Journal of
Biomolecular Research & Therapeutics

Jassim-Jabo J Biomol Res Ther 2015, 4:4
DOI:10.4172/2167-7956.1000e141

Editorial Open Access

3D Printing Technology in Pharmaceutical Drug Delivery: Prospects and Challenges

Assraa H Jassim-Jaboori and Moses O Oyewumi*

Department of Pharmaceutical Sciences, College of Pharmacy, Northeast Ohio Medical University, Rootstown, OH 44272, USA

Abstract

The recent FDA approval of the first ever three-dimensional (3D) printed-medicine underscores the potentials of 3D printing (3DP) technology in pharmaceutical drug delivery. This report evaluates the prospects of 3DP technology especially in the area of personalized medicines and offers our perspectives on potential challenges that may hamper a broad-based application in pharmaceutical drug delivery.

Introduction

Three-dimensional printing (3DP) technology relies on computer-aided designs to achieve unparalleled flexibility, time-saving, and exceptional manufacturing capability of pharmaceutical drug products. The process involves 3D proto-typing of layer-by-layer fabrication (via computer-aided design models) to formulate drug materials into the desired dosage form [1]. Ever since the development at Massachusetts Institute of Technology (1992) [2], 3DP is gaining increasing attention in pharmaceutical formulation development as an effective strategy to overcome some challenges of conventional pharmaceutical unit operations. For instance, the conventional manufacturing unit operation involving milling, mixing, granulation and compression can result in disparate qualities of the final products with respect to drug loading, drug release, drug stability and pharmaceutical dosage form stability [1-8]. The efforts in developing 3DP in pharmaceutical product development resulted in a landmark FDA approval (August, 2015) of Levetiracetam (SPRITAM®) tablets [9] (www.accessdata.fda.gov). Thus, in this report, we will assess the potentials, challenges and prospects of 3DP in pharmaceutical product development with particular attention on solid dosage forms as well as implantable drug delivery systems.

Advantages and Applications of 3DP in Pharmaceutical Drug Delivery

Fabrication of 3D objects can be achieved through a number of techniques (Table 1) such as inkjet based fabrication, Direct-Write, Zipdose, Thermal inkjet (TIJ) printing and Fused Deposition Modelling (FDM) [1,5-8,10-16]. Compared to conventional pharmaceutical product manufacturing process, 3DP offers a lot of attractive qualities, such as, (a) high production rates due to its fast operating systems, (b) ability to achieve high drug-loading with much desired precision and accuracy especially for potent drugs that are applied in small doses, (c) reduction of material wastage which can save in the cost of production and (d) amenability to broad types of pharmaceutical active ingredients including poorly water-soluble, peptides and proteins, as well as drug with narrow therapeutic windows [1-3,6,10,11,17].

3DP in pharmaceutical drug delivery is anticipated to excel tremendously in the area of personalized medicines. We have reached an era in pharmacy practice and medicine whereby "one size does not fit all" since medication must be tailored to individual patient's needs while taking into consideration 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 illnesses where patients must follow complicated treatment regimens involving multiple medicines and high frequency of dosing couples with side effects. In all these cases, medicine customization can be achieved through 3DP technology. This is possible due to flexibility in design, development and manufacture of single or multi-drug products with built-in immediate and controlled-release layers that can be tailored to unique patient's situations [18]. As such, we envision that through personalized 3DP medicines, health professionals will have the opportunity to consider a patient's pharmacogenetic profile before selecting the course of treatment [1,2,5,10,18].

It is anticipated that 3DP will continue to gain much attention in solid dosage forms as the most popular drug dosage forms. Solid dosage forms gain their popularity through many factors such as: ease of manufacture, pain avoidance, accurate dosing, and ability to achieve patient adherence to treatment. However, the multi-step nature of 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 suitability to limited categories of active ingredients. A number of 3DP approaches have been investigated to develop solid dosage forms (Tables 1 and 2).

We anticipate that implantable drug delivery systems will also benefit from 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. Meanwhile, 3DP techniques have been demonstrated to produce implants that have precisely defined, micro- and macro architectures that can effectively be applied in complex drug release (Tables 1 and 2). In addition, 3DP could offer advantages in optimizing the concentration of drug that are needed in implant preparation which could be relevant in improving drug efficacy and minimizing toxicity and side effects [19,20].

