Available online on 22.10.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Review Article

3D Drug Printing: A Swing from Laboratory Production to Computerized Production

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ABSTRACT

Three-Dimensional (3D) printing is a process where objects are made in successive layers under computer control by fusing or depositing materials. The objects can be of nearly any shape or geometry and come in a computer-aided (CAD) design from a 3D model. Since 3D printing began in 1984, it has changed enormously and has been used in a wide range of fields, including medicine and architecture. 3D printing moves rapidly and in future will transform and change the way we live and work from laboratory-based organs to pharmaceutical supplies. 3D printing in pharmaceuticals has been used to produce many novel dosage forms like microcapsules, complex drug-release profiles, nanosuspensions, and multilayered drug delivery devices. It also offers important advantages from the industrial point of view such as cost-efficiency, higher productivity, democracy-making and enhanced cooperation. Keeping in view the recent approval given by USFDA to many drug the focus has now shifted to the personalized medicine as it offers an important benefit to patients who need medications that have narrow therapeutic index or a higher predilection to be influenced by genetic polymorphisms. 3D printer is now seen as a valuable, efficient and economical tool to manufacture individualized medications, tailored to specific patients based on their needs and thereby change the future of pharmacy practice in general and pharmaceutical care in particular.

Keywords: Three-dimensional printing; manufacturing; personalized medicine; USFDA, Drugs

Article Info: Received 27 July 2019; Review Completed 08 Aug 2019; Accepted 18 Aug 2019; Available online 22 Oct 2019

Cite this article as:

Itoo A, Raza SN, Tariq U, Khan A, Bashir S, Khan NA, 3D Drug Printing: A Swing from Laboratory Production to Computerized Production, Journal of Drug Delivery and Therapeutics. 2019; 9(5-s):201-207

http://dx.doi.org/10.22270/jddt.v9i5-s.3255

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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 [35]. It is a method of manufacturing objects by fusing or depositing materials (such as plastics, metals, ceramics, powders, liquids, or even living cells) into layers to produce a 3D object. Additive processes are used in 3D printing, in which successive layers of material are placed under computer control, thus also called as additive manufacturing (AM) .These objects can be of almost any shape or geometry, and are produced from a 3D model as defined in a computer-aided design (CAD)[1,6].The 3D printing process was first described in the 1980s and since then 3D printing has been used in a wide range of fields, including architecture, medicine and food industry and recently in pharmaceutical manufacturing [6, 9].

As the pharmaceutical industry shifts from mass production to personalized medicine, 3D printing will become part of the drug production line, promising future production of drugs printed on demand, at custom dose levels, with increased productivity and cost-effectiveness[4,5].The USFDA approved 3D printed drug Levetiracetam (SPRITAM®) for the first time in 2015[4].

BACKGROUND

In 1884, when Charles Hull invented a stereo lithograph, 3D printing technology became apparent first[4,8,9]. He was then the co-founder of three-dimensional systems. The big development of the 3D system took place in 1992, when this year two 3D presses were developed, the 3D printer SLA (stereo lithographic device) and the SLS (selective laser sinters) 3D printer. The wax printer of Model Mark was launched in 1994. Aeromet invented 3D laser printing in 1997. 3D printing in 1999 led to new developments in medicine, as the first lab organ grown in humans is implanted.The first inject printer was developed by Object Geometries in 2000 and the first multicolor 3D press was made by Z Corporation. Solid imension produced the first 3D desktop printer in 2001. The first 3D printed functional kidney designed to filter blood and produce diluted urine in the animals was found to be revolutionizing in medicine in 2002. In 2006, the first SLS (Select Laser Sintering) press was developed to achieve a breakthrough in the mass customization and on-demand production of industrial components and prostheses. The SLC resulted in a 3D-printed prosthetic leg being taken by the first person in 2008.

The launch of the reprap project in 2005 marked the biggest advance of 3D printing technology, and in 2008 this project released Darwin, the first self-reproduction printer to print most of its own components. Organovo produced its first 3D bioprinted blood vessel in 2009. For the first time, 3D printing technology helps to develop robotics, 3D printed cars and even 3D printed silver and gold jewelry in 2011.The world's first 3d printed weapons was developed in 2013 and successfully shot [8,9]. The world's first 3D printed drug (Spitram) produced by Aprecia Pharmaceuticals was approved by the USFDA in 2015. In this context, the first 3D printed drug was developed. Spitram is produced by Aprecia using 3D printing platform with the ZipDose technology which creates high dose orodispersible formulations for the mouth with the liquid [1,4].

