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3D PRINTING: BASIC ROLE IN PHARMACY

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ABSTRACT
For regeneration of tissues and organs, many researchers used Computer-Aided Design (C.A.D) and Computer-Aided Manufacturing (C.A.M), the result of which many 3DP technologies like selective laser sintering, deposition modeling, inkjet-based printing and stereo lithography are introduced. Personalized medicine aims to tailor drug combination and dosage manufacturing to the specific needs of a patient by taking into consideration its genetic profile, phenotypic response, and path physiology. New technologies are needed to pharmaceutical tablets in a scalable manner, while meeting quality assurance regulatory standards. 3D Pharming, the use of 3D Printing to directly fabricate personalized pharmaceutical tablets, is under intense development by many investigators due to its unprecedented control for: 1) stability of multiple drugs within a pill; 2) precise dose of each drug; and 3) release kinetics of each component by incorporating designed structures that can modulate dissolution and diffusion profiles. Additionally, it has the potential to scale in order to meet the economics and quality that the pharmaceutical industry demands. This article reviews the types & techniques used for 3D printing of tablets, advantages, disadvantages and applications of 3D printing along with technologies used in the fabrication of Pharmaceutical dosage forms.

INTRODUCTION
Advances in the field of Pharmacogenomics, the study of how the genetic makeup of a person affects their particular drug response, are providing more precise information about the dosage and choice of drug that would best benefit a specific individual based on their genetic makeup.[1,2] Personalized medicine aims to provide patients with treatments tailored to their pathophysiology. This is done by coupling a patient's pharmacogenomics with information about their diet, environment, lifestyle, microbiome, and epigenetics.[3] This new approach for prescription drugs requires technology capable of producing tablets with a variety of dosage strengths in order to satisfy the specific medical needs of each individual. Currently, pharmaceutical companies manufacture tablets with universal predetermined dosage amounts.[4] This method requires large facilities with high production costs, trained personnel for its operation, and involves a variety of processing steps.[5] To make personalized medicine a reality, a paradigm shift in the way oral drug forms are currently manufactured is required. The new strategy should have the ability to reproducibly generate a wide range of dosages and have a short manufacturing time. These features would allow tablet manufacture technology to adapt to the rapid changeover of formulations experienced by scientists within R&D and clinical trial studies, accelerating drug development. Additionally, it should be economically viable, have minimal space and operational training requirements, comply with standards of regulation agencies and able to be digitally controlled by healthcare staff.[6,7] 3D printing was first demonstrated in 1996 as a promising candidate to replace conventional tableting techniques.[8] In 2015, the U.S. Food and Drug Administration agency (FDA) granted the approval of Spritam® (levetiracetam), the first 3D printed tablet for the treatment of epileptic seizures.[9] This landmark event marks a milestone in 3D Pharming and motivates further development of this technology towards the fabrication of customized tablets and improved personalized medicine. 3D Pharming promises to enable rapid point-of-care formulations with patient-specific dosages.[10] Furthermore, 3D Pharming provides control over drug release kinetics through methods that precisely manipulate the spatial distribution of multiple drugs within a pill, as well as their diffusion gradients.[11] This potential reduction in the number of tablets prescribed, combined with their improved efficacy, could result in enhanced patient compliance.[12] Finally, the economic benefits of this technology include reduced manufacturing and inventory wastes and the potential to grow to an industrialized scale. 3D printing is additive manufacturing process that is based on the advanced technology which is different from existing traditional techniques.[13]

History of 3-D printing

The brief history of 3 DP technologies is summarized in the table 1.[14.15]

S No.	Year	Work
1	May 1980.	Dr Kodama, in Japan was the very first person to fill patent application for RP technology. the full patent specification was subsequently not filed before the one-year deadline after the application
2	1983	Charles (Chuck) Hull, invented SLA machine
3	1986	the first patent was issued for stereo lithography apparatus(S.L.A)
4	1987	SLA-1, was introduced and sold in 1988
5	1987-89	Carl Deckard filed a patent in the US for the Selective Laser Sintering (SLS) RP process. This patent was issued in 1989
6	1989	Scott Crump filed a patent for Fused Deposition Modelling (F.D.M)-the proprietary technology
7	1996	Sanders Prototype (later Solidscape) and Z Corporation were set up
8	1997	Arcam was established
9	1998	Objet Geometries launched
10	2000	MCP Technologies (an established vacuum casting OEM) introduced the S. L. M technology
11	2002	Envision Tech was founded
12	January 2009	The first commercially available 3D printer in kit form and based on the RepRap concept was offered for sale.