***Corresponding author:** Moses Oyewumi, B. Pharm, Ph.D, Department of Pharmaceutical Sciences, Northeast Ohio Medical University, 4209 State Route 44, Rootstown, OH 44272, USA, Tel: 1-330-325-6669; Fax: 1-330-325-5936; E-mail: moyewumi@neomed.edu

Received November 10, 2015; **Accepted** November 18, 2015; **Published** November 25, 2015

Citation: Jassim-Jaboori AH, Oyewumi MO (2015) 3D Printing Technology in Pharmaceutical Drug Delivery: Prospects and Challenges. J Biomol Res Ther 4: e141. doi:10.4172/2167-7956.1000e141

Type of 3DP Technology	Details	Reference
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 form.	[1, 6, 8, 10-13]
Direct-write	Uses a computer-controlled translational stage that moves a pattern-generating device in order to achieve, layer-by-layer, 3D microstructure.	[15]
Zip Dose	Provides a personalized dose in addition to the delivery of a high drug-load with high disintegration and dissolution levels by manufacturing highly porous material.	[9]
Thermal Inkjet (TIJ) printing	TIJ system consists of a micro-resistor that heats a thin film of ink fluid (located in the ink reservoir) forming a vapor bubble that nucleates and expands to push the ink drop out of a nozzle. TIJ affords the opportunity of dispensing extemporaneous preparation/solution of drug onto 3D scaffolds (drug carriers/films).	[16, 21]
Fused deposition modelling (FDM)	The process can be applied to multiple dosage forms that apply polymers as part of the framework such as implants, zero-order release tablets, multi-layered tablets and fast-dissolving devices. In the process the polymer of interest is melted and extruded through a movable heated nozzle. The layer by layer ejection of the polymer is repeated along x-y-z stage, followed by solidification to create a shape previously defined by the computer aided design models.	[6, 10, 20, 22]

Table 1: Examples of current 3DP technologies in pharmaceutical drug delivery.

3DP Technology	Dosage Forms	Active Ingredients	Reference
Desktop 3D printer	Tablet	Guaifenesin	[11]
A laboratory- scale 3DP machine	Capsule	Pseudoephedrine hydrochloride	[3]
Fused Deposition Modelling (FDM)	Tablet	5-aminosalicylic acid (5-ASA, mesalazine) and 4-aminosalicylic acid (4-ASA)	[20]
3DP extrusion-based printing	Tablet	Captopril with Nifedipine and Glipizide	[18]
3DP technology	Tablet	Acetaminophen	[5]
Inkjet 3DP	Implant	Levofloxacin	[19]
3DP machine	Multi-drug implant	Rifampicin and Isoniazid	[14]
Inkjet 3DP	Nanosuspension	Folic Acid	[23]
Thermal Inkjet (TIJ) Printing	Solution	Salbutamol sulphate	[16]
Inkjet 3DP	Nanoparticles	Rifampicin	[12]
3D Extrusion Printing	Encapsulated within a polymer (PLGA) poly(vinyl alcohol) (PVA)	Dexamethasone- 21-phosphate disodium salt	[24]
Thermal Inkjet (TIJ) Printing	Solid dosage forms	Prednisolone	[21]

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

Challenges, Prospects and Our Perspectives

3DP technology has many anticipated advantages that are not yet proven; as such continuous clinical development of 3DP will require vision, money, and time [1,2,10]. 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 [2,10]. Thus, 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.

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.