WORKING OF 3D PRINTER

It all starts with making a virtual design of the object you want to create. This virtual design is made in a CAD (Computer Aided Design) file using a 3D modeling program or with the use of a 3D scanner (to copy an existing object). A 3D scanner makes a 3D digital copy of an object [9] to prepare a digital file for printing, the 3D modeling software "slices" the final model into hundreds or thousands of horizontal layers. When the sliced file is uploaded in a 3D printer, the object can be created layer by layer. The 3D printer reads every slice (as 2D image) and creates the object, fussing each layer with hardly any visible sign of the layers with the result three dimensional objects are formed [1,9].

3D PRINTING INDUSTRY

At present, the impact of 3D printing in medicine remains small. 3D printing is currently a $700 million industry, with only $11 million (1.6%) invested in medical applications. In the next 10 years, however, 3D printing is expected to grow into an $8.9 billion industry, with $1.9 billion (21%) projected to be spent on medical applications [6].

TYPES OF 3D PRINTING TECHNOLOGIES

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

Type of 3DP Technology	Details	Ref
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.	[26,27, 28, 29, 30]
Direct-write	Uses a computer-controlled translational stage that moves a pattern-generating device in order to achieve, layer-by-layer,3Dmicrostructure.	[31]
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.	[32]
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).	[22,25]
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.	[27,29, 16, 33]

APPLICATIONS OF 3D PRINTING

Manufacturing industries have been using 3D printers for more than decades, but mostly to make prototypes rapidly and cheaply. The majority are used as functional models, prototypes, and casting patterns, or for presentation models. As the technology is getting better and better more things are being printed as finished goods, around 28% of the output of 3D printers is now final products rather than prototypes, and this is expected to rise to 50% by 2016 and 80% by 2020.

Various applications of 3D printing but the focus of these applications is mainly on finished products [7].

A. **Hearing aids:** 3D printing technology for manufacturing hearing aids was introduced a decade ago and it has shortened the manufacturing process to three steps: scanning, modelling, and printing. Printers can print 65 hearing aid shells or 47 hearing aid moulds within 60 to 90 minutes. The printing speed helps manufacturers to adjust demand to supply [7].

B. **Automobile components:** 3D printing technology is used by BMW manufacturers to produce prototypes of metallic parts. This technology is used to produce engine parts of motor sports racing cars by utilising direct metal laser sintering process. Some luxury car manufacturers as Bentley and Rolls-Royce are using 3D printing technology to produce some parts more economically then conventional method of manufacturing. Tesla, the producer of electric cars, also produces automobile components by using 3D printers [7].

C. **Aircraft components:** European Aeronautic Defence and Space Company has developed the aircraft machined parts by 3D printing technology which are up to 65% lighter and equally strong compared to those manufactured by traditional methods.Airbus produced a door bracket for the A350-1000 in 2011 by using 3D printing technology. It takes the 200-Watt laser two hours to complete the print job of these components. The Boeing Company has been utilizing SLS (Selective Laser Sintering) for flight hardware in regular production since 2002, for both military and commercial programs. [7]

D. **Weapons:** The world's first handgun made almost entirely by a 3D printer was printed and tested in 2013. 15 out of 16 pieces were printed by a 3D printer using ABS plastic as a material [7].

E. **Sports:** For the first time Nike produced a part, the plate, of a sports shoe by using AM technique (Selective Laser Sintering technology) [7].

F. **Other applications:** A huge range of products are manufactured by 3D printing includes jewelry, games, fashion (E.g. belts, wallets), lamps, furniture, articles for dining and other accessories, gadgets and design articles.

Other applications exist also in the food sector. The University of Exeter developed a 3D printer for chocolate. The chocolate printer prints out chocolate layer by layer to create a 3D shape, without any molding tools. This gives the opportunity that own designs and chocolate articles can be created and printed out at local chocolate outlets [7].

Apart from the production of goods also the manufacturing of 3D printing machines has become a business, in 2008 first self-replicating printer was released that is able to print the majority of its own components [7, 9].