Advantages and applications of 3D printing.[16]

In comparison with convectional manufacturing technique used for the fabrication of dosage form 3D printing offers lot of advantages which includes:

a) High production rate due to fast operating system
b) Ability to include high drug loading with desired precision and accuracy
c) Low wastage of material which reduces the production cost
d) Adaptable to wide variety of pharmaceutical active ingredients including poorly soluble drugs, protein and peptides and the drugs having narrow therapeutic window.

3DP in pharmaceutical drug delivery has applications in the area of personalized medicines. It has been found that in present era of pharmacy practice and medicine "one size does not fit all" thereby medication must be designed as per the individual patient's needs while taking into consideration factors such as differences in genetic profiles, age, race, gender, epigenetic and environmental factors. Also, there are situations where the treatment regimens must be customized to improve patient's adherence to treatment. This is particularly important in treatment of chronic diseases where patients have to undergo through complicated treatment regimens involving multiple medicines and high dosing frequency couples with side effects. In all these cases, medicine customization can be achieved through 3DP technology. 3DP technology will continue to gain much attention in development of solid oral dosage forms as the most popular drug dosage forms. Solid dosage forms gain their popularity as it offers numbers of advantages such as: ease of manufacture, non invasive nature, accurate dosing, and ability to achieve patient adherence to treatment. However, the multi-steps involved in the manufacturing processes of solid dosage forms have been plagued by many challenges such as lengthy operational processes, batch-to-batch variations due to reliance on operator's judgments, material wastage, low drug loading capacity and adaptability to limited categories of active ingredients.[17]

Implantable drug delivery systems will also be benefited by 3DP technology especially in offering effective strategies to overcome limitations such as batch-to-batch variability of drug-excipient blend during implant preparation and inconsistent internal architecture of resultant implants. 3DP techniques have also been demonstrated to produce implants that have precisely defined, micro- and macro architectures that can effectively be applied in complex drug release. In addition, 3DP could offer advantages in optimizing the concentration of drug that are needed in implant preparation which could be beneficial in improving drug efficacy and minimizing toxicity and side effects.[18,19]

Types of 3D printing technologies

The types of 3D printing technologies currently used in pharmaceutical industry are as follows

Inkjet printing

In the technique, different combinations of active ingredients and excipients (ink) are precisely sprayed in small droplets (via drug on demand) or continuous jet method) in varying sizes layer by layer into a non-powder substrate. The technique encompasses powder-based 3D printing that uses a powder foundation (powder substrate) for the sprayed ink where it solidifies into a solid dosage.

Direct-write
Uses a computer-controlled translational stage that moves a pattern-generating device in order to achieve, layer-by-layer, 3D microstructure

Zip Dose
Provide a personalised dose in addition to the delivery of high drug loaded with high disintegration and dissolution level by manufacturing highly porous material.

Thermal inkjet printing
Thermal injet printer consist of micro resistor that heats the thin film of ink fluid forming a vapor bubbles that nucleates and expand to push ink drop out of a nozzle. Thermal inkjet printing can be used for dispensing extemporaneous preparation of drugs on the 3D scaffold that act as drug carriers.

Fused deposition modeling
Fused deposition modelling (FDM) technique involves the melting, extrusion, and layer by layer deposition of materials that after solidification result in objects with predetermined structures. To control the pore size and the configuration of the object, variables such as raster angle and thickness, space between rasters and the extrusion tip diameter can be varied. The appropriate heat transfer characteristics and rheological properties are the most critical material qualities used for FDM. Molten metal's, self-hardening waxes, and thermoplastic materials such as nylon, acrylonitrile butadiene styrene, and polyvinyl chloride have been utilized successfully for FDM. The advantages of FDM are its lower costs, the ability to print multiple polymers in a single structure, and the capacity to create hollow and porous objects with good mechanical strengths. These characteristics enable FDM as a suitable technique for the manufacturing of personalized tablets.[20,21]

3D Printing cycle.[22]
This cycle starts with the command of printing leads to chamber filling then deposition of powder from hopper after which layer is spreaded on platform and decomposition of binder take place. The binders solidify and powder recrystallized. Then cycle is repeated. The illustration of this 3D Printing cycle is given below Fig. 1.

