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Review Article

3D Printing

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ABSTRACT

The pharmaceutical industry is set to join the fourth industrial revolution with the 3D printing of medicines. The application of 3D printers in compounding pharmacies will turn them into digital pharmacies, wrapping up the telemedicine care cycle and definitively modifying the pharmacotherapeutic treatment of patients. Fused deposition modeling 3D printing technology melts extruded drug-loaded filaments into any dosage form; and allows the obtainment of flexible dosages with different shapes, multiple active pharmaceutical ingredients and modulated drug release kinetics in other words, offering customized medicine. This work aimed to present an update on this technology, discussing its challenges. The co-participation of the pharmaceutical industry and compounding pharmacies seems to be the best way to turn this technology into reality. The pharmaceutical industry can produce drug-loaded filaments on a large scale with the necessary quality and safety guarantees; while digital pharmacies can transform the filaments into personalized medicine according to specific prescriptions. For this to occur, adaptations in commercial 3D printers will need to meet health requirements for drug products preparation, and it will be necessary to make advances in regulatory gaps and discussions on patent protection. Thus, despite the conservatism of the sector, 3D drug printing has the potential to become the biggest technological leap ever seen in the pharmaceutical segment, and according to the most optimistic prognostics, it will soon be within reach.

Key words: Digital pharmacy; fused deposition modeling 3D printing; modified drug release; personalized medicines; telemedicine.

INTRODUCTION:

In the past decade, the use of 3D printers has grown dramatically for both industries and public. There has been increase in global sales of consumer-based printers by more than 33% over last 3 y, worth $4.1 billion in 2014 (Wohlers and Caffrey, 2015). The most renowned, distinct and novel solid dosage forms have been found to be fabricated by variety of three-dimensional printing (3DP) technologies (Yu et al., 2008; Sethia and Squillante, 2003; Ventola, 2014). 3DP or additive manufacturing (AM) is a process of making three dimensional solid objects from a digital file (Marzuka and Kulsum, 2016). 3DP

is unique and powerful technology that was first described by Charles Hull in 1986 and called it as "stereo lithography" (USFDA, 2014). It uses ". still file format" to interpret the data in Computer Aided Design file. These data instructions are then electronically communicated to the 3D printer. These instructions include the shape, size, texture, thickness of the object to be printed (Borukhovich, 2016). Hull later founded his own company as "3D system" where he designed a stereo lithography-based 3D printer and was commercially available in market in 1988 (Marzuka and Kulsum, 2016). Since then many companies developed 3D printers for commercial application. In 1987, Carl Deckard filed a patent for the selective laser sintering (SLS) rapid prototyping process in US and was issued in 1989. In the same year, Scott Crump, a co-founder of Stratasys Inc. filed a patent for a technology that is still used by the company i.e., fused deposition modelling (FDM) (Bhusnure et al., 2016). Hans Langer founded the EOS GmbH in Germany and further focused on the laser sintering (LS) process and now it is well known around the world for their quality outputs and applications in 3D printing and still is continuing to strengthen the production applications. Throughout the 1990's and early 2000's a host of new technologies continued to be introduced. The Solidscape and ZCorporation, Arcam, Object Geometries, MCP Technologies, EnvisionTec and ExOne were set up in 1996, 1997, 198, 2000, 2002 and 2005. These companies speeded the development of 3D printing across a global market. The terminology for all the applications was accepted to be additive manufacturing. These technologies were large, very expensive for small enterprises or individuals. However, in the last decade many new companies entered the market with small, cheaper and high-quality machines. The first small kit form 3D printer was made available in 2009, for the commercial application based on RepRap concept. Furthermore, in June 2012, alternate process of 3D printing utilizing DLP technology "B9Creator" was introduced. In same year, Form 1 was introduced utilizing stereo lithography (Bhusnure et al., 2016). From then, much more growth was observed in this field and the fact was demonstrated that the 3DP is having commercial applications in various industrial sectors. 3DP expanded rapidly and revolutionized health care as well (Schubert et al., 2014). The medical use of 3DP includes creation of custom prosthetics, body tissue, organ fabrication, anatomical models, dental implants, pharmaceutical research regarding drug dosage forms, drug delivery and discovery (Gosnear and Brettler, 2016). In December 2015, the FDA had approved more than 85 3D-printed medical devices (Acosta-Velez and Wu, 2016). Moreover, FDA also granted approval to first 3D printed tablet, Spritam (levetiracetam), manufactured by Aprecia Pharmaceuticals in 2015 (JassimJaboori and Oyewumi, 2015). Aprecia's product 'Spritam' is used to treat epilepsy, which showed a significant advancement for patients suffering from seizures. With this landmark milestone in 3D Pharming in market, the future of drug manufacturing could change drastically.