G. **Medical applications:** 3D printing has been applied in medicine since the early 2000s, when the technology was first used to make dental implants and custom prosthetics. Since then, the medical applications for 3D printing have evolved considerably. Recently published reviews describe the use of 3D printing to produce bones, ears, exoskeletons, windpipes, a jaw bone, eyeglasses, cell cultures, stem cells, blood vessels, vascular networks, tissues, and organs, as well as novel dosage forms and drug delivery devices [6].

H. **Dentistry:** 3D printing is widely used in dental labs, if takes the efficiencies of digital design to the production stage. By combining oral scanning, CAD/CAM design, and 3D printing, dental labs can accurately and rapidly produce Crowns, Bridges, Stone models and range of orthodontic appliances [7].

I. **Tissue:** For the first time in 2012 the lower jaw of a patient was completely replaced by an artificial jaw which was 3D printed. Titanium powder was used for printing the implant. 1 mm of the implant exists of 33 printed layers. The titanium body is coated with bio-ceramics. Parts of bones and more often parts from faces or ears are produced by 3D printers. Scientists developed an artificial ear with the help of 3D printing. This is purposely different from the natural human ear. An antenna which is part of the artificial ear registers frequencies a human cannot hear. Future applications in this sector are 3D printed organs. However, research in this area is still far away from practical applications which would mean transplantation [7].

J. Pharmaceutical Applications of 3D Printing

Pharmaceutical applications for 3D printing are expanding rapidly and are expected to revolutionize health care. 3D printing technologies are already being used in pharmaceutical research and fabrication. Advantages of 3D printing include precise control of droplet size and dose, high reproducibility, and the ability to produce dosage forms with complex drug-release profiles. 3D printing technology makes complex drug manufacturing processes more standardized, simpler and more viable. 3D printing technology is also valuable tool in the development of personalized medicine. 3D printing technology allows drug dosage forms, release profiles, and dispensing to be customized for each patient [6] .3D printing can lead to drugs actually manufactured by "precision drug dispensing". The drugs themselves could be tailored to meet various precise specifications and address the unique needs of individuals taking them [4,6]. Application of 3D printing technology in pharmaceutical manufacturing could have following potential benefits [6].

Personalized Medicine: The purpose of drug development should be to increase efficacy and decrease the risk of adverse reactions, a goal that can potentially be achieved through the application of 3D printing to produce personalized medications. Oral tablets are the most popular drug dosage form because of ease of manufacture, pain avoidance, accurate dosing, and good patient compliance. However, no viable method is available that could routinely be used to make personalized solid dosage forms, such as tablets. Oral tablets are currently prepared via well-established processes such as mixing, milling, and dry and wet granulation of powdered ingredients that are formed into tablets through compression or molds. Each of these manufacturing steps can introduce difficulties, such as drug degradation and form change, possibly leading to problems with formulation or batch failures. In addition, these traditional manufacturing processes are unsuitable for creating personalized medicines and restrict the ability to create customized dosage forms with highly complex geometries, novel drug-release profiles, and prolonged stability.

Personalized 3D-printed drugs may particularly benefit patients who are known to have a pharmacogenetic polymorphism or who use medications with narrow therapeutic indices. Pharmacists could analyze a patient's pharmacogenetic profile, as well as other characteristics such as age, race, or gender, to determine an optimal medication dose. A pharmacist could then print and dispense the personalized medication via an automated 3D printing system. If necessary, the dose could be adjusted further based on clinical response.

3D printing also has the potential to produce personalized medicines in entirely new formulations, such as pills that include multiple active ingredients, either as a single blend or as complex multilayer or multi-reservoir printed tablets.

Patients who have multiple chronic diseases could have their medications printed in one multidose form that is fabricated at the point of care. Providing patients with an accurate, personalized dose of multiple medications in a single tablet could potentially improve patient compliance [6].

Complex Drug-Release Profiles

The creation of medications with complex drug-release profiles is one of the most researched uses of 3D printing. Traditional compressed dosage forms are often made from a homogeneous mixture of active and inactive ingredients, and are thus frequently limited to a simple drug-release profile. However, 3D printers can print binder onto a matrix powder bed in layers typically 200 micrometers thick, creating a barrier between the active ingredients to facilitate controlled drug release. 3D-printed dosage forms can also be fabricated in complex geometries that are porous and loaded with multiple drugs throughout, surrounded by barrier layers that modulate release [6].

Oro-dispersible high-dose medications

3D printing technology helps to produce Oro-dispersible high-dose medications (up to 1000 mg) without using compression forces or traditional molding techniques.

