ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 13, Issue 12, 2020

Online - 2455-3891
Print - 0974-2441

Review Article

3D PRINTING OF PHARMACEUTICALS – LEADING TREND IN PHARMACEUTICAL INDUSTRY AND FUTURE PERSPECTIVES

SHANKHADIP NANDI*

Department of Pharmaceutics, Gitanjali College of Pharmacy, Birbhum, West Bengal, India. Email: shankhadipnandi@gmail.com

Received: 29 August 2020, Revised and Accepted: 28 September 2020

ABSTRACT

3D printing technology is a rapid prototyping process based on computer-aided design software that is proficient to construct solid objects with various geometrics by depositing numerous layers in a sequence. The major advantages of three-dimensional printing (3DP) technology over the traditional manufacturing of pharmaceuticals include the customization of medications with individually adjusted doses, on-demand tailored manufacturing, unprecedented flexibility in the design, manufacturing of complex and sophisticated solid dosage forms, and economic benefits. Recently, many researchers have been invested their efforts in applying 3DP technology to the pharmaceutical development of drug products and different drug delivery systems. Selective laser sintering, fused deposition modeling, semi-solid extrusion, stereolithography, etc., are the multiple 3DP technologies that can be established in several customized and programmable medicines. Sublingual, orodispersible, and fast-dissolving drug delivery formulations by 3DP technology have been already manufactured. Controlled-release formulations with different characteristics, doughnut-shaped multi-layered tablets with linear release kinetics, and drug-loaded tablets with modified-release characteristics are recently fabricated using 3DP. However, few 3DP methods produce uneven shapes of dosage forms and comparatively porous structures. Cost of transition, adaptation to the existing facility, achieving regulatory approval, etc., are the present challenges that can restrict the extensive application of 3DP technology to pharmaceutical products. Intense research work for modifying the 3DP methods is simultaneously sustained for by-passing the flaws and current limitations of this technology. 3DP technology can act as a convenient and potential tool for the pharmaceutical industry which will set a revolutionary manufacturing style in the near future to facilitate patient-centered health care.

Keywords: Computer-aided design, Three-dimensional printing, Stereolithography, Orodispersible, Fused deposition modeling, Linear release kinetics.

 DOI: http://dx.doi.org/10.22159/ajpcr.2020.v13i12.39584

INTRODUCTION

Drug delivery, a very frequently used and important terminology, belongs to the pharmaceutical sciences. It is the technology used for transporting a compound successively in the body as desired safely to achieve required therapeutic efficacy. New ideas for drug delivery are significantly evolving over the years from the era of conventional oral dosage forms to targeted release drug delivery systems for achieving better patient compliance [1-3]. In the last decade, considerable attention was focused on the development of novel drug delivery systems and patient-centric drug products. Within many discoveries of recent time, three-dimensional printing (3DP) is considered to be the most versatile and revolutionary technology in the pharmaceutical industry [4].

3DP follows additive manufacturing which is a rapid prototyping technology [5]. It is capable to print 3D objects by fusing multiple layers in a particular sequence controlled by computer-aided design (CAD) software [6-9]. Rapid advances in 3DP technology facilitate a wide range of pharmaceutical applications, including advancement in the design of drug delivery systems [10,11]. In the early 2000s, traditional prosthetics and dental implants were first fabricated with the application of 3DP. Now, it can be effectively used at the different stages of drug development process to eliminate the risk of failure [12,13].

Compared to the conventional technologies involved with manufacturing of pharmaceuticals, 3DP possess a lot of advantages such as high amount of drug loading ability, enhancement in productivity, personalization of medications with individually adjusted doses, on-demand production, the ability to fabricate potent drugs with high accuracy and precision, narrow therapeutic window, and cost effectiveness [14,15].

By utilizing the 3D printed drug delivery system, treatment can be customized for multi-drug therapy with the various dosing regimen. This technology can avoid batch-to-batch variation which is very commonly observed in the bulk manufacturing of traditional dosage forms [16,17]. Employment of 3DP technology also supports the development of numerous drug delivery systems such as oral controlled release systems, multi-layered tablets with linear release kinetics, immediate-release tablets, implants, modified release dosage forms, pills, and microchips [18-25]. Moreover, this technology is compatible to wide range of active pharmaceutical ingredients, including proteins, peptides, and poorly water-soluble drugs [26-29].

SPRITAM comprising Levetiracetam as an active pharmaceutical ingredient was the first FDA approved 3D-printed pill [2]. The product was manufactured by utilizing ZipDose technique which is depend on layer-by-layer powder bed fusion system [30].

This review will draw attention toward the significance and future perspectives of 3DP technology in pharmaceutical manufacturing through assessing the impact and implications of the technology. The study is also carried out to explore the different techniques involved with 3DP and to get a thorough outlook of the pharmaceutical products can be fabricated by the method.

DIFFERENT 3DP METHODS FOR PHARMACEUTICAL PRODUCT DEVELOPMENT

Depending on the source of material, energy sources, and other mechanical factors, different 3DP methods have been designed to develop a variety of pharmaceutical products. The different methods for 3D printing are shown in Fig. 1.