3DP is a layer-by-layer process capable of producing 3D drug products from digital design (Patil et al., 2016). 3DP technology based on computer aided design is used to achieve unparalleled flexibility, save time, and exceptional manufacturing capability of pharmaceutical drug products, to formulate drug materials into the desired dosage form (Bose et al., 2016). 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.

The Principle behind a 3D printer can be assumed to be similar to a regular printer. 3D printer consists of an extruder that moves horizontally on an axis which is held on top of

two axes that allow it to move back and forward in x-y plane to create the base of the object (USFDA, 2014). These two axes are attached to the sides of the printer. The only difference is the 3D printer has a base that moves vertically along the z axis to create the layers over the object. While printing the first layer the extruder remains at the top and moves only in 2D. The base that holds the substrate will decrease in height so that next layer could be built upon it. The process is repeated following the computer-aided drafting instructions until the object is built layer by layer. This process is referred to as additive manufacturing, rapid prototyping (RP), or solid freeform technology (SFF) (Zhang et al., 2016). 3D printers are used to print various porous scaffolds with controlled chemistry, interconnected porosity and special shapes. These prints are biodegradable and proved to be ideal for drug delivery abilities (Mok et al., 2016; Lee et al., 2016; Xu and wang, 2015; Liu et al., 2015; Wang, 2015). Some of the highly complex structures incorporating living cells can be created by this technique and has gained popularity and applicability in cancer treatment (Rijal and li, 2016; King et al., 2013; Katstram et al., 2000; Rowe et al., 2000).

Different types of drug delivery systems such as oral controlled release systems, micro pills, microchip, drug implants, fast dissolving tablets and multiphase release dosage forms have been developed using 3DP technology (Santini et al., 1999; Cima and cima, 1996; Monkhouse et al., 2000; Monkhouse et al., 2003; Maraie et al., 2018; Panda et al., 2015). Conventional methods for designing the dosage form for drug delivery includes multiple manufacturing steps such as granulation, extrusion or coating (Salem et al., 2017). However, with rise in market novel manufacturing technologies such as nano, micro-scale medicines, biomimetic particles, systemized liposomes, niosomes have emerged to be successful in saving cost and time (Shah and patel, 2016, Wang et al., 2013; Wang et al., 2013; Le et al., 1998). Thus, 3D printing naturally appeared to be an important tool in fulfilling the current requirements of the industry. 3D printing tool can be considered as an essential tool for designing simple as well complex, accurate, cost effective, structured, self-designed and controlled release drug delivery systems. Various technologies are used for 3D printing in drug dosage form development (Zhang et al., 2016). These technologies are: Inkjet printing, Fused deposition modelling, Stereolithography (SLA), Direct energy deposition, Direct write, Zip dose, Thermal inkjet, Selective laser sintering (Lewis, 2006). In inkjet printing, combination of active pharmaceutical ingredients and excipients are precisely sprayed on the substrate or base and are solidified to obtain desired product. In Fused deposition modelling the filament is melted in the head of the 3D printer through induced current heating and then a 3D structure is created by adding layer by layer (Schubert et al., 2014). Stereolithography is the technique in which a computer-controlled laser beam is used to solidify the liquid polymer or resin, thereby creating 3D structure. In directed energy deposition process a printing apparatus consist of a multi-axis robotic arm with a nozzle, an energy source (laser, electron, or plasma), and a substrate to deposit melted material. For creating a 3D structure, the melted materials by the energy source are deposited on the substrate through nozzles, and then harden (Yu et al., 2005). In Direct-write assembly a computer controlled translational stage is used that moves a pattern-generating device in order to achieve, layer by layer, the desired 3D microstructure. In zip dose method, aqueous fluid is used to bind the layers of powder together and method is repeated to get desired product. In thermal inkjet printing, the aqueous ink fluid is converted to vapor form through heat and moved out of nozzle resulting in droplet form. Selective laser sintering uses

small particles (powder) of polymer, glass, or ceramic that is fused together by high power laser heat to form a 3D structure. In sheet lamination technology, the external force, heat and pressure is used to add material in layers. These layers are then cut into desired shapes with the help of laser or blade and a 3D structure is created.

