiminOu, Gensheng Yang, European;3D printed tablets with internal scaffold structure using ethyl cellulose to achieve sustained ibuprofen release; Journal of Pharmaceutical Sciences;30 March 2018, Volume 115, P- 11-18
45. Alvaro Goyanes , Asma B.M. Buanz , GraceB. Hatton , Simon Gaisford , Abdul W. Basit.; 3D printing of modified-release aminosalicylate (4-ASA and 5-ASA) tablets;European Journal of Pharmaceutics and Biopharmaceutics;Volume 89, January 2015, P-157-162.
46. Christos I. Gioumouxouzis , Apostolos Baklavaridis , Orestis L. Katsamenis , Catherine K. Markopoulou , Nikolaos Bouropoulos, DimitriosTzetzis , Dimitrios G. Fatouros.;A 3D printed bilayer oral solid dosage form combining metformin for prolonged and glimepiride for immediate drug delivery.;European Journal of Pharmaceutical Sciences; , 30 July 2018,Volume 120, P- 40-52
47. Tochukwu C. Okwuosa, Dominika Stefaniak, Basel Arafat, Abdullah Isreb, Ka-Wai Wan.;A Lower Temperature FDM 3D Printing for the Manufacture of Patient-Specific Immediate Release Tablets.; Pharmaceutical Research; November 2016, Volume 33, Issue 11, P-2704–2712.
48. Alvaro Goyanes , Fabrizio Fina , Annalisa Martorana , Daniel Sedough , Simon Gaisford , Abdul W. Basit;Development of modified release 3D printed tablets (printlets) with pharmaceutical excipients using additive manufacturing.; International Journal of Pharmaceutics , 15 July 2017,Volume 527, Issues 1–2, P-21-30.
49. Tochukwu C. Okwuosa, Beatriz C. Pereira, Basel Arafat, Milena Cieszynska, Abdullah Isreb.; Fabricating a Shell-Core Delayed Release Tablet Using Dual FDM 3D Printing for Patient-Centred Therapy.; Pharmaceutical Research.; February 2017, Volume 34, Issue 2, P- 427–437.
50. Justyna Skowyra , Katarzyna Pietrzak , Mohamed A. Alhnan; Fabrication of extended-release patient-tailored prednisolone tablets via fused deposition modelling (FDM) 3D printing.; European Journal of Pharmaceutical Sciences; February 2015;Volume 68, 20, P-11-17.
51. MuznaSadia , Abdullah Isreb , Ibrahim Abbadi , Mohammad Isreb , David Aziz , Amjad Selo , Peter Timmins , Mohamed A. Alhnan.; From ‘fixed dose combinations’ to ‘a dynamic dose combiner’: 3D printed bi-layer antihypertensive tablets; European Journal of Pharmaceutical Sciences; 21 July 2018, Volume 123, P- 484-494.
52. Furqan A Manthal J Shah, Boosky S Solanki, Akanksha S Patel, Teja; G Soni, Dinesh O Shah.;Application of 3D printing technology in the development of novel drug delivery systems International journal of drug development and research, , March 30, 2017, 9:44-49.
53. Sandler N, Salmela I, Fallarero A, Rosling A, Khajeheian M, Kolakovic R, et al. ;Towards fabrication of 3D printed medical devices to prevent biofilm formation.; International Journal of Pharmaceutics; 2014,459:62-4
54. Masood SH.;Application of fused deposition modelling in controlled drug delivery devices.;Assembly Automation; 2007; 27:215-21.
55. Weisman JA, Nicholson JC, Tappa K, Jammalamadaka U, Wilson CG, Mills DK.; Antibiotic and chemotherapeutic enhanced three-dimensional printer filaments and constructs for biomedical applications.;International Journal of Nanomedicine 2015;10:357-70.
56. Melocchi A, Parietti F, Loreti G, Maroni A, Gazzaniga A, Zema L.; 3D printing by fused deposition modeling (FDM) of a swellable/erodible capsular device for oral pulsatile release of drugs.; Journal of Drug Delivery Science and Technology 2015; 30:360-7.
57. 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; 217:308-14.
58. Goyanes A, Buanz AB, Basit AW, Gaisford S.; Fused-filament 3D printing (3DP) for fabrication of tablets.; International Journal of Pharmaceutics ;2014;476:88-92.
59. 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;89:157-62.
60. Genina N, Holländer J, Jukarainen H, Mäkilä E, Salonen J et al.; Ethylene vinyl acetate (EVA) as a new drug carrier for 3D printed medical drug delivery devices.; European Journal of Pharmaceutical Sciences; 2016;90:53-63.