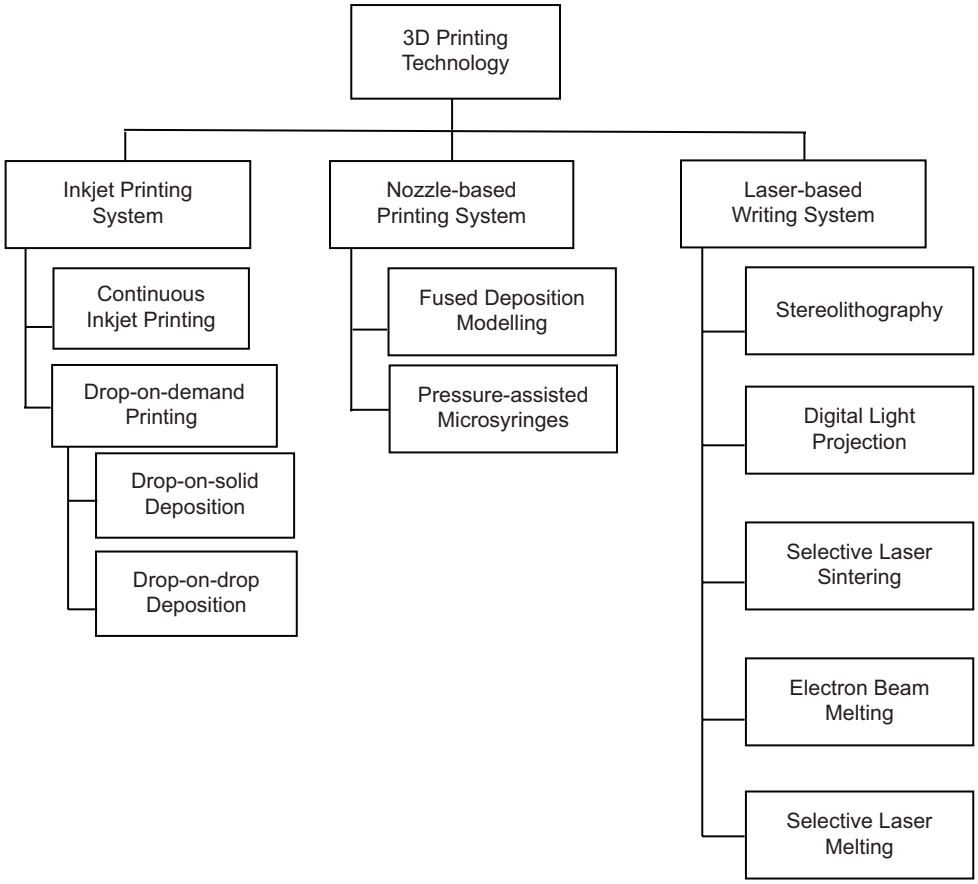

Fig. 1: Categorization of three-dimensional printing technology

Inkjet (IJ) printing system

This system is originated from a similar technique generally utilized for computer-operated inkjet printing. For pharmaceutical implementation of the system, drug solutions are used instead of ink and standard paper with palatable sheets is considered as substrates [31]. This system is classified into two methods, that is, continuous inkjet (CI) printing and drop-on-demand (DOD) printing.

In CI printing, the liquid ink is streamed in a constant flow through an orifice ranging from 50 to 80 μm diameter in the presence of a high-pressure pump. The liquid ink is disrupted into drops at a predetermined speed, size, and specific intervals by applying a piezoelectric crystal. Formation of the electrostatic field is capable to control these parameters [25].

In DOD printing, ink droplets of 10–50 μm diameter with a volume of 1–70 pL are formed [32]. Thermal head and piezoelectric crystal are used as printer heads in the DOD printing. In thermal head of DOD printing, the liquid ink is heated locally at a temperature up to 300°C. It causes formation of bubbles that eject the ink to print. However, application of this thermal head is limited to only volatile liquids. In addition, drugs and pharmaceutical ingredients may be degraded by high vapor pressure for using such a high temperature [7].

When piezoelectric crystal is used for DOD printing, the shape of piezoelectric crystal is changed rapidly that results swift change in volume. An acoustic pulse is created for ejection of the ink [33]. Compared to the thermal head, this piezoelectric crystal in DOD printing can be applied to an extensive variety of liquids. Furthermore, there is no chance of degradation of any drugs since this DOD printing can be functioned at room temperature [7]. Hence, the piezoelectric crystal is more suitable for DOD printing to accomplish pharmaceutical applications [32].

The DOD printing system can be categorized into two subtypes, that is, drop-on-solid deposition and drop-on drop deposition [7]. Drop-on-solid deposition is also known as powder bed fusion, drop on-powder, plaster printing, drop-on-bed deposition, or binder jetting 3DP. This system spreads the solid material in the form of powder on the uppermost portion of a stage which is 200 μm in height followed by spraying a liquid ink as the binder solution on the powders. Then, the stage is pull down, and the specified process is again repeated until the formation of a 3D structure by adhering the consecutive layers [7,34].

The ink droplets of 100 μm diameter are ejected from the printer head onto each other to generate a solid layer in the drop-on-drop deposition method. Thickness of the successive layers is lesser than the ink droplet size and the layers result the formation of a high-resolution 3D structure. This deposition method is proficient of fabricating microscopic drug delivery systems [35,36].

Drop-on-solid deposition system in DOD printing appears to be more applicable for the pharmacoprinting of an extensive range of drugs as compared to drop-on-drop deposition. However, the inkjet printing system enables an important benefit of controlling the dose combination and drug release pattern perfectly [25,37].

Nozzle-based printing system

Nozzle-based printing system has been invented to overcome the limitations of inkjet printing system that includes its applicability to only low therapeutic doses, insufficient hardness, difficulty in multiple layer printing, longer drying time, and formation of a rough surface [25,38]. In nozzle-based printing system, drugs, polymers, and other solid components are mixed with the binder solution. This mixture is then delivered through a nozzle and the subsequent layers are deposited directly to generate a three-dimensional object [39]. This

system can be classified into two methods, that is, fused deposition modeling (FDM) and pressure-assisted microsyringes (PAM) [35].

