Made-on-demand, complex and personalized 3D-printed drug products

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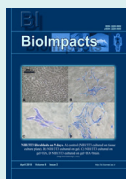
Summary

Layer-by-layer fabrication of three dimensional (3D) objects from digital models is called 3D printing. This technology established just about three decades ago at the confluence of materials science, chemistry, robotics, and optics researches to ease the fabrication of UV-cured resin prototypes. The 3D technology was rapidly considered as a standard instrument in the aerospace, automotive, and consumer goods production factories. Nowadays, research interests in the 3D printed products have been raised and achieved ever-increasing traction in the pharmaceutical industry; so that, the first 3D printed drug product was approved by FDA in August 2015. This editorial summarizes the competitive advantages of the 3D printing for the made-on-demand, personalized and complex products, manufacturing of which establish opportunities for enhancing the accessibility, effectiveness, and safety of drugs.

Author's Biosketch

Professor Khosro Adibkia (Pharm.D., Ph.D.) is a Professor of Pharmaceutics in Tabriz University of Medical Sciences. He has received Ph.D. from Tabriz University of Medical Sciences in Pharmaceutics. He spent a six month (2007-2008) research fellow at Gent University in the field of Pharmaceutical Nanobiotechnology. He has authored over 100 publications in various areas of nanotechnology and pharmaceutics (H-index=19). He has also achieved outstanding research awards from Iranian Ministry of Health and Education. He is the winner of the Rhazes Research prize (one of the most valuable prizes in Iran) at 2008 as well. Furthermore, he has been selected as a Member of the Iranian National Elites Organization since 2008. In the recent years, he has focused on the preparation and physicochemical evaluation of novel drug delivery systems.

A controlled drug release behavior can be designed by drug delivery systems (DDSs) that enhance the safety and effectiveness of various drugs, providing patient compliance and convenience by establishing drugs with excellent distribution and absorption. Recent attempts in the drug delivery field included the development of targeted/smart DDSs,[1,2] and formulations of DDSs with sustained-/controlled-release behavior(s).[3-5] Different materials have been used in DDSs and the material inventory is continuously expanding especially in the targeted/ controlled delivery areas. In parallel with the advancement of new materials for DDSs, new procedures and techniques of material fabrication have been developed. This approach provides alternative methods for controlling the release behaviors by the controlled distribution of drugs within a given polymeric compound instead of designing another new host substance. Nowadays, numerous attempts have been made to produce the 3D, from macro to nanoscale systems, made of thermoplastic[6] and thermoset[7] polymers; polyelectrolytes;[8] hydrogels[9] and powders[10] that could be used in the tissue engineering[11]; complex microfluidics devices[12] and DDSs.[13] Various strategies have been used to accurately produce the 3D structures, including ink-jet deposition, material jetting, extrusion-based 3D printing, powder bed fusion, stereo-lithography (also known as photo-polymerization), pen-based 3D printing and 3D-printed molds. These techniques have widely been used in the pharmaceutical industry. Nevertheless, directed energy deposition, laminated object manufacturing and electro-spinning are examples of the methods that are not assembled with the 3D printing methods and are applied in drug product manufacturing.[14]

The 3D printing is a time-saving method with good flexibility and unique manufacturing abilities, which uses a computer-aided design (CAD) to produce drug

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products. In other words, layer-by-layer fabrication of the desired dosage forms is carried out based on a CAD model by using suitable drug materials.[15] The 3D printing is discerned from the traditional manufacturing processes by three attributes, i.e., the complicatedness of product, individualization, and on-demand formulation. Unsurprisingly, these features impel the advancement of the 3D printed drug compositions.

Increase in the product complicatedness

Due to the possibility for a drug release behavior to be affected by a drug products structure, new opportunities are created in DDSs by manufacturing complex 3D structures. In this regard, the US FDA has approved a 3D printed drug (SPRITAM®) with an entire porous structure (bound powders without using compression), which permits a super fast disintegration of levetiracetam tablets (up to 1000 mg in seconds when taken with a sip of water).[16] Dissolution rate enhancement strategies include high surface area objects printing[17] and amorphous dispersions printing by hot melt extrusion-based printers.[18] Potent active pharmaceutical ingredients may also be manufactured with advanced production options of the 3D printing methods. In addition to the ability to create immediate-release formulations using 3D printing, products with modified release behavior can be developed by these techniques. The complexity enhancement of the 3D printed products could critically control the drug targeting and release kinetics.[19-21]

Personalization

In comparison with the traditional processes, the 3D printing approach seems to simplify the personalization, in large part because the physical equipment modification is harder than the digital design modification. Besides, the automated 3D printing may have imperceptible operating costs. Briefly, individualized, multiple and small batches could be economically fabricated by the 3D printing process, including personalized implants medicines to improve the patients' compliance. In this way, the amount of delivered drug to a patient can be tailored based on the patient's metabolism and weight.[22] Another aspect of dosing individualization is the multi-medication printing to bring together all medications of a patient into one daily dose.[23] Personalized drug administration considering population variation in the drug metabolism and patient anatomy have also stated by the researchers.[24,25] Implants personalization and drug-loaded implants permit their printing that meet the patients' anatomical characteristics.[26, 27]

