Three dimensional (3D) drug printing: A revolution in Pharmaceutical Science

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ABSTRACT

Three-dimensional (3D) printing is a manufacturing method in which objects are made by fusing or depositing materials in successive layers laid down under computer control. 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). Since the inception of 3D printing in 1984 it has evolved immensely and has been used in many fields including medicine, architecture and more recently in pharmaceutical manufacturing. From lab grown organs to drug delivery devices, 3D printing is advancing rapidly and in future course of time it is going to transform and change the way we live and work.

3D printing in pharmaceuticals has been used to produce many novel dosage forms like microcapsules, Complex Drug-Release Profiles, nano-suspensions, and multilayered drug delivery devices. From industrial point of view it also offers important advantages like, cost-effectiveness, increased productivity, democratization of design and manufacturing, and enhanced collaboration. Keeping in view the recent approval given by USFDA to the first 3D printed antiepileptic 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 indices 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.

INTRODUCTION

Three-dimensional (3D) printing is a manufacturing method in which objects are made by fusing or depositing materials (such as plastic, metal, ceramics, powders, liquids, or even living cells) in layers to produce a 3D object. In 3D printing, additive processes are used, in which successive layers of material are laid down 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)(Razelle Kurzrock, David J. Stewart2015; C. Lee Ventola 2014).The process of 3D printing was first described in the 1980s, and since then 3-D printing has been used in many fields, such as architecture, medicine, food industry, and recently in pharmaceutical manufacturing (C. Lee Ventola 2014; A Brief History Of 3d Printing). As the Pharmaceutical Industry shifts from mass manufacturing to personalized medicine, 3D printing will become the part of drug production line, as it promises future production of drugs printed on demand, to custom doses, with increased productivity and cost effectiveness (Robert J. Szczebra 2015Tom Schneider, Emily Apel, Peter Brost, et al, 2014), and for the first time in 2015 3D printed drug was approved by USFDA (Robert J. Szczebra 2015).

The objective is to conduct systemic literature review of 3D printing.

- To access the impact and implications of 3D printing technology in pharmaceutical manufacturing.
- To understand the role and importance of 3D drug printing in personalised medicine.

HISTORY OF 3D PRINTING

3D printing technology first becomes visible in 1884, when Charles Hull invents Stereo lithography (Robert J. Szczebra 2015; AV Plastics; A BRIEF HISTORY OF 3D PRINTING). He went on to become the co-founder of 3D Systems. In 1992 there was the big development

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in 3D system as two 3D printers were developed in this year, SLA (stereo lithographic apparatus) 3D printer machine and SLS (selective laser sintering) 3D printer machine. In1994 Model Mark's wax printer was released. Aeromet in 1997 invents laser 3D printing. Development of engineered organs by 3D printing in 1999 brings new advances in medicine, as first lab-grown organ is implanted in humans. Object Geometries in 2000 developed the first inject printer, in the same year Z Corporation made first multicolor 3D printer. In 2001first desktop 3D printer was made by Solid imension. 2002 was found to be revolutionizing for medical field as first 3D printed functional kidney was engineered that is able to filter blood and produce diluted urine in an animal. In 2006 there was a breakthrough in mass customization and on-demand manufacturing of industrial parts and prostheses, as the first SLS (selective laser sintering) machine was developed. It was the outcome of the SLC that in 2008 the first person walks on a 3D-printed prosthetic leg. There was a biggest advancement in 3D printing technology when the RepRap project was launched in 2005, and in 2008 this project releases Darwin, the first self-replicating printer that is able to print the majority of its own components. In 2009 first 3D bio printed blood vessel was produced by Organovo. In 2011 3D printing technology for the first time helps to develop robotic aircraft, 3D printed car, and even 3D printed silver and gold jewelry. Customized prosthetic lower jaw was produced for the first time in 2012 by Doctors and engineers of Netherland by using 3D printer, which was subsequently implanted into an 83-year old woman. In 2013 World's first 3D printed gun was designed, which fired successfully(Av Plastics; A Brief History Of 3d Printing) In 2015 there was a groundbreaking advancement in the Pharmaceutical field as first 3D printed drug (Spitram) manufactured by Aprecia Pharmaceuticals was approved by USFDA. Spitram is produced by Aprecia using ZipDose technology by utilizing 3D printing platform that creates Orodispersible formulations of high-dose medications, designed to disintegrate in the mouth with just a sip of liquid (Razelle Kurzrock, David J. Stewart 2015; Robert J. Szczebra 2015).