The 3D printer as a valuable tool is used to create customized medications with tailored release profiles and changing the way patients take their medications. It could easily create polypill containing all the medication needed to cure chronic disease in 1 pill. The 3D printing in medical field has found to provide many benefits, such as customization and personalization of medical products, drugs, and equipment; advancement in release pattern, cost effectiveness, increased productivity and the democratization of design and manufacturing (Ventola, 2014). Moreover, 3D printing technologies may transform pharmacy practice by allowing medications to be truly individualized and tailored specifically to each patient, although technical and regulatory hurdles remain. Further study and use of 3D printing technology may offer an important benefit to patients who need medications that have narrow therapeutic indices or a higher predilection to be influenced by genetic polymorphisms. Pharmaceutical drug research and development could be improved drastically by 3D printing.

Possibilities with the 3D printing techniques

- 3D printing is applied in industries such as food, aerospace, automotive, jewelry, military, medical and dental.
- It is often used for rapid prototyping but within the aerospace industry it is used for actual production of final parts.
- The possibility to modify the design of a given part at will is a huge benefit for production.
- Within the pharmaceutical industry the ability to play with e.g. surface area and shape in general may provide interesting possibilities.
- 3D printing aka solid free-form technology (SFF), rapid prototyping (RP) and additive manufacturing (AM) (USFDA, 2014).
- 1986 Charles Hull field first stereolithographic patent alongside starting the company “3D systems” and developing the .STL file format.
- 1990 Fused deposition modeling (FDM) was developed by Scott Crump at Stratasys.
- 1993 MIT Professors Emanuel Sachs and Michael Cima patented first device named ”3D printer” that could print plastic, metal and ceramic parts.
- 3D printing enables more flexible manufacturing. Thus, may also enable more flexible manufacturing of pharmaceuticals. Aprecia Pharmaceuticals have recently received FDA approval for a 3D printed orally disintegrating tablet and have started production.

Benefits of 3D Printing Technology

1. Faster Production:

3D printing is quicker than conventional manufacturing including injection molds and subtractive production. Think the speed of a sports car versus the speed of a horse cart. Both will reach their destination, but the time difference is significantly huge. From a prototype to a final product, 3D printing tests ideas and designs quickly.

Faster design and prototype production mean more time to iterate the prototype

and find product market fit before competitors. 3D printing production takes just hours. Conversely, testing ideas and designs with conventional manufacturing methods can take up days, if not several weeks.

2. Easily Accessible:

3D printing has been around for decades, but it really did not take off until 2010. The explosion of 3D printing interests has brought easier to use software and hardware to consumers as more competition has entered the space.

3. Better Quality:

Traditional manufacturing methods can easily result in poor designs, and therefore poor-quality prototypes. Imagine a scenario where someone wants to bake a cake by combining all the ingredients together, mixing them up, and putting them in the oven to cook. If the elements did not mix well, the cake will have issues such as air bubbles or a failure to cook thoroughly. That is how subtractive, or injection molds can sometimes be. You are not assured of quality 100 percent of the time. 3D printing allows the step-by-step assembly of the object, which guarantees enhanced designs and eventually better-quality objects.

4. Tangible Design and Product Testing:

There's no way seeing a product on the screen or virtually can compare to the actual feel of a prototype. 3D printing offers that benefit. It is possible to experience the touch and feel of the product prototype to physically test it and find flaws in the design. If a problem is found, you can modify the CAD file and print out a new version by the next day.

5. Cost-effectiveness:

Labor costs play a huge role in determining the amount of money to be spent in developing a prototype. Traditional prototyping methodologies including production runs and injection mold are costly as they require a lot of human labor. Labor costs are also very high with conventional subtractive manufacturing. You need experienced machine operators and technicians to handle the production. Also, you must pay these laborers and use expensive machinery. With 3D printing, however, labor can be as little as one person issuing a print command.

6. Creative Designs and Customization Freedom:

Traditional manufacturing techniques are good at creating millions of copies of the same thing. It results in same dull and boring designs without the capacity to be improved much. Making each design unique with these techniques is extraordinarily hard.

3D printing allows for endless personalization, which makes it much simpler to accommodate personal touches that are requested from customers. Your imagination is the only limitation. You can make a crown that is precisely engineered to fit in someone's mouth for example. This cuts down on the number of visits that a patient needs to make sure they have a properly fitting crown.

7. Unlimited Shapes and Geometry:

Old methods of manufacturing rely on molds and cutting technologies to generate the desired shapes. Designing geometrically complex shapes can be hard and expensive with this technology. 3D

printing takes on this challenge with ease and there's not much the technology can't do with the proper support material.