FDM is one of the most frequently explored 3DP system which is also known as fused filament fabrication [40,41]. In FDM, the drug and thermoplastic polymers are mixed together, followed by incubation in a suitable solvent or melted together, applying hot-melt extrusion technique at an appropriate temperature [42]. Then, the molten mass is extruded into filament using a high-temperature nozzle and the layers formed are deposited on a plate with instant solidification [20]. FDM offers several advantages such as cost-effective manufacturing process, good mechanical strength, ability to modify the drug release kinetics, and fabrication of highly complex therapeutic agents with difficult geometries [32]. FDM printer is capable to fabricate gastroretentive floating 3D-printed tablets by applying hot-melt extrusion after creating the drug-loaded filaments [43]. FDM printing technology has been used to design an enormous diversity of drug delivery systems in the recent development of pharmaceuticals [44-52]. With the several advantages for its pharmaceutical applications, there are also some drawbacks like non-availability of biodegradable thermoplastic polymers which possess good melt viscosity characteristics for their extrusion, high temperature used for extrusion [35].

In PAM, a microsyringe is used to extrude the liquid materials of adequate viscosity [7]. The microsyringe used is capable to move around similar to an inkjet printer head, and the liquid material is released by the aid of compressed air. PAM facilitates in the formation of complex drug delivery systems, microstructured product of 5–10 μm, or less diameter [53]. This method of 3DP involves room temperature to operate in a constant flow. Similar to PAM, another system using piston-assisted microsyringe (PAM2) has been developed to release the printing material through a stepper motor instead of compressed air [54].

Laser-based writing system

This system is based on the theory of photopolymerization, in which free radicals are released upon successful interaction between the photoinitiator and ultraviolet light [14]. Stereolithography (SLA) is a solid freeform fabrication method based on laser oriented printing. A high-energy ultraviolet light beam in the form of a laser is focused and scanned over the uppermost portion of a liquid resin for its controlled solidification by photopolymerization [55]. The polymerized layers are formed and the process in continued until a solid 3D object is found [35]. SLA is a highly accurate technique that produces the 3D object of good surface quality. This method has been already used to create oral dosage forms of paracetamol and aspirin in 5% and 2.5%, respectively, and also widely used in tissue engineering and designing of implants [56,57]. Research studies revealed so many optimistic possibilities of SLA such as fabrication of dosage forms from 28 different drugs in a single print cycle, capability to moderate the drug release pattern from printed products, and production of multi-layered and multi-drug tablets to achieve personalized patient-specific medication [56,58].

Based on the same principle of SLA and digital light projection (DLP), another 3DP method has been developed [59]. As compared to SLA, DLP method offers comparatively faster construction of the 3D object and makes easy to adjust the thickness of polymerized layers [35,60].

Selective laser sintering (SLS) employs the raw materials in powder form and a high power laser is used to melt it followed by fusing of powdered materials together [61]. SLS possesses several advantages such as chemical resistance, speed of printing, and product of higher strength [35]. SLS has been utilized to develop numerous drug delivery systems such as small oral dosage forms with controlled release characteristics, single miniprintlets of paracetamol, and dual miniprintlets of paracetamol with ibuprofen [41].

Electron beam melting and selective laser melting are also some methods, according to laser-based writing system which is broadly used in drug-loaded implants [62].

Three-dimensional bioprinting

3D-bioprinted drug delivery system, a novel approach, has been involved for the treatment of bone fractures and defects. Controlled release of simvastatin through the system for at least 20 days is able to cause bone healing and repairing [63]. A research study effectively proved the efficiency of the system using pectin-based bio-ink to build 3D-bioprinted wound dressings with sufficient antimicrobial activity [64].

Embedded 3DP (e-3DP)

e-3DP, a rapid prototyping technology, in which a deposition nozzle is used to extrude a viscoelastic ink at a predetermined path into a solidifying reservoir. The products are printed by using e-3DP at a temperature 70℃ followed by solidification at room temperature. By the alteration of the printing pattern, the dose of printed dosage forms can be changed. This new method of 3DP proved its capability by fabricating chewable tablets with dual drug loading and several oral dosage forms with personalized dosing [65].

There are many other 3DP methods which have been developed, including laminated object manufacturing, stencil printing, multi-jetting modeling, semisolid extrusion printing, and selective heat sintering which are not widely explored for pharmaceutical applications. However, the versatility of the mentioned methods, recent advancement in material sciences, will facilitate different novel approaches toward drug delivery system in the near future [35,41].

FABRICATION OF PHARMACEUTICALS BY APPLYING 3DP

The presently available methods for 3DP technology are majorly involved to fabricate the oral solid and transdermal drug delivery systems. However, research work is continued to discover the possibilities for designing the 3D printing protocol of other drug delivery systems. After the innovation of 3DP technology, it was first applied to fabricate immediate-release tablets containing a single drug. Due to its simple operational technique, FDM was utilized to produce such type of tablets [66-68]. On successful fabrication of the dosage forms, other 3D methods were then also involved for pharmaceutical research and designing of the medicaments.

3DP technology is capable to manufacture the dosage form of complex drugs in a standard and simple way. This technology allows the dosage forms to release the drugs as per need of patients. A wide range of drug release profile for the oral solid dosage forms using single or multiple active pharmaceutical ingredients (polypill) has been successfully developed by applying different methods of 3D printing, as shown in Table 1 [69-82]. High dose (up to 1000 mg) of orodispersible tablets, sublingual, and other fast-dissolving formulations that disintegrate rapidly in the oral cavity has been manufactured using 3D printing [83-86].