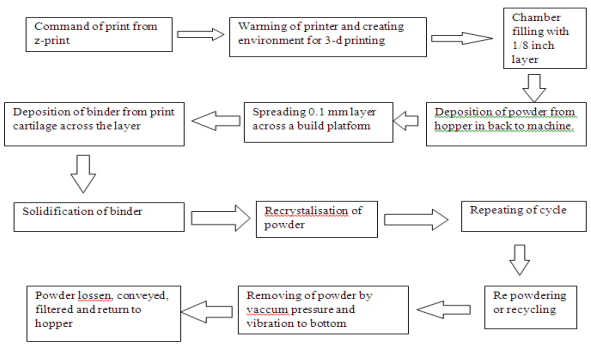

Figure 1: 3 D printing cycle

Work done on 3D Printing technology
Wu *et al.* conducted the first experiments involving 3D Pharming by printing multi-drug delivery devices in 1996.[23] In this study, the release profiles of methylene blue and alizarin yellow dyes were controlled by manipulating the three -dimensional position of dyes within the device, its microstructure and chemical composition. A square grid pattern of 5 cells composed of polyethylene oxide (PEO) was printed and dyes were localized in predefined patterns within the squares. A poly caprolactone (PCL) sheet was printed at the top and bottom of this grid to seal it and prevent dye diffusion upon resorption, yielding a two dimensional diffusion profile limited to the plane of the device. *In vitro* release studies showed a multiphasic release profile of the dyes incorporated.

Kastra *et al*. demonstrated that the drug release mechanisms of 3 D printed tablets could be controlled by the chemical properties of the binder utilized and its final concentration within the pill.[24] Eudragit E-100, a cationic methacrylic ester copolymer soluble under acidic conditions below pH 5, was used as a binder to fabricate cellulose tablets with erosion dominated drug release mechanism. Tablets with diffusion controlled release profiles were made by utilizing Eudragit RLPO as binder. Eudragit RLPO is a permeable and insoluble ammonio-methacrylic acid copolymer and its properties have no dependence on pH. Dissolution studies of these tablets in simulated intestinal fluid demonstrated an increase in drug release time with increased binder content within the tablet printed. The hardness and friability of the designed drug delivery devices were comparable to commercially available compressed tablets.

Rowe *et al.* made use of diverse binders to fabricate tablets with complex drug release profiles.[25] A device with an immediate-extended release profile of the molecule chlorpheniramine was fabricated by using E-100 as a binder for half of the pill and E-RLPO for the second half. The immediate release section delivered the full load of chlorpheniramine maleate within the first 30 minutes of the dissolution process. The extended release part maintained a sustained release for a period of 6 hours.

A tablet with a pulse release profile of diclofenac was designed to made drug release in both gastric and intestinal fluid by using various binders sensitive to pH values characteristic of these areas. E-100 was used to print a section of the pill sensitive to the low pH found in gastric fluid, whereas Eudragit L-100, an anionic methacrylic ester copolymer sensitive to solutions with pH values above 6, was used to achieve drug release in intestinal fluid.

Wang *et al.* fabricated cubic drug delivery devices with a near zero controlled release profile containing eudoephedrine hydrochloride [26]. The device was

composed of hydroxypropyl methylcellulose (HPMC) and Kollidon SR as main materials. The cubic shell portion of the device was printed by utilizing a 15% triethyl citrate solution in ethanol as binder. An inner cubic core was printed with an aqueous binder containing 50% by weight of pseudoephedrine hydrochloride. The drug release mechanism of the system follows diffusion of drug present in the inner core.

Yu *et al.* formulated tablets by pre-mixing the active ingredient acetaminophen with the main excipient located in the powder bed.[27] The tablets of acetaminophen with concentrations as high as 68% by weight were produced. Furthermore, a zero-order release profile was achieved by printing insoluble layers at the top and bottom of the cylindrical device, resulting in a two-dimensional release profile.