8. Can Implement Assorted Raw Materials:

Product designers must keenly calculate their steps when it comes to materials to use with either subtractive or injection mold manufacturing. Mass manufacturing doesn't support the blending of raw materials as it can be expensive. Furthermore, combining chemical and physical elements is complicated. 3D printing easily accommodates a diverse range of raw material including glass, metal, paper, ceramics, biomaterial, silver, etc.

9. Less Waste Production:

CNC is cutting and injection molding result in a lot of wasted resources. Both involve the removal of materials from solid blocks. Unlike these two, 3D printing only uses material that is needed to create a prototype part – no more, no less. Additionally, reusing the materials from a 3D print is relatively straight forward. As a result, additive manufacturing creates very little waste, and saves a company a lot of money.

10. Risk Reduction:

When it comes to product manufacturing, a good designer knows that proper design verification is crucial before investing in an expensive molding tool. 3D printing technology enables product designers to verify product prototypes before starting out on substantial manufacturing investments that can sometimes be disastrous.

3D printing enables you to turn a concept into reality faster than you can imagine. Products are built quickly and cheaply. The technology will no doubt continue to transform every industry, changing the way we work and live in future (Katakam et al., 2015).

Disadvantages

1. **Decrease in Manufacturing Jobs**: The decreases in manufacturing jobs will greatly affect the economy of countries that rely on many low skill jobs.

2. **Limited Size:** The size of objects created with 3d printers is currently limited however, soon; large items such as architectural structures can be created using 3d printing.

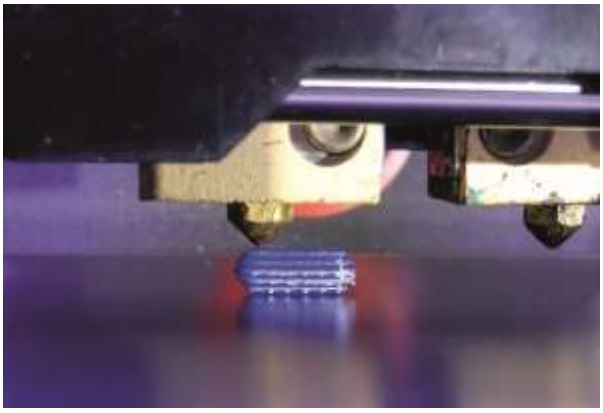
3. **Limited Raw Materials:** Traditional manufacturing of products has an enormous range of raw materials that can be used. Presently 3d printers can work up to approximately 100 different raw materials and creating products that uses moreraw materials are still under development.

4. **Violation of Copyrights:** The biggest disadvantage of 3d printing is Counterfeiting. Anyone who gets a hold of a blueprint will be able to counterfeit products easily. It will become more common and tracing the source of the counterfeited items will be nearly impossible. Many copyright holders will have a hard time protecting their rights and businesses producing unique products will suffer.

5. **Production of Dangerous Items:** With 3d printers, plastic knives, guns and any other hazardous objects can be created. It makes easier for terrorists and criminals bring a weapon without being detected (Buanz et al., 2011).

6.

3D printing: the future of manufacturing medicine?



Imagine a pediatrician talking to a four-year-old child who is having trouble adjusting to taking daily doses of steroids after being diagnosed with Duchene muscular dystrophy the previous month. "What's your favorite animal?" she asks. "A zebra," quietly replies the child, who we will call Sam. The pediatrician smiles as she makes a note on her office computer. "But not a black and white one, a blue and green one," adds Sam, with a little more confidence. Later, the toddler watches with wide eyes as the uniquely coloured, zebra-like tablets appear from a three-dimensional (3D) printer in the hospital pharmacy.

This story may sound far-fetched, but 3D printing promises a future of drugs printed on demand, to custom doses, and the possibility that cost may no longer be a barrier to making niche medicines. And children could be among the patients to benefit most.

"This technology could revolutionize the way we look at children's medicines, both in terms of what they take and the ability to keep changing the dose as they grow," says Steve Tomlin, consultant pharmacist at Evelina London Children's Hospital, UK. Having a 3D printer in a hospital pharmacy could make weekly medication changes simple, personalized, and even fun (Melendez et al., 2008).

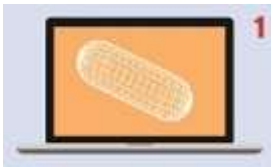
A 3D printer works by adding materials layer by layer until a 3D shape emerges. So far, different 'inks' have been used to print everything from pizza to heart valves. If a 3D printer ink that is laced with a drug can be developed, then why not print tablets as well?