3DP-based implants are developed to create complex micro- and macro-structures in a single system. In recent studies, it has been found that multiple drugs can be loaded in the 3DP-based implants to achieve instant therapeutic efficacy, as shown in Table 2 [87-90]. An implant loaded with odd number layers of levofloxacin and even number layers of tobramycin was capable to release the drugs stepwise in a sustained manner for about 2 months. By retaining ideal drug concentration, the drug-device controlled chronic osteomyelitis in rabbits [90]. Nowadays, bone defect can be treated by fabricating scaffolds utilizing 3DP technology through merging the calcium phosphate cement with vascular endothelial growth factor-loaded hydrogel strands [91]. For the treatment of bone tuberculosis, pancreatic cancer, and any other chronic diseases, 3DP-structured multi-drug implants could be a promising approach due to their ideal pharmacological action, site-selective drug release, and cytocompatibility [87,89]. The usefulness of biodegradable implants structured by 3DP technology has been suggested for effective local delivery of anticancer drugs [87].

Table 1: Application of three-dimensional printing in fabricating oral solid dosage forms

Dosage form	Release pattern	API(s)	Three-dimensional printing method used	Reference
Single API tablet	Immediate	Paracetamol	Extrusion	[69]
Single API tablet	Extended	Theophylline	FDM	[70]
Single API tablet	Extended	Prednisolone	FDM	[71]
Single API tablet	Controlled	Pseudoephedrine HCl	Inkjet printing	[72]
Dual compartment tablet	Modified	Rifampicin, isoniazid	FDM	[73]
Single API tablet	Extended	4-aminosalicylic acid/paracetamol	Stereolithography	[16]
Multi-layered tablet	Modified	Acetaminophen	Inkjet printing	[74]
Enteric-coated tablet	Delayed	Paracetamol	FDM	[21]
Gastro-floating tablet	Extended	Dipyridamole	Extrusion	[75]
Single API tablet	Controlled	Ropinirole HCl	Inkjet printing	[76]
Single API tablet	Extended	Fluorescein	FDM	[77]
Caplet	Modified	Paracetamol/caffeine	FDM	[66]
Polypill	Immediate/ Sustained	Aspirin, hydrochlorothiazide, pravastatin, atenolol, and ramipril	Extrusion	[78]
Polypill	Controlled	Captopril, nifedipine, and glipizide	Extrusion	[79]
Bi-layer tablet	Immediate/ sustained	Guaifenesin	Extrusion	[28]
Caplet	Controlled	Budesonide	FDM	[20]
Single API tablet	Controlled	Fenofibrate	Inkjet printing	[80]
Shell-core tablet	Delayed	Theophylline, budesonide, and diclofenac sodium	Dual FDM	[81]
Dual pulsatory tablet	Immediate	Diclofenac sodium	Inkjet printing	[82]

Table 2: Application of three-dimensional printing for developing implants

API(s)	Release pattern	Reference
Poly(lactide-co-glycolide) and polycaprolactone, 5-fluorouracil	Controlled release	[87]
Levofloxacin	Complex drug release	[88]
Isoniazid and rifampicin	Programmed release	[89]
Levofloxacin and tobramycin	Sustained and programmed release	[90]

Table 3: Application of three-dimensional printing for developing microneedles

API(s)	Three-dimensional printing method used	Reference
Rhodamine	Continuous liquid interface production	[92]
Dacarbazine	Multi-material microstereolithography	[93]
Fluorescein	FDM	[94]
Insulin	Stereolithography	[95]
Diclofenac	Three-dimensional printing	[96]

3DP technology facilitates to fabricate sophisticated microneedles of complex geometries. The microneedles formed are uniform in shape, radius of the needle tip is less than 3.5 μm and 400–1000 μm in height [92]. Microneedles fabricated by 3DP have been revealed their potency in the delivery of vaccines, insulin, treatment of skin carcinoma using microstereolithography, trigger finger using microneedle splint, etc., as shown in Table 3 [92-96].

Apart from these applications, fabrication of DNA biosensors with superior selectivity, biomimetic constructs for different stages of drug discovery and development, 3D tissue models, and nanoparticles of controlled size targeting tumor cell has been also reported [13,97].

CURRENT CHALLENGES AND FUTURE PERSPECTIVES OF 3DP TECHNOLOGY

There are few challenges that 3DP technology faces have to be overcome for its wide application in the pharmaceutical industry at a large scale. In the post-processing stage of fabrication, this technology is unable to produce the product with the desired accuracy. The product also needs a finishing operation like polishing to achieve the final shape. A number of physical and technical parameters related to 3D printing such as thermal conductivity, viscoelastic property, physicochemical characteristics of liquid ink, and printability must be reviewed cautiously [14]. Friability of the dosage forms fabricated by 3DP methods, especially powder bed fusion, is higher as compared to the same produced by conventional manufacturing. The choice of potential raw materials, colorants presently available for 3DP technology, is quite limited as compared to traditional manufacturing processes [25].

SPRITAM is the only 3D-printed product manufactured by Aprecia Pharmaceuticals which got USFDA approval in 2015. However, fulfilling the regulatory requirements for the 3D-printed products in a positive manner will be the obvious way for the extensive pharmaceutical application of this technology at industrial scale [27]. 3DP technology may result massive job loss of a large number of human labor associated with conventional manufacturing processes. Besides this extreme truth, increasing the value of skilled professionals in the field of CAD design, materials engineering, information technology, mathematics, and automation required for the technology will create a huge job prospect.