3D printer stitches together multiple layers of powdered medication using an aqueous fluid to produce a porous, water-soluble matrix that rapidly disintegrates with a sip of liquid[1].

3D PRINTED PHARMACETICAL FORMULATIONS

First 3D printed drug [Spitram (levetiracetam)] manufactured by Aprecia Pharmaceuticals was approved by USFDA [1,4,11]. Spitram is produced by using Aprecia's ZipDose technology [3,4,11]. This Technology is Aprecia's unique delivery platform which is designed to enable delivery of high-dose medications in a rapidly disintegrating form [3,4,12].

ZipDose Technology product candidates are assembled layer-by-layer without using compression forces or traditional molding techniques. Thin layers of powdered medication are repeatedly spread on top of one another, as patterns of liquid droplets (an aqueous fluid) are deposited or printed onto selected regions of each powder layer. Interactions between the powder and liquid bond these materials together at a microscopic level [4,12].

This platform yields highly porous structures even at high loading and doses of drug. The result is the creation of Aprecia's unique ZipDose Technology product candidates that are designed to:

- Rapidly disintegrate on contact with liquid by breaking the bonds created during the 3D printing process.
- Support dose loading up to 1,000 mg.
- Allows the application of enhanced taste-masking techniques [3,12].

Unique Dosage Forms: These dosage forms are produced using "inkjet-based 3D printing drug fabrication", inkjet printers are used to spray formulations of medications and binders in small droplets at precise speeds, motions, and sizes onto a substrate. The most commonly used substrates include different types of cellulose, coated or uncoated paper, microporous bioceramics, glass scaffolds, metal alloys, and potato starch films, among others. Investigators have further improved this technology by spraying uniform "ink" droplets onto a liquid film that encapsulates it, forming microparticles and nanoparticles. Such matrices can be used to deliver small hydrophobic molecules and growth factors.

In "powder-based 3D printing drug fabrication", the inkjet printer head sprays the "ink" onto the powder foundation. When the ink contacts the powder, it hardens and creates a solid dosage form, layer by layer. The ink can include active ingredients as well as binders and other inactive ingredients. After the 3D-printed dosage form is dry, the solid object is removed from the surrounding loose powder substrate.

This technology also offers the ability to create limitless dosage forms that are likely to challenge conventional drug fabrication. 3D printers have already been used to produce many novel dosage forms, such as: microcapsules, hyaluronan-based synthetic extracellular matrices, antibiotic printed micropatterns, mesoporous bioactive glass scaffolds, nanosuspensions, and multilayered drug delivery devices [6].

Drugs with complex geometries: 3D printing technology can be used to create medicinal tablets in various odd shapes that would be difficult to produce via traditional manufacturing methods. Researchers of the University College London (UCL) School of Pharmacy and FabRx, Ltd. In their study designed five tablets, each with a distinctly different shape — a cube, pyramid, cylinder, sphere, and torus (i.e. ring/donut) using auto CAD software. The sizes and shapes of each tablet were varied using the scale function of the software to fabricate tablets with a constant surface area (275 mm2), surface area/volume ratio (1:1), or weight (500 mg). In all cases, however, the ratio of the length, width, and height of each shape was kept constant. Finally, researchers printed each tablet using the drug-infused filament and a "MakerBot Replicator 2X Desktop 3D printer". Once the tablets were printed, researchers conducted dissolution tests to determine the drug release profile of each pill. They found that when the surface area of the printed tablets was kept constant, the drug release rates were the fastest in the pyramid-shaped tablet, followed by the torus, cube, sphere, and finally the cylinder. This order is directly correlated with the tablets' surface area/volume ratio, with the pyramid tablet having the highest value and the cylinder the lowest. This led the researchers to conclude that the geometrical shape of a tablet undoubtedly influences its drug release profile. The visual appearance of a tablet is a very important consideration for patients. In particular, tablet size and shape are critical to patient medication adherence [2].