This is an idea that has caught the imagination of several academics and pharmaceutical companies, who are aiming to develop not just the technology, but the quality control needed to bring 3D printing to pharmacies.

"The potential of 3D printing is about being able to deliver what you want when you want," says engineer Ricky Wildman from University of Nottingham in the UK. Wildman is trying to find the right materials that can be used as inks to make tablets with varying doses of drugs. Wildman is looking at inkjet 3D printing. Picture that familiar clunky printer that sits in your office or study and squirts out different coloured inks to print your photographs. Well Wildman has replaced coloured inks with polymers, drugs and other materials used in pill manufacture. The tablet is then printed layer by layer, by squirting out these ingredients into the desired shape and letting them set.

Wildman is looking closely at the materials he prints with. "In inkjet we're exploring the way you can create suspensions and liquid-based materials that can be triggered to make solids," he says. But he acknowledges that real-world applications are some years off, perhaps 5, 10 or even 15 years hence (Melendez et al., 2008).

How does 3D Printing works?



1.An original idea is designed using a digital modeling programme such as CAD or animation modeling software.

2. Once the designed is completed, the file is sent to the 3D printer. The 3D printer makes passes over build plate, depositing layer upon layer of material to create the finished product.

A. Filament guide tube: The material, in this case a blend of polymer and drug is fed through the tube.

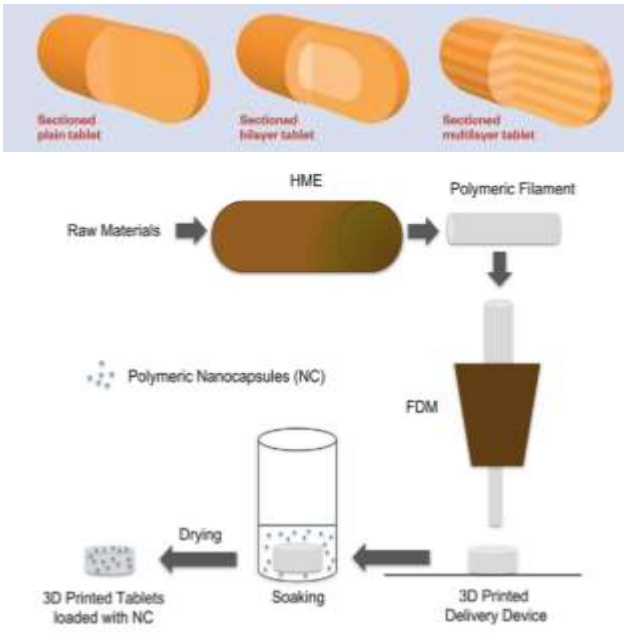
B. Extruder: Melts the drug polymer tube.

C. Gantry: Allows the extruder to move from side to side and front to back.

D. Extrusion nozzle: Molten filament is fed through the nozzle.

E. Moves down once each layer is finished, thus helping the nozzle build additional layers.

3. The different layers are fused throughout the process to create a single 3D object.



(Schematic represent of the proposed process to prepare 3D printed tablets loaded with polymeric Nano capsule. HEM: Hot melt extrusion, FDM: Fused deposition molding)

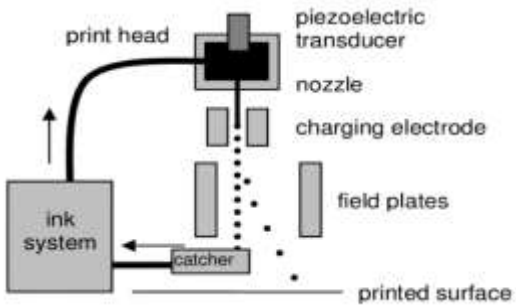
Classification of 3D printing

1. Inkjet printing method:

In this method, combination of active pharmaceutical ingredients and excipients are precisely sprayed on the substrate in the form of droplets based on two techniques, that is, continuous and drop on demand. In continuous jet printing, the stream of droplets is continuously sprayed on the substrate or deviated towards the waste line when not in use. However, in drop on demand method, the required number of droplets are sprayed on the substrate and closed when not in need. This makes it more useful and prevents wastage that cannot be obtained in continuous jet printing [9]. Inkjet printing was used to fabricate controlled release tablet of felodipine as hypertensive and polyvinyl pyrrolidine as an excipient (USFDA, 2014).