Yu *et al.* produced FDTs with average disintegration times of 23.4 seconds.[28] This was achieved by printing tablets with compact top, bottom, and lateral layers, while leaving loose powder in the middle section of the pill resulting in an area of high porosity and permeability. Binder was dispensed in selected areas of the middle section of the pill to increase its mechanical stability. In vitro dissolution tests showed that 98.5% of the active acetaminophen was released within 2 minutes. The FDTs had an acceptable harness value of 63.4 ± 5.4 N/cm^2. However, friability studies demonstrated an unsatisfactory mass loss of 3.55 ± 1.16%. This was corrected in a further study by incrementing the number of binder passes through the printing process and not printing selected areas in the middle section of the tablet, resulting in a net weight loss of 0.92 ± 0.14%.[37] Net weight loss values below 1% are considered acceptable based on regulations by the United state Pharmacopeia (USP).

Khaled *et al.* in 2014 used concept of extruding active material using 3d Pharming. The printed tablets containing guaifenesin, used as expectorant was fabricated. The fabricated tablets contained an immediate release compartment composed of HPMC 2910 as binder, in combination with microcrystalline cellulose and sodium starch glycolate as disintegrants. The other half of the pill featured a sustained release section constituted of HPMC 2208 and poly (acrylic acid) as hydrophilic matrix. These materials were processed separately and combined with the active, resulting in the synthesis of two viscous pastes that were used as feedstock for the printing process.[29]

Khaled *et.al* used 3D printing of tablets containing multiple drugs with defined release profiles. The author employed three-dimensional (3D) extrusion-based printing as a medicine manufacturing technique for the production of multi-active tablets with well-defined and separate controlled release profiles for three different drugs, captopril, nifedipine and glipizide. The printed formulations were evaluated for drug release using USP dissolution testing. It was found that the captopril portion showed the intended zero order drug release of an osmotic pump and the nifedipine and glipizide portions showed either first order release or Korsmeyer-Peppas release kinetics dependent upon the active/excipient ratio used.[30]

Scoutaris *et al.* demonstrate the viability of using an ink-jet printer to produce a formulation capable of controlling the release of a drug [31]. This was shown for the drug felodipine, an antihypertensive, with polyvinyl pyrrolidone (PVP) as an excipient**.** Examples of some of the solid dosage forms developed using 3D technology were summarised in table no. 2.

Table 2: Examples of pharmaceutical formulations that were developed by 3DP technology

3DP Technology	Dosage Forms	Active Ingredients
Desktop 3D printer	Tablet	Guaifenesin[32]
A laboratory- scale 3DP machine	Capsule	Pseudoephedrine hydrochloride[33]
Fused Deposition Modelling (FDM)	Tablet	5-aminosalicylic acid (5-ASA, mesalazine) and 4-aminosalicylic acid (4-ASA)[34]
3DP extrusion-based printing	Tablet	Captopril with Nifedipine and Glipizide[35]
3DP technology	Tablet	Acetaminophen[36]
Inkjet 3DP	Implant	Levofloxacin[37]
3DP machine	Multi-drug implant	Rifampicin and Isoniazid[38]
Inkjet 3DP	Nanosuspension	Folic Acid[39]
Thermal Inkjet (TIJ) Printing	Solution	Salbutamol sulphate[40]
Inkjet 3DP	Nanoparticles	Rifampicin[41]
3D Extrusion Printing	Encapsulated within a polymer (PLGA) poly(vinyl alcohol) (PVA)	Dexamethasone- 21-phosphate disodium salt[42]
Thermal Inkjet (TIJ) Printing	Solid dosage forms	Prednisolone[43]

Challenges and future Prospects

3DP technology has many anticipated advantages that are not yet proven; as such continuous clinical development of 3DP will require vision, money, and time .We envisage that activities to develop 3DP from a broader appeal clinically will include (i) optimization and improvement of software performance, (ii) development of new excipients or assessment of old