Based on the ability to print the on-demand personalized dosage forms, it is aimed to convert the current pharmacies into digital pharmacies. To fabricate, the personalized medications as per prescription digital pharmacies can transform the drug-loaded filaments with essential quality which is initially to be developed by the pharmaceutical companies on a large scale. The collaboration between pharmaceutical industry and the digital pharmacies seems to be a conceivable pathway to turn this 3DP technology into reality [98]. The process of manufacturing, transportation, and distribution of medicines to the market by pharmaceutical companies can be replaced by forwarding the formulation databases to the pharmacies for on-demand drug printing. This drastic change in the traditional cycle of manufacturing to distribution seems to be more cost-effective [27].

Endless research work progressed for refinement in 3DP methods may overcome the current technical, physical, and regulatory challenges in the near future [34]. One of the ongoing research studies evidenced some versatile biocompatible raw materials having the ability to modify their characteristics under the influence of external factors. Based on this feasibility, the structural modification has been created, termed as “4D printing” [99,100].

CONCLUSION

Various methods of 3DP technology make it possible to develop highly sophisticated dosage forms with different shapes, allow to fabricate flexible dosages with single or multiple active pharmaceutical ingredients, and offer a wide range of drug release kinetics. 3DP technology is anticipated to play a major role in the movement toward personalized and tailored medications. Rapid advancement and progressed research for 3DP technology will be broadly applicable to the numerous drug delivery systems and accelerate the transformation of pharmacy practice according to individualized medication. It has been noticed that through the flexibility, speed of production, and precision of 3DP, use of the technology for manufacturing and distribution of drugs play a significant role in the current scenario of pharmaceutical industry. However, the pharmaceutical industry has been prepared to percept the fourth industrial revolution with the broad-spectrum manufacturing of customized medicines by 3DP.

AUTHOR'S CONTRIBUTIONS

As this review article is solely authored by Mr. Shankhadip Nandi, Assistant Professor of Gitanjali College of Pharmacy, he is the only person who made a substantial contribution in conception of this topic, procurement, and understanding of the information in the article. Completion of literature review followed by drafting and reviewing the article judgmentally, necessary revisions required as per reviewers' comments have done by the author. He has given final approval of the version to be published.

CONFLICTS OF INTEREST

The author confirms that there are no such conflicts of interest to publish this review article.

AUTHOR'S FUNDING

None.