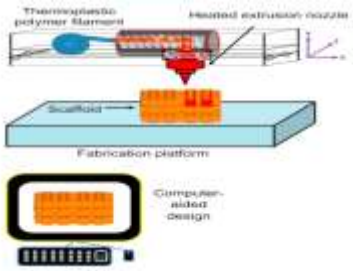
2. Fused deposition method:

FDM was the technique patented by Scott Crup, co-founder of Stratasy ltd and was



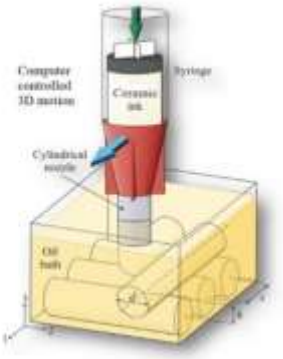
developed due to the limitations found in inkjet printing. This involves the melting of the raw material or polymers, extrusion and layer by layer deposition. Then the material is solidified, and the desired object is formed. The shape and pore size of the object can be varied by varying the raster thickness, angle, space between raster and rheological properties [52]. This method can be used for manufacturing solid dosage forms such as zero

order release tablets, multi layered tablets, fast dissolving tablets. Fused deposition modeling technique was used to fabricate a tablet of prednisolone loaded poly vinyl alcohol (PVA) filaments with extended release (USFDA, 2014).



3. Direct inkjet writing method:

Direct inkjet writing helps in designing a complex 3D shaped tablet or any other object without the need of any expensive equipment or tooling. This gives finer sized structures and shapes. This method acquires a computer-controlled stage, in which a pattern generated device or ink deposition nozzle moves to create product with controlled 3D shapes and size. Various ink designs are employed in direct writing technique such as colloidal suspension, gels, waxes, dilute fluids, polymer melts etc. These inks are then solidified by either of following methods: liquid evaporation, gelation or solvent and temperature phase changes (Gibson et al., 2015).

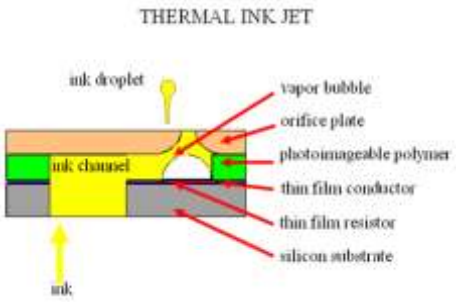


4. Zip dose method:

This technique was developed by MIT in late 1980's. In this method aqueous fluid is used to bind the layers of powder together. This technique is used for formulating a tablet with high dose and rapid disintegration [53]. In this process, a layer of powder is deposited as a substrate and a liquid or binding fluid is applied to form interaction between the powder and liquid binder. This process is repeated several times, until desired product of optimal size and shape is produced. This leads to formation of highly porous dosage form and with high drug loading.

5. Thermal inkjet printing method:

This type of printers has a resistor that produces heat when current is induced, this heat, heats up the aqueous ink fluid which converts it into vapour form that moves out of a nozzle resulting in droplet form. This technique requires high temperature that may degrade the heat sensitive material. So, this factor reduces its pharmaceutical applications [54,55]. Since 2010, the American Society for Testing and Materials (ASTM) group ―ASTM F42–Additive Manufacturing, developed précised set of standards to classify the Additive Manufacturing processes into different categories (Marzuka and Kulsum, 2016).



6. Binder deposition method:

In this process, the inkjet printers spray formulation of drug or binder onto the powder bed in the form of small droplets at optimum speed. The liquid formulation is the binder which is available in the printer whereas the API and excipients are the powder bed. The API in the form of solution or suspension can also be jetted onto the powder bed (Centers for Disease Control and Prevention, 2015).

7. Material jetting method:

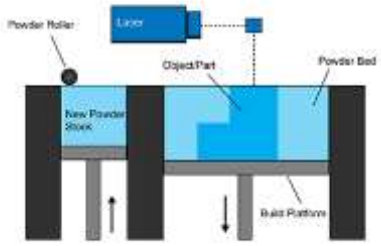
A liquid formulation containing polymers, solution, suspension or UV curable resins can be jetted from the printer that solidifies rapidly and provides product geometry. It has 100 mm droplet size that gave it more resolution. The researchers have adopted this technology to make micro particles for drug delivery system (Schubert et al., 2014).

8. Extrusion method:

Material is extruded from the automated nozzle onto the substrate. As in powder bed deposition, it does not have powder bed and require higher support material. The materials that can be extruded are molten polymers, suspensions, semisolids, pastes (Marzuka and Kulsum, 2016).