61. Sadia M, Sośnicka A, Arafat B, Isreb A, Ahmed W, et al.; Adaptation of pharmaceutical excipients to FDM 3D printing for the fabrication of patient tailored immediate releasetablets.; International journal of Pharmaceutics;20 November 2016,513:65968.
62. Aprecia Pharmacuticals. FDA approves the first 3D printed drug product aprecia introduces its first product using the ZipDose® formulation platform for the treatment of epilepsy; 2015.
63. Herbert Reitsamer ,Johannes Khinast.; 3D printing of oraldrugs: a new reality or hype.;Expert Opinion on Drug Delivery;05 Sep 2017 , Volume 15, 2018 - Issue 1.
64. Emily Matchar; The Future of 3D-Printed Pills; SMITHSONIAN.COM ;AUGUST 20, 2015[https://www.smithsonianmag.com/innovation/future-3d-printed-pills-180956292]
65. Marzuka SK, Kulsum JU.; 3D Printing: a new avenue in pharmaceuticals.;World Journal of Pharmaceutical Research.;2016;5:1686-701.
66. Bala R, Madaan R, Kaur A, Mahajan K.;3D printing: basic role in pharmacy.; European Journal of Biomedical and Pharmaceutical Sciences ;2017;4:242-7.
67. Khaled SA, Burley JC, Alexander MR, Yang J, Roberts CJ.; 3D printing of tablets containing multiple drugs with defined release profiles.;International journal of pharmaceutics .; 2015,494: 643-650.
68. Rattanakit P, Moulton SE, Santiago KS, Liawruangrath S, Wallace GG. Extrusion printed polymer structures: a facile and versatile approach to tailored drug delivery platforms.; International journal of pharmaceutics ;2012;422:254-63
69. Hollander J, Genina N, Jukarainen H, Khajeheian M, Rosling.; 3D printed UV light cured poly dimethylsil oxane devices for drug delivery.;International journal of pharmaceutics; 2016;5173(17)31071-31072.
70. Vinod G. Gokhare, D. N. Raut, D. K. Shinde; Review paper on 3D-Printing Aspects and Various Processes Used in the

3D-Printing; International Journal of Engineering Research & Technology; 2017,Vol. 6, Issue 06.
71. Wu G, Wu W, Zheng Q, Li J, Zhou J, et al.; Experimental study of PLLA/INH slow release implant fabricated by three dimensional printing technique and drug release characteristics in vitro.; Biomedical engineering; 2014 Jul 19;13:97
72. Thomas D, Tehrani Z, Redfearn B.; 3-D printed composite microfluidic pump for wearable biomedical applications.; Additive Manufacturing ;2016;9:30-8.
73. Yu DG, Shen XX, Branford WC, Zhu LM, White K, Yang XL.; Novel oral fast disintegrating drug delivery devices with predefined inner structure fabricated by three dimensional printing.; Journal of Pharmacy and Pharmacology;2009;61:323-9.
74. Goyanes A, Wang J, Buanz A, Martinez-Pacheco R, Telford R.; 3D printing of medicines: engineering novel oral devices with unique design and drug release characteristics. Molecular Pharmaceutics; 2015; 12:4077-84.
75. Yi HG, Choi YJ, Kang KS, Hong JM, Pati RG.;A 3D-printed local drug delivery patch for pancreatic cancer growth suppression.; Journal of Controlled Release ;2016;238:231-41.
76. Gbureck U, Vorndran E, Müller FA, Barralet JE.; Low temperature direct 3D printed bioceramics and biocomposites as drug release matrices.; Journal of Controlled Release 2007;122:173-80.
77. Rowe C, Katstra W, Palazzolo R, Giritlioglu B, Teung P.; Multi mechanism oral dosage forms fabricated by three dimensional printing. Journal of Controlled Release 2000;66:11-7.
78. Katstra W, Palazzolo R, Rowe C, Giritlioglu B, Teung P, et al. ;Oral dosage forms fabricated by Three Dimensional Printing.; Journal of controlled release; 2000; 66:1-9.
79. Boetker J, Water JJ, Aho J, Arnfast L, Bohr A, et al. ;Modifying release characteristics from 3D printed drug-eluting products. ;European Journal of Pharmaceutical Sciences. 2016, 90:47-52.
80. Sonal Kushwaha.; Application of Hot Melt Extrusion in Pharmaceutical 3D Printing, Journal of Bioequivalence & Bioavailability; 2018, Vol 10(3): 54-57.