TABLE 2: EXAMPLES OF PHARMACEUTICAL FORMULATIONS THAT WERE DEVELOPED BY 3D PRINTING TECHNOLOGY

3DP Technology	Dosage Forms	Active Ingredients	Ref
Desktop 3D printer	Tablet	Guaifenesin	[14]
A laboratory- scale 3DP machine	capsule	Pseudoephedrine hydrochloride	[15]
Fused Deposition Modelling (FDM)	Tablet	5-aminosalicylic acid (5-ASA, mesalazine) and 4-aminosalicylic acid (4-ASA)	[16]
3DP extrusion-based printing	Tablet	Captopril with Nifedipine and Glipizide	[17]
3DP technology	Tablet	Acetaminophen	[18]
Inkjet 3DP	Implant	Levofloxacin	[19]
3DP machine	Multi-drug implant	Rifampicin and Isoniazid	[20]
Inkjet 3DP	Nanosuspension	Folic Acid	[21]
Thermal Inkjet (TIJ) Printing	Solution	Salbutamol sulphate	[22]
Inkjet 3DP	Nanoparticles	Rifampicin	[23]
3D Extrusion Printing	Encapsulated within apolymer(PLGA)poly(vinyl alcohol) (PVA)	Dexamethasone- 21-phosphate disodium salt	[24]
Thermal Inkjet (TIJ) Printing	Solid dosage forms	Prednisolone	[25]

WHY 3D PRINTING?

The application of 3D printing in Pharmaceuticals can provide many benefits, including: cost-effectiveness; increased productivity; the democratization of design and manufacturing; and enhanced collaboration [6].

Increased Cost Efficiency: The most important benefit offered by 3D printing is the ability to produce items cheaply. [4,6] Conventional method of drug manufacturing are less cost effective then 3D printing technology, because conventional method uses a lot of processes such as mixing, milling, dry or wet granulation, compression or molding etc. 3D printing can also reduce manufacturing costs by decreasing the use of unnecessary resources. For example, a pharmaceutical tablet weighing 10 mg could potentially be custom-fabricated on demand as a 1 mg tablet. Some drugs may also be printed in dosage forms that are easier and more cost-effective to deliver to patients [6].

Enhanced Productivity: 3D printing technology is much faster than traditional method of drug manufacturing, which uses various processes such as mixing, milling, dry or wet granulation, compression or molding that makes it time consuming. In addition to speed, other qualities, such as the resolution, accuracy, reliability, and repeatability of 3D printing technologies, are also improving [6].

Environment friendly: 3D printing technology claims to have more environmental benefits than traditional drug manufacturing methods which needs huge setup to manufacture a pill[7].

Democratization and Collaboration: Another beneficial feature offered by 3D printing is the democratization of the design and manufacturing of goods [6].

BARRIERS AND CHALLENGES

Post-processing: In many cases, 3D printer is unable to generate components with the desired accuracy and only produce products with nearly final shape. These products may then require a finishing operation, such as grinding or polishing, to produce the final product [7].

Limitations of Materials: The choice of different raw materials as feedstock for 3D printers is still rather limited. There might be physical and technical limitations regarding the diversity of potential raw materials [7].

Massive job loss: 3D printing technology will fall somewhere between the extremes of creating and destroying jobs. Currently, 3D printing serves as an indispensable tool for rapid prototyping, but as systems improve and become mainstream in manufacturing, 3Dprinting technology will likely replace unskilled human labour needed for subtractive manufacturing processes. At the same time, skilled jobs in CAD design, math, materials engineering, and automation oversight will become more valuable [5].

Regulatory Concerns: Securing approval from regulators is another significant barrier that may impede the widespread pharmaceutical application of 3D printing. Only one dosage form printed by Aprecia pharmaceuticals has received the FDA's approval till this date. However, fulfilling more demanding FDA regulatory requirements could be a hurdle that may impede the availability of 3D-printed drugs on a large scale [6].

FUTURE TRENDS

3DP technology has many anticipated advantages that are not yet proven; as such continuous clinical development of 3DP will require vision, money, and time [26,29]. 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 [26,29]. 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.

CONCLUSION

In conclusion,3D printing technology is expected to play an important role in the trend toward personalized medicine, through its use in customizing nutritional products, organs, and drugs.3D printing technology is expected to be especially common in pharmacy settings. The manufacturing and distribution of drugs by pharmaceutical companies could conceivably be replaced by emailing databases of medication formulations to pharmacies for on-demand drug printing. This would cause existing drug manufacturing and distribution methods to change drastically and become more cost-effective. If most common medications become available in this way, patients might be able to reduce their medication burden to one polypill per day, which would promote patient adherence [6]. 3D printing technologies are going to transform pharmacy practice by allowing medications to be truly individualized and tailored specifically to each patient, although technical and regulatory hurdles remain [4,6].

Conflicts of Interest:

There exists no conflict of interest.

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