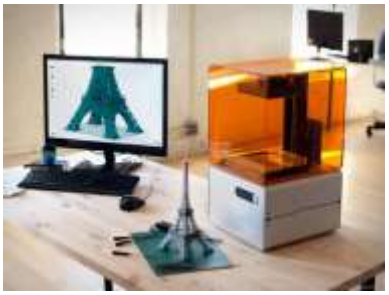
9. Powder bed fusion method:

As the name indicates, it involves the fusion or binding of low melting point with high melting point binders. The laser beam supplies the heat required for the binding. It is a rapid process, but comparatively more complex than extrusion method (Sandler et al., 2014).



10. Photo polymerization method:

It includes the polymerisation reaction between the liquid resins on exposure to UV or high energy light source. It requires photopolymerizable raw material for pharmaceutical manufacturing. An example of drug delivery application is 3D printing of photopolymerizable hydrogels (Sandler et al., 2014).

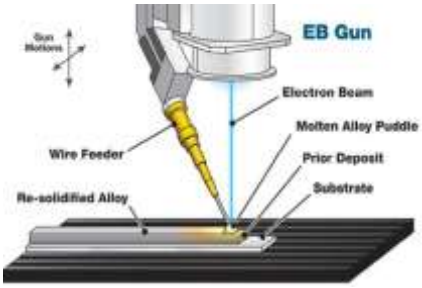


11. Pen based 3DP method:

In this process, the layer by layer assembly is manually controlled with hand held device (Masood, 2007).

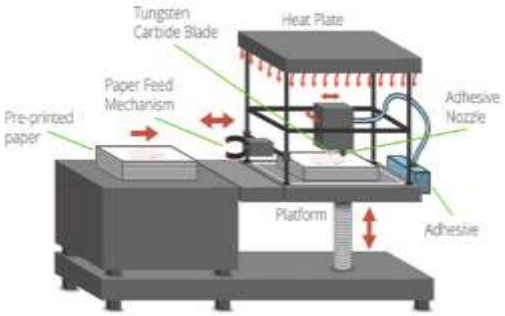
12. Direct energy deposition method:

In this process the raw materials are melted by a laser or electron beam energy sources as they are deposited. This method uses the material that cannot be extruded such as powder or other raw materials (Masood, 2007).



13. Sheet lamination method:

It is an automated laser-cutting and sheet-by-sheet assembly of products. This process is



quick and inexpensive although it has low-resolution and more useful than most printing methods(Masood, 2007).

Resolving drug manufacture using 3D printing

Fabrication of various novel drug delivery systems using 3D printers

Drug delivery refers to delivery of a pharmaceutical active ingredient (API) in the body or at the site of action to achieve its desired therapeutic effect. The idea of drug delivery has greatly progressed over the years from conventional dosage forms to novel target drug delivery systems (Water et al., 2015). Therefore, the conventional method like direct tableting are now progressively evolved towards multi-step manufacturing technologies, including granulation, extrusion or coating processes, to allow the development of controlled-release systems. Now-a day's novel concepts of formulation have emerged (e.g., nano-scale medicines, biomimetic particles, functionalized liposomes) as well as more sophisticated manufacturing methods (Melocchi et al., 2015; Goyanes et al., 2015). Thus, 3D printing process naturally appeared to be an essential tool in research and development area to fit with actual industrial directions of reducing both time and costs in the early stage of a novel manufacturing concept, reducing the inherent risk of new development to fail at later stages (Goyanes et al., 2014; Goyanes et al., 2015). 3D printing in pharmaceutical industry represents a well-designed tool for designing simple, accurate, cheap, structured and tailored drug delivery systems (Genina et al., 2016). This flexibility can offer many novel strategic approaches for the research and development of controlled-release drug delivery systems (Buanz et al., 2014). In the last 15 years (**Table I**), a large variety of 3D printing techniques have been introduced into the rapid prototyping (RP) industry (Scoutaris et al., 2011).

Challenges and future of 3D printing in pharmaceutical sector

We already discussed about the possibilities and technological challenges presented by different 3D printing technologies, during the formulation of various dosage forms, to this day. However, for 3D printing to thrive well in

pharmaceutical sector, various other issues need to be addressed. Some of the issues like quality control of printed dosage forms, legal and regulatory matters, cost-effectiveness, availability of materials and equipment needed to produce medicine of better quality, if solved in future, would ascertain the success of the 3D printing in this area.