On-demand manufacturing

Products with various qualities can be produced by the 3D printer within minutes like a home ink-jet printer.[28] Public health could be beneficiaries of on-demand manufacturing via various methods, including direct printing of drugs onto the patients, printing timely or other resource strained conditions (as for instances emergency rooms, disaster regions, ambulances, operating rooms, military operations and intensive care units), and low stability drugs printing for an urgent consumption.[29-31] While on patients printing seems to be imaginative, jetting and extrusion methods have been conducted to make the on-demand scaffolds and gels for the tissue engineering[30] and wound healing.[31] The drug product formulation by the conventional methods need an automotive manufacturing techniques, while the 3D-printed products could be generated with minimum effort by a simple 3D printing system, which may enable faster formulation and optimization of a drug product during drug development.

In conclusion, the 3D printing as an automated layer-by-layer production method has the capability of producing on-demand, personalized and complex products. As discussed, researchers have innovated various 3D printing techniques to enhance the drugs efficacy, safety, and tolerability. The US FDA approved 3D-printed drug has proven the commercial and industrial feasibility of this technology. Finally, it should be noted that many health-related authorities encourage the development of science and technologies to establish manufacturing procedures (for instance, tablet printing) and complex dosage forms for improving clinical outcomes.

Ethical approval
Not applicable.

Competing interests
There is none to be declared.

References

1. Ward C, Langdon SP, Mullen P, Harris AL, Harrison DJ, Supuran CT, et al. New strategies for targeting the hypoxic tumour microenvironment in breast cancer. *Cancer Treat Rev* **2013**; 39: 171-9. doi: 10.1016/j.ctrv.2012.08.004

2. Cui J, Yan Y, Wang Y, Caruso F. Templated Assembly of pH-Labile Polymer-Drug Particles for Intracellular Drug Delivery. *Adv Funct Mater.* **2012**; 22: 4718-23. doi: 10.1002/adfm.201201191

3. Garjani A, Barzegar-Jalali M, Osouli-Bostanabad K, Ranjbar H, Adibkia K. Morphological and physicochemical evaluation of the propranolol HCl–Eudragit® RS100 electrosprayed nanoformulations. *Artif Cells Nanomed Biotechnol.* **2018**; 46:749-56. doi: 10.1080/21691401.2017.1337027.

4. Shimoni O, Postma A, Yan Y, Scott AM, Heath JK, Nice EC, et al. Macromolecule Functionalization of Disulfide-Bonded Polymer Hydrogel Capsules and Cancer Cell Targeting. *ACS Nano* **2012**; 6: 1463-72. doi: 10.1021/nn204319b

5. Deng C, Jiang Y, Cheng R, Meng F, Zhong Z. Biodegradable polymeric micelles for targeted and controlled anticancer drug delivery: Promises, progress and prospects. *Nano Today* **2012**; 7: 467-80. doi: 10.1016/j.nantod.2012.08.005

6. Brown TD, Dalton PD, Hutmacher DW. Direct writing by way of melt electrospinning. *Adv Mater* **2011**; 23: 5651-7. doi: 10.1002/adma.201103482

7. Lebel LL, Aissa B, El Khakani MA, Therriault D. Ultraviolet-assisted direct-write fabrication of carbon nanotube/polymer nanocomposite microcoils. *Adv Mater* **2010**; 22: 592-6. doi: 10.1002/adma.200902192

8. Gratson GM, García-Santamaría F, Lousse V, Xu M, Fan S, Lewis JA, et al. Direct-Write Assembly of Three-Dimensional Photonic Crystals: Conversion of Polymer Scaffolds to Silicon Hollow-

Woodpile Structures. *Adv Mater* **2006**; 18: 461-5. doi: 10.1002/adma.200501447

9. Zheng J, Xie H, Yu W, Tan M, Gong F, Liu X, et al. Enhancement of Surface Graft Density of MPEG on Alginate/Chitosan Hydrogel Microcapsules for Protein Repellency. *Langmuir* **2012**; 28: 13261-73. doi: 10.1021/la302615t

10. Gbureck U, Vorndran E, Müller FA, Barralet JE. Low temperature direct 3D printed bioceramics and biocomposites as drug release matrices. *J Control Release* **2007**; 122: 173-80. doi: 10.1016/j.jconrel.2007.06.022

11. Kong YL, Gupta MK, Johnson BN, McAlpine MC. 3D printed bionic nanodevices. *Nano Today* **2016**; 11: 330-50. doi: 10.1016/j.nantod.2016.04.007

12. Knowlton S, Yu CH, Ersoy F, Emadi S, Khademhosseini A, Tasoglu S. 3D-printed microfluidic chips with patterned, cell-laden hydrogel constructs. *Biofabrication* **2016**; 8: 025019. doi: 10.1088/1758-5090/8/2/025019