81. Feng, X.; Zhang, F.; Twin-screw extrusion of sustained-release oral dosage forms and medical implants.; Drug Delivery and Translational Research. ;2017. P-1–20
82. Repka, M.A.; Bandari, S.; Kallakunta, V.R.; Vo, A.Q.; McFall, H.; Pimparade, M.B.; Bhagurkar, A.M. ;Melt extrusion with poorly soluble drugs—An integrated review.; International Journal of Pharmaceutics. ;2018, 535, 68–85
83. Sampada Upadhye;Hot melt extrusion – optimelt™ Hot Melt Extrusion Technology to Improve Bioavailability of Poorly Soluble Drugs; drug development and delivery;2015
84. Goyanes A, Martinez PR, Buanz A, Basit AW, Gaisford S Effect of geometry on drug release from 3D printed tablets.; International Journal of Pharmaceutics ;2015,494: 657-663.
85. Sadia M, Arafat B, Ahmed W, Forbes RT, Ahlnan MA ;Channelled tablets: An innovative approach to accelerating drug release from 3D printed tablets. journal of the Controlled Release 2018; 269: 355-363.
86. Genina N, Hollander J, Jukarainen H, Makila E, Salonen J. ;Ethylene vinyl acetate (EVA) as a new drug carrier for 3D printed medical drug delivery devices.; EuropeanJournal of Pharmaceutical Sciences ; 2016,90: 53-63
87. Gioumouxouzis CI, Katsamenis O, Bouropoulos N, Fatouros DG .;3D printed oral solid dosage forms containing hydrochlorothiazide for controlled drug delivery. ;Journal of Drug Delivery Science and Technology .; 2017 ,40: 164-171.
88. Genina N, Janßen EM, Breitenbach A, Breitkreutz J, Sandler N ; Evaluation of different substrates for inkjet printing of rasagiline mesylate.; European Journal of Pharmaceutics and Biopharmaceutics ;2013,85: 1075-1083
89. Latief A, Suhardi P, Badri C. Three-dimensional model printing in oral and maxillofacial reconstructive surgery: comparison of three-dimensional models and multislice computed tomography scans; International Journal of Applied Pharmaceutics; 2017,9:74-8.
90. Pamela Robles; Production of medicines using stereolithography (SLA) 3D printing, fab Rx; September 28, 2017
91. Nikhil A; 3D Printing Processes - Vat Photo polymerisation; engineering guarge[https://www.engineersgarage.com/articles/3d-printing-processes-vat-photo-polymerisation]
92. Jie Wang , Alvaro Goyanes , Simon Gaisford , Abdul W. Ba sit.;Stereolithographic (SLA) 3D printing of oral modified-r elease dosage forms.; International journal of pharmaceutics; 30 April 2016, Volume 503, P- 207-212
93. 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;234:41-8.
94. Fina F, Madla CM, Goyanes A, Zhang J, Gaisford S, Basit AW.; Fabricating 3D printed orally disintegrating printlets using selective laser sintering.; International Journal of Pharmaceutics.; 2018,541(1–2):101–107.
95. Vijay Laxmi Kalyani; Future Communication Technology: A Comparison Between Claytronics And 3-D Printing; Journal of Management Engineering and Information Technology (JMEIT),2016, Volume -3, Issue- 4.
96. Preis M, Öblom H.; 3D-printed drugs for children-are we ready yet?.; American Association of Pharmaceutical Scientists.; 2017,18:303–8.
97. Prasad LK, Smyth H. ;3D printing technologies for drug delivery: A review.; Drug Development and Industrial Pharmacy.;2016;42:1019–31.
98. Ventola CL;Medical applications for 3D printing: Current and projected uses. Pharmacology & Therapeutics ; 2014;39(10):704-711.
99. Alhnan MA, Okwuosa TC, Sadia M, Wan KW, Ahmed W, Arafat B, et al. ;Emergence of 3D printed dosage forms: Opportunities and challenges.; Pharmaceutical Research. 2016;33:1817–32.
100. Katakam P, Dey B, Assaleh FH, Hwisa NT, Adiki SK, et al. ; Top-Down and Bottom-Up Approaches in 3D Printing Technologies for Drug Delivery Challenges.; Critical Reviews in Thereapeutic Drug Carrier System ;2015;32: 61-87.

Cite this article as:

L. Srinivas *et al*. 3D printing in pharmaceutical technology: A review. Int. Res. J. Pharm. 2019;10(2):8-17 http://dx.doi.org/10.7897/2230-8407.100234

Source of support: Nil, Conflict of interest: None Declared