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Review Article

3D PRINTING FOR THE FUTURE OF PHARMACEUTICALS DOSAGES FORMS

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ABSTRACT

With the rapid pace of development in industrial sector, the pharma sector and researchers involved are equally contributing in developing the latest technology for the growth and development. The computer-aided designs and manufacturing that provides 3 Dimensional printed dosage forms is the new step being taken into consideration. With the FDA approval to first 3D printed tablet in August 2015, Spritam, 3 Dimensional printing (3DP) has become the all new method for preparation of drug delivery system. 3D printing has the capability of dispensing the drug more accurately, precisely, and the layer by layer assembly helps in forming complex composition and geometries. 3D printing enables the preparation of personalised dosage form and tailored release profiles. 3D printing can be seen as future of solid dosage forms produced on demand, with customised dose and possibly lower in cost. It can help in reducing side effects caused by excessive doses. This review highlights the 3D printing technology and its applications in growth of pharmaceutical sector. An overview of reviews was conducted to locate published literature between 2000 and 2017.

Keywords: 3D, Computer aided design, FDM, Spritam, FDA

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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 [1]. The most renowned, distinct and novel solid dosage forms have been found to be fabricated by variety of three-dimensional printing (3DP) technologies [2-4]. 3DP or additive manufacturing (AM) is a process of making three dimensional solid objects from a digital file [5]. 3DP is unique and powerful technology that was first described by Charles Hull in 1986 and called it as "stereolithography" [6]. It uses ".stl file format" to interpret the data in Computer Aided Design file. These data instructions are then electronically communicated to the 3D printer [7]. These instructions include the shape, size, texture, thickness of the object to be printed [8]. 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 [5]. 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) and was issued in 1992 [9]. 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 utilising DLP technology "B9Creator" was introduced. In same year, Form 1 was introduced utilising stereolithography [10]. 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 [12]. 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 [11]. In December 2015, the FDA had approved more than 85 3D-printed medical devices [12]. Moreover, FDA also granted approval to first 3D printed tablet, Spritam (levetiracetam), manufactured by Aprecia Pharmaceuticals in 2015 [13]. 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 [9].

3DP is a layer-by-layer process capable of producing 3D drug products from digital design [14]. 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 [15]. 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 [6]. 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) [16]. 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 [17-21]. Some of the highly complex structures incorporating living cells can be created by this technique and has gained popularity and applicability in cancer treatment [22-25].

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 [26-31]. Conventional methods for designing the dosage form for drug delivery includes multiple manufacturing steps such as granulation, extrusion or coating [32]. However, with rise in market novel manufacturing technologies such as nano, micro-scale medicines, biomimetic particles, systemised liposomes, niosomes have emerged to be successful in saving cost and time [33-35]. Thus, 3D printing naturally appeared to be an important tool in fulfilling the current requirements of the industry [36-38]. 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 [39-43]. Various technologies are used for 3D printing in drug dosage form development [16]. These technologies are: Inkjet printing, Fused deposition modelling, Stereolithography (SLA), Direct energy deposition, Direct write, Zip dose, Thermal inkjet, Selective laser sintering [44]. 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 [10]. Stereolithography is the technique in which a computer controlled laser beam is used to solidify the liquid polymer or resin, thereby creating 3D structure. [44] 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 [45]. 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 [46]. 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 vapour 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 customised 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 [4]. 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.

Historical journey of 3D printing

In 1996, the very first experiment was conducted on 3D pharming by printing multi delivery device. Methylene blue and alizarin yellow dyes were positioned in the 3D form in the device; its microstructure and composition were manipulated and was made controlled release. A square pattern of polyethylene oxide (PEO) was printed and dyes were localised in the square. A top and bottom sheet of Poly caprolactone was printed to seal it and prevent diffusion. This device showed a multiphasic release profile of dyes [13].

The drug release of tablet (3D printed) can be manipulated by changing the chemical properties and composition of binder. A cationic methacrylic ester (Eudragit E-100) was used to fabricate cellulose tablets. Eudragit RLPO was used to formulate tablets of controlled release profiles. It was noted that the increase in binder concentration within tablet increased the drug release time which was demonstrated by dissolution studies in stimulated intestinal fluid. The hardness and friability of the 3D printed tablet were comparable to commercially available compressed tablets [6]. E-100 and Eudragit RLPO were used as binder to fabricate chlorpheniramine to make immediate-extended release tablet respectively. The immediate release (IR) section delivered the drug within the first 30 min of dissolution process. The extended release (ER) section delivered the drug for a period of 6 h.