Table I: Fabrication of dosage forms by 3D printing technology

3D printing	Dosage form	Drug
FDM	Catheter	Nitrofurantoin
FDM	Implant CR	Dye
FDM	General Device	Gentamicin sulphate, Methotrexate
FDM	Implant	Nitrofurantoin, Hydroxyapatite
FDM	Tablet ER	Prednisolone
FDM	Tablet MR	Acetaminophen
FDM	Capsule-shaped tablets	Budesonide
FDM	Capsules IR, MR	Acetaminophen, Furosemide
FDM	Tablet (IR, SR)	Pravastatin, Atenolol, Ramipril, Aspirin, Hydrochlorothiazide
FDM	Tablet	Fluorescein
FDM	Tablet (MR)	5-aminosalicylic acid and 4-aminosalicylic acid
FDM	T-shaped (IU, SC rods)	Indomethacin
FDM	Tablets (IR)	5-Aminosalicylic acid, Captopril, Theophylline and Prednisolone
Thermal Inkjet printer	Tablet	Prednisolone
Inkjet Printing	Implant	Levofloxacin
Thermal inkjet printer	Solution	Salbutamol
Inkjet printing	nanoparticles	Rifampicin
Thermal inkjet printer	Solid dispersion	Felodipine
Thermal inkjet printer	Nano suspension	Folic acid

Desktop 3D printer	Tablet	Guaifenesin
A lab-scale 3DP machine	Capsule	Pseudoephedrine HCl
3DP	Tablet	Acetaminophen
3DP	Multi-drug implant	Rifampicin, Ionized
Extrusion printing	Tablet	Captopril, Nifedipine, Glipizide
3D printer	Micro fluidic pump	Saline solution
3D printer	Fast disintegrating	Paracetamol
Electro hydrodynamic atomization technique	Patterned micron scaled structures	Tetracycline hydrochloride
Stereolithography 3DP	Tablets (MR)	4-aminosalicylic acid and Paracetamol
3D printer	Capsule-shaped solid devices	Acetaminophen and Caffeine
3D printer	Biodegradable patch	5-Fluorouracil
3D printer	Microporousbioceramics	Tetracycline, Vancomycin, Ofloxacin
3D printer	Oral pulsatile tablet	Chlorpheniramine maleate, Diclofenac sodium
Extrusion printer	Drug encapsulated film of PLGA and PVA	Dexamethasone
Stereolithography printer	Anti-acne patch	Salicylic acid
3D printer	Tablets	Paracetamol
Piezoelectric inkjet printer	Micro particles	Paclitaxel

Concerns regarding quality control and regulatory issues

The first and foremost dispute regarding the application of 3D printing technology might be the concerns regarding quality control. Even though various studies have proven the feasibility of production of different dosage forms, regulatory requirements could be an obstacle to be cleared. FDA has already accepted the use of 3D printing in production of medical devices with about 200 FDA-approved 3D-printed devices available that can be tailored to fit a patient's anatomy. A workshop entitled “Additive Manufacturing of Medical Devices: An Interactive Discussion on the Technical Considerations of 3D Printing” was held by FDA to discuss about optimal characterization and assessment methods for the final finished devices, as well as optimal

process validation and acceptance methods for these devices. As a result, FDA developed guidance for industry and food and drug administration staffs which was broadly organized into two topic areas: Design and Manufacturing Considerations and Device Testing Considerations (Chia et al., 2015; Goole and Amighi, 2016). Also, FDA has recently approved the 3D printed solid dosage form for the treatment of epilepsy. However, 3D printing is quite different from the conventional manufacturing processes, and hence, the quality control process should also be different. As such, concerns regarding critical parameters affecting the printability of various materials into drug products, critical process parameters for various printing technologies, assessment of the performance of 3D printed drug products, proper *in-vitro* release study procedure, sterilization issues, critical characteristics of intermediate products such as filaments, inkjets, and photopolymers, etc. still exists. To address these concerns the Office of Testing and Research (OTR) in Center for Drug Evaluation and Research (CDER)'s Office of Pharmaceutical Quality is conducting research to further understand the application of this technology to drug products. Proper analysis techniques and parameters, from the design of the dosage forms to the finished products, should be developed. Owing to the numerous benefits of additive manufacturing in the pharmaceutical sector in terms of precision medicine and reduction of conventional manufacturing constraints, development of proper quality control for 3D-printed products seems like the next step.

CONCLUSION

3D printing technology is a growing trend towards advanced drug delivery. This technology has the built-in flexibility of personalized and customized medicines. Moreover, it may transform the conventional pharmacy practice by allowing medications to be truly individualized to a patient. Furthermore, it enables preparation of dosage forms with accurate dose, shape and size control. It can be assumed that in coming era 3DP can revolutionize the manufacturing processes of pharmaceutical formulations with improved safety and efficacy.

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