13. Alhijjaj M, Belton P, Qi S. An investigation into the use of polymer blends to improve the printability of and regulate drug release from pharmaceutical solid dispersions prepared via fused deposition modeling (FDM) 3D printing. *Eur J Pharm Biopharm* **2016**; 108: 111-25. doi: 10.1016/j.ejpb.2016.08.016

14. Norman J, Madurawe RD, Moore CM, Khan MA, Khairuzzaman A. A new chapter in pharmaceutical manufacturing: 3D-printed drug products. *Adv Drug Deliv Rev* **2017**; 108: 39-50. doi: 10.1016/j.addr.2016.03.001

15. Ursan ID, Chiu L, Pierce A. Three-dimensional drug printing: a structured review. *J Am Pharm Assoc (2003)* **2013**; 53: 136-44. doi: 10.1331/JAPhA.2013.12217

16. Zieverink J. First Fda-Approved Medicine Manufactured Using 3D Printing Technology Now Available. Ohio: Blue Ash; **2016**.

17. Goyanes A, Robles Martinez P, Buanz A, Basit AW, Gaisford S. Effect of geometry on drug release from 3D printed tablets. *Int J Pharm* **2015**; 494: 657-63. doi: 10.1016/j.ijpharm.2015.04.069

18. Genina N, Holländer J, Jukarainen H, Mäkilä E, Salonen J, Sandler N. Ethylene vinyl acetate (EVA) as a new drug carrier for 3D printed medical drug delivery devices. *Eur J Pharm Sci* **2016**; 90: 53-63. doi: 10.1016/j.ejps.2015.11.005

19. Katakam P, Dey B, Assaleh FH, Hwisa NT, Adiki SK, Chandu BR, et al. Top-down and bottom-up approaches in 3D printing technologies for drug delivery challenges. *Crit Rev Ther Drug Carrier Syst* **2015**; 32: 61-87.

20. Khaled SA, Burley JC, Alexander MR, Yang J, Roberts CJ. 3D printing of tablets containing multiple drugs with defined release profiles. *Int J Pharm* **2015**; 494: 643-50. doi: 10.1016/j.ijpharm.2015.07.067

21. Inzana JA, Trombetta RP, Schwarz EM, Kates SL, Awad HA. 3D printed bioceramics for dual antibiotic delivery to treat implant-associated bone infection. *Eur Cell Mater* **2015**; 30: 232-47. doi: 10.22203/eCM.v030a16

22. Skowyra J, Pietrzak K, Alhnan MA. Fabrication of extended-release patient-tailored prednisolone tablets via fused deposition modelling (FDM) 3D printing. *Eur J Pharm Sci* **2015**; 68: 11-7. doi: 10.1016/j.ejps.2014.11.009

23. Khaled SA, Burley JC, Alexander MR, Roberts CJ. Desktop 3D printing of controlled release pharmaceutical bilayer tablets. *Int J Pharm* **2014**; 461: 105-11. doi: 10.1016/j.ijpharm.2013.11.021

24. Sun Y, Soh S. Printing Tablets with Fully Customizable Release Profiles for Personalized Medicine. *Adv Mater* **2015**; 27: 7847-53. doi: 10.1002/adma.201504122

25. Linares OA, Daly D, Linares AD, Stefanovski D, Boston RC. Personalized Oxycodone Dosing: Using Pharmacogenetic Testing and Clinical Pharmacokinetics to Reduce Toxicity Risk and Increase Effectiveness. *Pain Med* **2014**; 15: 791-806. doi: 10.1111/pme.12380

26. Gross BC, Erkal JL, Lockwood SY, Chen C, Spence DM. Evaluation of 3D printing and its potential impact on biotechnology and the chemical sciences. *Anal Chem* **2014**; 86: 3240-53. doi: 10.1021/ac403397r

27. Jonas O, Landry HM, Fuller JE, Santini JT Jr, Baselga J, Tepper RI, et al. An implantable microdevice to perform high-throughput in vivo drug sensitivity testing in tumors. *Sci Transl Med* **2015**; 7: 284ra57. doi: 10.1126/scitranslmed.3010564

28. Srai JS, Badman C, Krumme M, Futran M, Johnston C. Future supply chains enabled by continuous processing--opportunities and challenges. May 20-21, 2014 Continuous Manufacturing Symposium. *J Pharm Sci* **2015**; 104: 840-9. doi: 10.1002/jps.24343

29. Han YL, Hu J, Genin GM, Lu TJ, Xu F. BioPen: direct writing of functional materials at the point of care. *Sci Rep* **2014**; 4: 4872. doi: 10.1038/srep04872

30. Skardal A, Mack D, Kapetanovic E, Atala A, Jackson JD, Yoo J, et al. Bioprinted amniotic fluid-derived stem cells accelerate healing of large skin wounds. *Stem Cells Transl Med* **2012**; 1: 792-802. doi: 10.5966/sctm.2012-0088

31. Earls A, Baya V. The road ahead for 3-D printers. *PwC Technology Forecast* **2014**; 2: 2-11