excipients for application in 3D formulations; and (iii) development and optimization of manufacturing process for a wide range of drug products and (iv) clinical studies to assess efficacy, safety and stability of new 3D-based formulations. 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. It is important to rule out tampering of the dose or drug through the process to ensure there is no adulteration or mix-up of treatment regimens among patients. It is also anticipated that regulatory stipulations for 3DP formulations will be stringent in order to rule out illegal printing of drug products depending on the drug product, it is expected that a broad-based application of 3DP in pharmaceutical drug delivery will be greatly impacted by regulatory concerns and the need to have built-in tamper-proof strategies. Although, 3DP is an adaptable technique for a broad range of pharmaceutical active ingredients, it is important to note that the impact of 3DP on physicochemical properties of a drug and excipients must be established on a case by case basis. This is because it is widely known that the therapeutic efficacy of any drug is affected by properties like drug-excipient interaction, polymorphic changes and stability in the dosage form. It can be anticipated that a faster way to broaden areas of application of 3DP in pharmaceutical drug delivery is to combine 3DP with conventional pharmaceutical technologies. Such hybrid systems will apply the proven effectiveness of conventional pharmaceutical technologies as well as exploit all the benefits of 3DP with respect to customization, precision and reduction of material wastage.

CONCLUSION

In conclusion, 3DP technology opens the door to a new era of advanced drug delivery with built-in flexibility that is well suited for personalized/customized medicines. We believe that with patience and perseverance, 3DP will continue to revolutionize the development of new generations of pharmaceutical formulations that are safe and effective.

REFRENCES

1. Jan de Gans B, Duineveld PC, SchubertUS. Inkjet printing of polymers: state of the art and future developments, *Adv. Mater*. 2004; 16: 203–213.
2. Sachs E.M. *et al.* (1994) three dimensional printing techniques. US Patent 5, 340, 656.
3. Iulia D. Ursan, BA; Ligia Chiu, BS; Andrea Pierce, BS. Three dimensional drug printing: a structured review *J Am Pharm Assoc* 2003; 2013(53):136-144.
4. Hideo Kodama, "A Scheme for Three-Dimensional Display by Automatic Fabrication of Three-Dimensional Model," IEICE TRANSACTIONS on Electronics (Japanese Edition), April, 1981; J64-C(4): 237–241.
5. Hull CW: Apparatus for production of three-dimensional objects by stereolithography. US4575330, 1986.
6. Hull CW: Method for production of three-dimensional objects by stereolithography US4929402, 1990.
7. Hull CW, Spence ST, Albert DJ et al.: Method and apparatus for production of high resolution three-dimensional objects by stereolithography. US5184307, 1993.
8. Masood SH: Application of fused deposition modelling in controlled drug delivery devices. Assembly Automation, 2007; 27(3): 215-221.
9. Sandler N, Salmela I, Fallarero A et al.: Towards fabrication of 3D printed medical devices to prevent biofilm formation. International Journal of Pharmaceutics, 2014; 459(1–2): 62-64.
10. 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; 357-370.
11. Khaled SA, Burley JC, Alexander MR, Roberts CJ: Desktop 3D printing of controlled release pharmaceutical bilayer tablets. International Journal of Pharmaceutics, 2014; 461(1–2): 105-111.
12. 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(2): 643-650.
13. Khaled SA, Burley JC, Alexander MR, Yang J, Roberts CJ: 3D printing of five-in- one dose combination polypill with defined immediate and sustained release profiles. Journal of Controlled Release, 2015; 217: 308-314.
14. Goyanes A, Buanz ABM, Basit AW, Gaisford S: Fused-filament 3D printing (3DP) for fabrication of tablets. International Journal of Pharmaceutics, 2014; 476(1–2): 88-92.
15. Goyanes A, Robles Martinez P, Buanz A, Basit AW, Gaisford S: Effect of geometry on drug release from 3D printed tablets. International Journal of Pharmaceutics, 2015; 494(2): 657-663.
16. 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 releaseof drugs. Journal of Drug Delivery Science and Technology, 2015.
17. Pillay V, Choonara ye.3D printing in drug delivery formulation: you can dream it, Design it and print it. How about patent it? Recent Pat Drug Deliv Formul. 2015; 7.
18. Yu DG, Zhu LM, Branford-White CJ, Yang XL Three dimensional printing in Pharmaceutics: Promises and problem J Pharm Sci. 2008; 97(9): 3666-90.
19. I. Gibson, D. Rosen, and B. Stucker. Additive Manufacturing Technologies: 3DPrinting, Rapid Prototyping, and Direct Digital Manufacturing, 2nd ed. (2015) New York: Springer.