REFERENCES

1. Maroni A, Melocchi A, Parietti F, Foppoli A, Zema L, Gazzaniga A. 3D printed multi-compartment capsular devices for two-pulse oral drug delivery. J Control Release 2017;268:10-8.
2. 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.
3. Karri SR, Reddy VV, Radhakrishna K, Ganesh GN. Development of osmotically controlled oral drug delivery system for nateglinide an anti-diabetic drug. Int J Pharm Pharm Sci 2014;6:120-25.
4. Jamróz W, Szafraniec J, Kurek M, Jachowicz R. 3D printing in pharmaceutical and medical applications-recent achievements and challenges. Pharm Res 2018;35:176.
5. Ursan ID, Chiu L, Pierce A. Three-dimensional drug printing: A structured review. J Am Pharm Assoc 2013;53:136-44.
6. Jun XY, Yan W, Qiang W, Qi WC, Zhong HX, Fen Z, *et al*. Structural broadband absorbing metamaterial based on three-dimensional printing technology. Acta Phys Sin 2018;67:084202.
7. Goole J, Amighi K. 3D printing in pharmaceutics: A new tool for designing customized drug delivery systems. Int J Pharm 2016;499:376-94.
8. Tofail SA, Koumoulos EP, Bandyopadhyay A, Bose S, O'Donoghue L, Charitidis C. Additive manufacturing: Scientific and technological challenges, market uptake and opportunities. Mater Today 2017;21:22-37.
9. Mannan A, Mubeen H. Digitalisation and automation in pharmaceuticals from drug discovery to drug administration. Int J Pharm Pharm Sci 2018;10:1-10.
10. Chia HN, Wu BM. Recent advances in 3D printing of biomaterials. J Biol Eng 2015;9:4.
11. Liaw CY, Guvendiren M. Current and emerging applications of 3D printing in medicine. Biofabrication 2017;9:024102.
12. Maulvi FA, Shah MJ, Solanki BS, Patel AS, Soni TG, Shah DO. Application of 3D printing technology in the development of novel drug delivery systems. Int J Drug Dev Res 2017;9:44-9.
13. Peng W, Datta P, Ayan B, Ozbolat V, Sosnoski D, Ozbolat IT. 3D bioprinting for drug discovery and development in pharmaceutics. Acta Biomater 2017;57:26-46.
14. Jose PA, Christoper PG. 3D printing of pharmaceuticals-a potential technology in developing personalized medicine. Asian J Pharm Res Dev 2018;6:46-54.
15. Kumar AE, Devi GC, Sharada N. A review on novel approach to pharmaceutical drug delivery: 3D printing. Int J Pharm Sci Res 2019;10:1575-81.
16. Wang J, Goyanes A, Gaisford S, Basit AW. Stereolithographic (SLA) 3D printing of oral modified-release dosage forms. Int J Pharm 2016;503:207-12.
17. Yu DG, Branford-White C, Ma ZH, Zhu LM, Li XY, Yang XL. Novel drug delivery devices for providing linear release profiles fabricated by 3DP. Int J Pharm 2009;370:160-6.
18. Goyanes A, Buanz AB, Hatton GB, Gaisford S, Basit AW. 3D printing of modified-release aminosalicylate (4-ASA and 5-ASA) tablets. Eur J Pharm Biopharm 2015;89:157-62.
19. Fu J, Yu X, Jin Y. 3D printing of vaginal rings with personalized shapes for controlled release of progesterone. Int J Pharm 2018;539:75-82.
20. Goyanes A, Chang H, Sedough D, Hatton GB, Wang J, Buanz A, *et al*. Fabrication of controlled-release budesonide tablets via desktop (FDM) 3D printing. Int J Pharm 2015;496:414-20.
21. Goyanes A, Fina F, Martorana A, Sedough D, Gaisford S, Basit AW. Development of modified release 3D printed tablets (printlets) with pharmaceutical excipients using additive manufacturing. Int J Pharm 2017;527:21-30.
22. Li Q, Wen H, Jia D, Guan X, Pan H, Yang Y, *et al*. Preparation and investigation of controlled-release glipizide novel oral device with three-dimensional printing. Int J Pharm 2017;525:5-11.
23. Siyawamwaya M, Toit LC, Kumar P, Choonara YE, Kondiah PP, Pillay V. 3D printed, controlled release, tritherapeutic tablet matrix for advanced anti-HIV-1 drug delivery. Eur J Pharm Biopharm 2019;138:99-110.
24. Sun Y, Soh S. Printing tablets with fully customizable release profiles for personalized medicine. Adv Mater 2015;27:7847-53.
25. Alhnan MA, Okwuosa TC, Sadia M, Wan KW, Ahmed W, Arafat B. Emergence of 3D printed dosage forms: Opportunities and challenges. Pharm Res 2016;33:1817-32.
26. 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.
27. Ventola CL. Medical applications for 3D printing: Current and projected uses. Pharm Ther 2014;39:704-11.
28. Khaled SA, Burley JC, Alexander MR, Roberts CJ. Desktop 3D printing of controlled release pharmaceutical bilayer tablets. Int J Pharm 2014;461:105-11.
29. Katstra WE, Palazzolo RD, Rowe CW, Giritlioglu B, Teung P, Cima MJ. Oral dosage forms fabricated by three dimensional printing. J Control Release 2000;66:1-9.
30. Jassim-Jaboori AH, Oyewumi MO. 3D printing technology in pharmaceutical drug delivery: Prospects and challenges. J Biomol Res Ther 2015;4:e141.
31. Meléndez 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. J Pharm Sci 2008;97:2619-36.
32. Konta AA, Garcia-Piña M, Serrano DR. Personalised 3D printed medicines: Which techniques and polymers are more successful? Bioengineering 2017;4:79-94.
33. de Gans BJ, Duineveld PC, Schubert US. Inkjet printing of polymers: State of the art and future developments. Adv Mater 2004;16:203-13.
34. 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.
35. Park BJ, Choi HJ, Moon SJ, Kim SJ, Bajracharya R, Min JY, *et al*. Pharmaceutical applications of 3D printing technology: Current understanding and future perspectives. J Pharm Investig 2019;49:575-85.
36. Sumerel J, Lewis J, Doraiswamy A, Deravi LF, Sewell SL, Gerdon AE, *et al*. Piezoelectric ink jet processing of materials for medical and biological applications. Biotechnol J 2006;1:976-87.
37. 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. Int J Pharm 2012;427:305-10.
38. Dimitrov D, Schreve K, de Beer N. Advances in three dimensional printing-state of the art and future perspectives. Rapid Prototyp J