A diclofenac tablet was designed consisting of 2 sections with varied binders in both sections. First section was fabricated using E-100 which is sensitive to the low pH found in gastric fluid and release within stomach whereas Eudragit L-100 which is sensitive to pH values above 6 and release within intestinal fluid [9]. Endoephedrine hydrochloride was used to fabricate cubic drug delivery devices with a near zero controlled release profile. The device consisted of hydroxypropyl methyl cellulose (HPMC) and Kollidon SR as main materials, 15% triethyl citrate solution as shell portion in ethanol as binder and 50% by weight of Pseudoephedrine HCl was printed in the inner cubic core. The drug released by diffusion of drug present in inner core. Active ingredient 68% of acetaminophen and main excipients were pre-mixed in the powder bed. Further, a top and bottom of the cylindrical device was printed with insoluble layers to achieve zero order release [9]. Fast dissolving tablet were prepared with compact layers at the top, bottom and lateral layers and loose powder with binder inside the pill to increase the stability of the pill. The disintegration time was found to be 23.4 s and *in vitro* dissolution showed release within 2 min [47].

Extrusion 3D printing concept was used to fabricate tablet containing Guaifenesin as expectorant. The tablet contained HPMC 2910 as binder, microcrystalline cellulose and sodium starch glycolate as disintegrant in one portion and make it immediate release compartment. The other portion of tablet consisted of HPMC 2208 and poly acrylic acid as hydrophilic matrix processed separately and active ingredient was combined to form 2 viscous pastes used as feedstock. This portion was achieved as sustained release compartment [9]. Furthermore, a multiple drug release profile tablet was formulated in which three different drugs: captopril, nifedipine and glipizide were used to formulate the tablet. The formulation was evaluated for dissolution and it was found that captopril showed zero order release of an osmotic pump whereas, nifedipine and glipizide showed either first order release or Korsmeyer-Peppas release kinetics depending on the active/excipient ratio used [6].

Classification of 3D printing

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 are continuously sprayed on the substrate or deviated towards the waste line when not in use. However, in drop on demand method, the required amount 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 [6].

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 [48]. This method can be used for manufacturing solid dosage forms such as zero order release tablets, multi layered tablets, fast dissolving tablets. Fused deposition modelling technique was used to fabricate a tablet of

prednisolone loaded poly vinyl alcohol (PVA) filaments with extended release [6].

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 [46].

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 [49]. 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.

Thermal inkjet printing method

This type of printers have 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 [50, 51]. 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 [5]. These are as follows:

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 [52].

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 [10].

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 [5].

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 [52].

Photo polymerisation 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 [52].

Pen based 3DP method

In this process, the layer by layer assembly is manually controlled with hand held device [53].

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 [53].

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 [53].

Pharmaceutical potentials of 3D printing

The processes that are traditionally adopted by pharmaceutical industries such as milling, mixing, granulation and compression sometimes results in uneven qualities of the final products depending on the factors such as drug loading, drug release, drug stability and pharmaceutical dosage form stability. On the other hand, 3D printing, as a powerful tool technology, has competitive advantages such as improved R and D productivity, improved safety, efficacy and accessibility of medicine [5]. The major advantages of 3D printing that makes it much more attracting are:

Personalised medication

Some patients respond differently to same drugs. 3DP could help the physician or the pharmacist to produce the optimal dose of medication as per their age, race and gender. Furthermore, it allows the formation of single pill containing layers of multiple ailments that the patients need for the treatment [4].

Tailored medication

3D printing allows the production of medication as per the required needs of the patients. In case of pediatrics dose, the range of dose may vary and hence, this method can be easily adopted. Similarly, the shape of the dosage form can be altered for the patients with swallowing difficulties. 3DP is highly flexible and simple method to change the shape and size of the dosage form [54].

Create complex shapes

3DP allows formations of complex shapes and that too with accurate dose of medication or API, even as low as 10-12 mole tablets which helps in reducing the side effects that are seen due to excessive doses. As compared to conventional methods where complex geometries were not possible it can be achieved easily by 3D printing. Similarly, different shapes and sizes also results in different release profile. Complex shapes results in modified release, adjust drug loading and mask the taste of the medication [54].

Sustained release

Drug release can be easily controlled and targeted by 3D printing. It can be adopted by printing a binder in the layers of the matrix powder. This creates a barrier between the layers of API and allows variation in release profile.

Unique dosage form

In pharmaceutical production process, 3D printing can be used to create unique and limitless dosage forms. 3DP is used to create novel dosage forms [55].

Mini dispenser unit

The set up for 3D printers require minimal space allowing them to fit in any environment, are cost effective. 3D printing is a computer aided design that means it can be controlled using computer software and network. Moreover, 3D printing technologies allows individualization of medication. These characteristics allows 3D printer to function as a mini-dispenser to potentially bring tablet manufacturing closer to patients [54].