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(3d Printing.Com). 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 (Razelle Kurzrock, David J. Stewart 2015; 3D PRINTING.COM).

3D Printing Industry

According to Wohler Report 2017 3D printing is currently a $6.063 billion industry, with $667 million (11%) invested in medical applications. By 2027 3D printing industry is expected to grow into an $40 billion industry (Wohlar report 2017).

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 80% by 2020.Various applications of 3D printing but the focus of these applications is mainly on finished products (H. Stahl 2013 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 (H. Stahl 2013b).

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 (H. Stahl 2013 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.

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.

Sports: For the first time Nike produced a part, the plate, of a sports shoe by using AM technique (Selective Laser Sintering technology) (H. Stahl 2013 d).

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. 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.

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 (C. Lee Ventola 2014).

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.

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. (H. Stahl 2013)

Pharmaceutical Applications for 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 (Lee H & Cho D-W; 2016 b). 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 (C. Lee Ventola et .al; 2014). 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 (Robert J. Szczebra 2015; C. Lee Ventola 2014). Application of 3D printing technology in pharmaceutical manufacturing could have following potential benefits (C. Lee Ventola 2014).

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 (Nagarajan N et.al 2018). 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 (C. Lee Ventola 2014).

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 (Mazhar.M; 2015). 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 (C. Lee Ventola 2014).

Orodispersible high-dose medications

3D printing technology helps to produce Orodispersible 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 (ZipDose Technology).

First FDA approved drug (2015)

First 3D printed drug [Spitram (levetiracetam)] manufactured by Aprecia Pharmaceuticals was approved by USFDA (Razelle Kurzrock, David J. Stewart 2015; Robert J. Szczebra 2015; ZipDose Technology). Spitram is produced by using Aprecia's ZipDose technology (Dominic Basulto 2015; Robert J. Szczebra 2015; ZipDose Technology).

This Technology is Aprecia's unique delivery platform which is designed to enable delivery of high-dose medications in a rapidly disintegrating form. (Dominic Basulto 2015; Robert J. Szczebra 2015; 3D Printing; Aprecia Pharmaceuticals).

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 (Robert J. Szczebra 2015; 3D Printing; Aprecia Pharmaceuticals).

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 3DP process. Support dose loading up to 1,000 mg. Allow the application of enhanced taste-masking techniques (Dominic Basulto 2015; 3D Printing; Aprecia Pharmaceuticals).

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 bio ceramics, 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 micro particles 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 micro patterns, mesoporous bioactive glass scaffolds, nanosuspensions, and multilayered drug delivery devices (Alford PW.et.al 2010a).

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(Lee H & Cho D-W; 2016 b) 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(Alford PW.et.al 2010b). 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 is critical to patient medication adherence. (Alvaro Goyanes, Pamela Robles Martinez, Asma Buanz, et al. 2015).

3D printing : Need

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 (C. Lee Ventola 2014).

Increased Cost Efficiency

The most important benefit offered by 3D printing is the ability to produce items cheaply (Robert J. Szczebra 2015; C. Lee Ventola 2014). 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 (C. Lee V.et.al; 2014)

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 (C. Lee Ventola 2014).

Environment friendly

3D printing technology claims to have more environmental benefits than traditional drug manufacturing methods which needs huge setup to manufacture a pill (H. Stahl 2013).

Democratization and Collaboration

Another beneficial feature offered by 3D printing is the democratization of the design and manufacturing of goods (C. Lee Ventola 2014).

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 (H.Stahl 2013a).

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 (H. Stahl 2013b).

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 (Tom Schneider, Emily Apel, Peter Brost, et al. 2014).

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 (C. Lee Ventola 2014).

Future trends and 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. This technology is expected to increased due to be 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 (C. Lee Ventola

2014 a) . This 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 (Robert J. Szczebra 2015; C. Lee Ventola 2014 b) .

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