2006;12:136-47.
39. Vaezi M, Seitz H, Yang S. A review on 3D micro-additive manufacturing technologies. Int J Adv Manuf Technol 2013;67:1721-54.
40. 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.
41. Mathew E, Pitzanti G, Larrañeta E, Lamprou DA. 3D printing of pharmaceuticals and drug delivery devices. Pharmaceutics 2020;12:266.
42. Masood SH. Application of fused deposition modelling in controlled drug delivery devices. Assem Autom 2007;27:215-21.
43. Giri BR, Song ES, Kwon J, Lee JH, Park JB, Kim DW. Fabrication of intragastric floating, controlled release 3D printed theophylline tablets using hot-melt extrusion and fused deposition modeling. Pharmaceutics 2020;12:77.
44. Stewart SA, Domínguez-Robles J, Mcilorum, VJ, Mancuso E, Lamprou DA, Donnelly RF, *et al*. Development of a biodegradable subcutaneous implant for prolonged drug delivery using 3D printing. Pharmaceutics 2020;12:105.
45. Lamichhane S, Park JB, Sohn DH, Lee S. Customized novel design of 3D printed pregabalin tablets for intra-gastric floating and controlled release using fused deposition modeling. Pharmaceutics 2019;11:564.
46. Dumpa NR, Bandari S, Repka MA. Novel gastroretentive floating pulsatile drug delivery system produced via hot-melt extrusion and fused deposition modeling 3D printing. Pharmaceutics 2020;12:52.
47. Alhijjaj M, Nasereddin J, Belton P, Qi S. Impact of processing parameters on the quality of pharmaceutical solid dosage forms produced by fused deposition modeling (FDM). Pharmaceutics 2019;11:633.
48. Domínguez-Robles J, Mancinelli C, Mancuso E, García-Romero I, Gilmore BF, Casettari L, *et al*. 3D printing of drug-loaded thermoplastic polyurethane meshes: A potential material for soft tissue reinforcement in vaginal surgery. Pharmaceutics 2020;12:63.
49. Tidau M, Kwade A, Finke JH. Influence of high, disperse API load on properties along the fused-layer modeling process chain of solid dosage forms. Pharmaceutics 2019;11:194.
50. Arany P, Róka E, Mollet L, Coleman AW, Perret F, Kim B, *et al*. Fused deposition modeling 3D printing: Test platforms for evaluating post-fabrication chemical modifications and *in-vitro* biological properties. Pharmaceutics 2019;11:277.
51. Domínguez-Robles J, Martin NK, Fong ML, Stewart SA, Irwin NJ, Rial-Hermida MI, *et al*. Antioxidant PLA composites containing lignin for 3D printing applications: A potential material for healthcare applications. Pharmaceutics 2019;11:165.
52. Chew SL, de Mohac LM, Raimi-Abraham BT. 3D-printed solid dispersion drug products. Pharmaceutics 2019;11:672.
53. Vozzi G, Flaim C, Ahluwalia A, Bhatia S. Fabrication of PLGA scaffolds using soft lithography and microsyringe deposition. Biomaterials 2003;24:2533-40.
54. Tirella A, Vozzi F, Vozzi G, Ahluwalia A. PAM2 (piston assisted microsyringe): A new rapid prototyping technique for biofabrication of cell incorporated scaffolds. Tissue Eng Part C Methods 2010;17:229-37.
55. Shende P, Agrawal S. Integration of 3D printing with dosage forms: A new perspective for modern healthcare. Biomed Pharmacother 2018;107:146-54.
56. Healy AV, Fuenmayor E, Doran P, Geever LM, Higginbotham CL, Lyons JG. Additive manufacturing of personalized pharmaceutical dosage forms via stereolithography. Pharmaceutics 2019;11:645.
57. Melchels FP, Feijen J, Grijpma DW. A review on stereolithography and its applications in biomedical engineering. Biomaterials 2010;31:6121-30.
58. Robles-Martinez P, Xu X, Trenfield SJ, Awad A, Goyanes A, Telford R, *et al*. 3D printing of a multi-layered polypill containing six drugs using a novel stereolithographic method. Pharmaceutics 2019;11:274.
59. Kim K, Han S, Yoon J, Kwon S, Park HK, Park W. Lithographic resolution enhancement of a maskless lithography system based on a wobulation technique for flow lithography. Appl Phys Lett 2016;109:234101.
60. Madzarevic M, Medarevic D, Vulovic A, Sustersic T, Djuris J, Filipovic N, *et al*. Optimization and prediction of ibuprofen release from 3D DLP printlets using artificial neural networks. Pharmaceutics 2019;11:544.
61. Awad A, Fina F, Trenfield SJ, Patel P, Goyanes A, Gaisford S, *et al*. 3D printed pellets (miniprintlets): A novel, multi-drug, controlled release platform technology. Pharmaceutics 2019;11:148.
62. Bikas H, Stavropoulos P, Chryssolouris G. Additive manufacturing methods and modelling approaches: A critical review. Int J Adv Manuf Technol 2016;83:389-405.
63. Kondiah PJ, Kondiah PP, Choonara YE, Marimuthu T, Pillay V. A 3D bioprinted pseudo-bone drug delivery scaffold for bone tissue engineering. Pharmaceutics 2020;12:166.
64. Andriotis EG, Eleftheriadis GK, Karavasili C, Fatouros DG. Development of bio-active patches based on pectin for the treatment of ulcers and wounds using 3D-bioprinting technology. Pharmaceutics 2020;12:56.
65. Rycerz K, Stepien KA, Czapiewska M, Arafat BT, Habashy R, Isreb A, *et al*. Embedded 3D printing of novel bespoke soft dosage form concept for pediatrics. Pharmaceutics 2019;11:630.
66. Goyanes A, Kobayashi M, Martínez-Pacheco R, Gaisford S, Basit AW. Fused-filament 3D printing of drug products: Microstructure analysis and drug release characteristics of PVA-based caplets. Int J Pharm 2016;514:290-5.
67. Okwuosa TC, Stefaniak D, Arafat B, Isreb A, Wan KW, Alhnan MA. A lower temperature FDM 3D printing for the manufacture of patient-specific immediate release tablets. Pharm Res 2016;33:2704-12.
68. Sadia M, Sośnicka A, Arafat B, Isreb A, Ahmed W, Kelarakis A, *et al*. Adaptation of pharmaceutical excipients to FDM 3D printing for the fabrication of patient-tailored immediate release tablets. Int J Pharm 2016;513:659-68.
69. Khaled SA, Alexander MR, Wildman RD, Wallace MJ, Sharpe S, Yoo J, *et al*. 3D extrusion printing of high drug loading immediate release paracetamol tablets. Int J Pharm 2018;538:223-30.
70. Pietrzak K, Isreb A, Alhnan MA. A flexible-dose dispenser for immediate and extended release 3D printed tablets. Eur J Pharm Biopharm 2015;96:380-87.
71. 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.
72. Wang CC, Motwani MR, Roach WJ, Kay JL, Yoo J, Surprenant HL, *et al*. Development of near zero-order release dosage forms using three-dimensional printing (3-DP) technology. Drug Dev Ind Pharm 2006;32:367-76.
73. Genina N, Boetker JP, Colombo S, Harmankaya N, Rantanen J, Bohr A. Anti-tuberculosis drug combination for controlled oral delivery using 3D printed compartmental dosage forms: From drug product design to *in vivo* testing. J Control Release 2017;268:40-8.
74. Yu DG, Yang XL, Huang WD, Liu J, Wang YG, Xu H. Tablets with material gradients fabricated by three-dimensional printing. J Pharm Sci 2007;96:2446-56.
75. Li Q, Guan X, Cui M, Zhu Z, Chen K, Wen H, *et al*. Preparation and investigation of novel gastro-floating tablets with 3D extrusion-based printing. Int J Pharm 2018;535:325-32.
76. Clark EA, Alexander MR, Irvine DJ, Roberts CJ, Wallace MJ, Sharpe S, *et al*. 3D printing of tablets using inkjet with UV photoinitiation. Int J Pharm 2017;529:523-30.
77. Goyanes A, Buanz AB, Basit AW, Gaisford S. Fused-filament 3D printing (3DP) for fabrication of tablets. Int J Pharm 2014;476:88-92.
78. 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. J Control Release 2015;217:308-14.
79. 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.
80. Kyobula M, Adedeji A, Alexander MR, Saleh E, Wildman R, Ashcroft I. 3D inkjet printing of tablets exploiting bespoke complex geometries for controlled and tuneable drug release. J Control Release 2017;261:207-15.
81. Okwuosa TC, Pereira BC, Arafat B, Cieszynska M, Isreb A, Alhnan MA. Fabricating a shell-core delayed release tablet using dual FDM 3D printing for patient-centred therapy. Pharm Res 2017;34:427-37.
82. Rowe CW, Katstra WE, Palazzolo RD, Giritlioglu B, Teung P, Cima MJ. Multimechanism oral dosage forms fabricated by three dimensional printing. J Control Release 2000;66:11-7.
83. Jamróz W, Kurek M, Łyszczarz E, Szafraniec J, Knapik-Kowalczuk J, Syrek K, *et al*. 3D printed orodispersible films with aripiprazole. Int J Pharm 2017;533:413-20.
84. Solanki NG, Tahsin M, Shah AV, Serajuddin AT. Formulation of 3D printed tablet for rapid drug release by fused deposition modeling: Screening polymers for drug release, drug-polymer miscibility and printability. J Pharm Sci 2018;107:390-401.
85. Musazzi UM, Selmin F, Ortenzi MA, Mohammed GK, Franzé S, Minghetti P, *et al*. Personalized orodispersible films by hot melt ram extrusion 3D printing. Int J Pharm 2018;551:52-9.
86. Kempin W, Domsta V, Grathoff G, Brecht I, Semmling B, Tillmann S,