20. J. Norman., R. D. Mudarawe, C. M. V. Moore, M. A. Khan, A. Khairuzzama, A New chapter in pharmaceutical manufacturing: 3D-printed drug products, Advanced Drug Delivery Reviews 2016, doi:10.1016/j.addr.2016.03.001.
21. Eric Richmond 3D Printing (3DP) for Pharmaceutical Solid Dosage Forms – A Follow- up FDA, News, Science and technology, sept.30; 2015.
22. Patricia Van Arnum . The future of dosage forms Pharmaceutical technology 2014; 38(1).
23. Katstra, W.E., Palazzolo, R.D., Rowe, W.C., Giritlioglu, B., Teung, P., Cima, M.J., Oral dosage forms fabricated by three dimensional printing. J. Control. Release, 2000; 66: 1.
24. United States Food and Drug Adminsitration. Additive Manufacturing of Medical Devices Public Workshop – Transcript for October 8th (2014) Available from: http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM425399.pdfG.
25. Skowyra J., Pietrzak K., Alhnan M.A. Fabrication of extended-release patient- tailored prednisolone tablets via fused deposition modelling (FDM) 3D printing. European Journal of Pharmaceutical Sciences, 2015; 68: 11-7.
26. SPRITAM [package insert]. East Windsor, N. J. Aprecia Pharmaceuticals Company 2015. Data on file. Aprecia Pharmaceuticals Company.
27. Centers for Disease Control and Prevention. Epilepsy Fast Facts. March 12, 2015.Available: http://www.cdc.gov/epilepsy/basics/fast-facts.htm. Accessed July 29, 2015.
28. Chen P. H, *et al.*, Prevalence of Perceived Dysphagia and Quality-of-Life Impairment in a Geriatric Population. Dysphagia. 2009; 24(1): 1-6.
29. Ekberg O. *et al.*, Social and psychological burden of dysphagia; its impact on diagnosis and treatment. Dysphagia. 2002; 17: 139-146.
30. Davis K. L, Candrilli S. D, Edin H. M. Prevalence and Cost of Nonadherence with Antiepileptic Drugs in an Adult Managed Care Population. Epilepsia. 2008; 49.
31. Stegemann S, Gosch M, Breitkreutz J. Swallowing dysfunction and dysphagia is an unrecognized challenge for oral drug therapy. International Journal of Pharmaceutics. 2012; 430: 197-206.
32. Cramer J. A, Glassman M, Rienzi V. The relationship between poor medication compliance and seizures. Epilepsy and Behavior. 08/2002; 3(4): 338-342.
33. N. Scoutaris et al.ink jet printing as noval medicine formulation technique Journal of controlled *Release* 2011; 156: 179–185
34. Goyanes A, Wang J, Buanz A, Martínez-Pacheco R, Telford R, Gaisford S, Basit AW. 3D printing of medicines: Engineering novel oral devices with unique design and drug release characteristics. Molecular Pharmaceutics. 2015; 12(11): 4077-84.
35. Kolakovic R, Viitala T, Ihalainen P, Genina N, Peltonen J, Sandler N. Printing technologies in fabrication of drug delivery systems. Expert Opin Drug Deliv. 2013; 10(12): 1711-23.
36. Jacob J, Coyle N, West TG, Monkhouse DC, Surprenant HL, Jain NB: Rapid disperse dosage form containing levetiracetam. WO2014144512 A1, (2014).
37. Yu DG, Yang XL, Xu HB, ZENG FD. Application of three-dimensional printing in pharmaceutics. Chinese New Drugs Journal. 2005; 14(7): 843.
38. 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(2): 643-50.
39. Preis M, Breitkreutz J, Sandler N. Perspective: concepts of printing technologies for oral film formulations. International journal of Pharmaceutics. 2015; 494(2): 578-584.
40. Kazi Marzuka S. and Jasvi Umme Kulsum. 3d printing: a new avenue in Pharmaceuticals. World journal of Pharmaceutical research. 2016; 5(5): 1686-1701.
41. Gross BC, Erkal JL, Lockwood SY, et al. Evaluation of 3D printing and its potential impact on biotechnology and the chemical sciences. Anal Chem 2014; 86; (7): 3240–3253.
42. Prasad LK, Smyth H. 3D Printing technologies for drug delivery: a review. Drug development and industrial pharmacy. 2016 Jul 2; 42(7): 1019-31.