References

1. Ursan ID, Chiu L, Pierce A (2013) Three-dimensional drug printing: a structured review. J Am Pharm Assoc 53: 136-144.
2. Yu DG, Zhu LM, Branford-White CJ, Yang XL (2008) Three-dimensional printing in pharmaceutics: promises and problems. J Pharm Sci 97: 3666-3690.
3. Wang CC, Tejwani Motwani MR, Roach WJ, Kay JL, Yoo J, et al. (2006) Development of near zero-order release dosage forms using three-dimensional printing (3-DP) technology. Drug Dev Ind Pharm 32: 367-376.
4. Rowe CW, Katstra WE, Palazzolo RD, Giritlioglu B, Teung P, et al. (2000) Multimechanism oral dosage forms fabricated by three dimensional printing. J Control Release 66: 11-17.
5. Yu DG, Yang XL, Huang WD, Liu J, Wang YG, et al. (2007) Tablets with material gradients fabricated by three-dimensional printing. J Pharm Sci 96: 2446-2456.
6. Katakam P, Dey B, Assaleh FH, Hwisa NT, Adiki SK, et al. (2015) Top-Down and Bottom-Up Approaches in 3D Printing Technologies for Drug Delivery Challenges. Crit Rev Ther Drug Carrier Syst 32: 61-87.
7. Moulton SE and Wallace GG (2014) 3-dimensional (3D) fabricated polymer based drug delivery systems. J Control Release 193: 27-34.
8. Sachs E, Cima M, Cornie J (1992) Three dimensional printing: rapid tooling and prototypes directly from a CAD model. Journal of Manufacturing Science and Engineering 114: 481-488.
9. Aprecia Pharmaceuticals (2015) FDA APPROVES THE FIRST 3D PRINTED DRUG PRODUCT Aprecia Introduces its First Product Using the ZipDose® Formulation Platform for the Treatment of Epilepsy.
10. Ventola CL (2014) Medical Applications for 3D Printing: Current and Projected Uses. P&T 39: 704-711.
11. Khaled SA, Burleya JC, Alexandera MR, Roberts CJ (2014) Desktop 3D printing of controlled release pharmaceutical bilayer tablets. Int J Pharm 461: 105-111.
12. Gu Y, Chen X, Lee JH, Monteiro DA, Wang H, et al. (2012) Inkjet printed antibiotic- and calcium-eluting bioresorbable nanocomposite micropatterns for orthopedic implants. Acta Biomater 8: 424-431.
13. Sandler N, Maattanen A, Ihalainen P, Kronberg L, Meierjohann A, et al. (2011) Inkjet printing of drug substances and use of porous substrates-towards individualized dosing. J Pharm Sci 100: 3386-3395.
14. Wu W, Zheng Q, Guo X, Sun J, Liu Y (2009) A programmed release multi-drug implant fabricated by three-dimensional printing technology for bone tuberculosis therapy. Biomed Mater 4: 065005.
15. Lewis JA and Gratson GM (2004) Direct writing in three dimensions. Materials today 7: 32-39.
16. Buanz AB, Saunders MH, Basit AW, Gaisford S (2011) Preparation of personalized-dose salbutamol sulphate oral films with thermal ink-jet printing. Pharm Res 28: 2386-2392.
17. Katstra WE, Palazzolo RD, Rowe CW, Giritlioglu B, Teung P (2000) Oral dosage forms fabricated by three dimensional printing. J Control Release 66: 1-9.
18. Khaled SA, Burley JC, Alexander MR, Yang J, Roberts CJ (2015) 3D printing of tablets containing multiple drugs with defined release profiles. Int J Pharm 494: 643-650.
19. Huang W, Zheng Q, Sun W, Xu H, Yang X (2007) Levofloxacin implants with predefined microstructure fabricated by three-dimensional printing technique. Int J Pharm 339: 33-38.
20. Goyanes A, Buanz AB, Hatton GB, Gaisford S, Basit AW (2015) 3D printing of modified-release aminosalicylate (4-ASA and 5-ASA) tablets. Eur J Pharm Biopharm 89: 157-162.
21. Melendez PA, Kane KM, Ashvar CS, Albrecht M, Smith PA (2008) Thermal inkjet application in the preparation of oral dosage forms: dispensing of prednisolone solutions and polymorphic characterization by solid-state spectroscopic techniques. J Pharm Sci 97: 2619-2936.
22. Chen H, Fuhlbrigge TA, Zhang G (2007) Application of fused deposition modelling in controlled drug delivery devices. Assembly automation 27: 215-221.
23. Pardeike J, Strohmeier DM, Schrödl N, Voura C, Gruber M, et al. (2011) Nanosuspensions as advanced printing ink for accurate dosing of poorly soluble drugs in personalized medicines. Int J Pharm 420: 93-100.
24. Rattanakit P, Moulton SE, Santiago KS, Liawruangrath S, Wallace GG (2012) Extrusion printed polymer structures: a facile and versatile approach to tailored drug delivery platforms. Int J Pharm 422: 254-263.