et al. Immediate release 3D-printed tablets produced via fused deposition modeling of a thermo-sensitive drug. Pharm Res 2018;35:124.
87. Yi HG, Choi YJ, Kang KS, Hong JM, Pati RG, Park MN, *et al*. A 3D-printed local drug delivery patch for pancreatic cancer growth suppression. J Control Release 2016;238:231-41.
88. Huang W, Zheng Q, Sun W, Xu H, Yang X. Levofloxacin implants with predefined microstructure fabricated by three-dimensional printing technique. Int J Pharm 2007;339:33-8.
89. Wu W, Zheng Q, Guo X, Sun J, Liu Y. A programmed release multi-drug implant fabricated by three-dimensional printing technology for bone tuberculosis therapy. Biomed Mater 2009;4:065005.
90. Wu W, Ye C, Zheng Q, Wu G, Cheng Z. A therapeutic delivery system for chronic osteomyelitis via a multi-drug implant based on three-dimensional printing technology. J Biomater Appl 2016;31:250-60.
91. Ahlfeld T, Akkineni AR, Förster Y, Köhler T, Knaack S, Gelinsky M, *et al*. Design and fabrication of complex scaffolds for bone defect healing: Combined 3D plotting of a calcium phosphate cement and a growth factor-loaded hydrogel. Ann Biomed Eng 2017;45:224-36.
92. Johnson AR, Caudill CL, Tumbleston JR, Bloomquist CJ, Moga KA, Ermoshkin A, *et al*. Single-step fabrication of computationally designed microneedles by continuous liquid interface production. PLoS One 2016;11:e0162518.
93. Lu Y, Mantha SN, Crowder DC, Chinchilla S, Shah KN, Yun YH, *et al*. Microstereolithography and characterization of poly(propylene fumarate)-based drug-loaded microneedle arrays. Biofabrication 2015;7:045001.
94. Luzuriaga MA, Berry DR, Reagan JC, Smaldone RA, Gassensmith JJ. Biodegradable 3D printed polymer microneedles for transdermal drug delivery. Lab Chip 2018;18:1223-30.
95. Pere CP, Economidou SN, Lall G, Ziraud C, Boateng JS, Alexander BD, *et al*. 3D printed microneedles for insulin skin delivery. Int J Pharm 2018;544:425-32.
96. Lim SH, Ng JY, Kang L. Three-dimensional printing of a microneedle array on personalized curved surfaces for dual-pronged treatment of trigger finger. Biofabrication 2017;9:015010.
97. Loo AH, Chua CK, Pumera M. DNA biosensing with 3D printing technology. Analyst 2017;142:279-83.
98. Araújo MR, Sa-Barreto LL, Gratieri T, Gelfuso GM, Cunha-Filho M. The digital pharmacies era: How 3D printing technology using fused deposition modeling can become a reality. Pharmaceutics 2019;11:128.
99. Khoo ZX, Teoh JE, Liu Y, Chua CK, Yang S, An J, *et al*. 3D printing of smart materials: A review on recent progresses in 4D printing. Virtual Phys Prototyp 2015;10:103-22.
100. Mitchell A, Lafont U, Hołyńska M, Semprimoschnig C. Additive manufacturing-a review of 4D printing and future applications. Addit Manuf 2018;24:606-26.