Integrated with health care network

Physicians and pharmacists can modify the next dose or drug combinations according to patient's need. As 3D printers are remotely controlled, 3D printing can became easily accessible to the patients. Hence, this improves the patients' compliance and shortens the time of clinical response to patient's needs [54].

Accelerated disintegration

3D printing makes a huge difference with powder compression in terms of disintegration process. The pattern of powder aggregation is different in both the conventional and newer method. In 3D printing powder binding strength is higher in the periphery and lowers in the centre which leads to rapid disintegration of tablets. Aprecia's Zip Dose® has found to disintegrate in less than 10s whilst containing a high dose of piracetam (1000 mg) [54].

Tool less

3DP can eliminate the need for tool production and therefore, reduced cost, lead time and labour associated with it.

Sustainable/eco friendly

3D printing being a new and emerging technology is energy-efficient and provides environmental efficiencies. It utilises up to 90% of standard materials, and, therefore, creates less waste. It has stronger design that imposes a reduced carbon footprint compared with traditionally manufactured products.

Short production time

3D printers are time efficient which shortens the product development design cycles.

Manufacturing process

The manufacturing process is quite easier and cost effective. The time of processing is less due to improved tools, less waste and takes fewer steps to assemble the setup and also reduce lead time via functional integration of parts.

Engineering and maintenance

3D printers have more flexible set up and maintenance processes. It is cost-efficient industrial engineering.

Logistic

3D printing is promising tool whereby products can be manufactured on demand and place where needed which reduces the inventory and logistics handling and moreover the transportation and related costs [5].

Table 1: Fabrication of dosage forms by 3D printing technology

3D printing	Dosage form	Drug	Reference
FDM	Catheter	Nitrofurantoin	[56]
FDM	Implant CR	Dye	[57]
FDM	General Device	Gentamicin sulphate, Methotrexate	[58]
FDM	Implant	Nitrofurantoin, Hydroxyapatite	[59]
FDM	Tablet ER	Prednisolone	[5]
FDM	Tablet MR	Acetaminophen	[60]
FDM	Capsule-shaped tablets	Budesonide	[61]
FDM	Capsules IR, MR	Acetaminophen, Furosemide	[6]
FDM	Tablet (IR, SR)	Pravastatin, Atenolol, Ramipril, Aspirin, Hydrochlorothiazide	[62]
FDM	Tablet	Fluorescein	[63]
FDM	Tablet (MR)	5-aminosalicylic acid and 4-aminosalicylic acid	[64]
FDM	T-shaped (IU, SC rods)	Indomethacin	[65]
FDM	Tablets (IR)	5-Aminosalicylic acid, Captopril, Theophylline and Prednisolone	[66]
Thermal Inkjet printer	Tablet	Prednisolone	[67]
Inkjet Printing	Implant	Levofloxacin	[55]
Thermal inkjet printer	Solution	Salbutamol	[68]
Inkjet printing	nanoparticles	Rifampicin	[69]
Thermal inkjet printer	Solid dispersion	Felodipine	[70]
Thermal inkjet printer	Nano suspension	Folic acid	[71]
Desktop 3D printer	Tablet	Guaifenesin	[72]
A lab-scale 3DP machine	Capsule	Pseudoephedrine HCl	[5]
3DP	Tablet	Acetaminophen	[73]
3DP	Multi-drug implant	Rifampicin, Isoniazid	[5]
Extrusion printing	Tablet	Captopril, Nifedipine, Glipizide	[40]
3D printer	Microfluidic pump	Saline solution	[74]
3D printer	Fast-disintegrating	Paracetamol	[75]
Electro hydrodynamic atomization technique	Patterned micron scaled structures	Tetracycline hydrochloride	[76]
Stereolithography 3DP	Tablets (MR)	4-aminosalicylic acid and Paracetamol	[77]
3D printer	Capsule-shaped solid devices	Acetaminophen and Caffeine	[78]
3D printer	Biodegradable patch	5-Fluorouracil	[79]
3D printer	Microporous bioceramics	Tetracycline, Vancomycin, Ofloxacin	[80]
3D printer	Oral pulsatile tablet	Chlorpheniramine maleate, Diclofenac sodium	[81]
Extrusion printer	Drug encapsulated film of PLGA and PVA	Dexamethasone	[82]
Stereolithography printer	Anti-acne patch	Salicylic acid	[83]
3D printer	Tablets	Paracetamol	[84]
Piezoelectric inkjet printer	Microparticles	Paclitaxel	[85]

CR-controlled release, IR-immediate release, MR-modified release, ER-extended release, IU-Intrauterine, SC-Subcutaneous

Worldwide: USA-FDA approved 3D printed drug product

In August 2015, Aprecia pharmaceuticals introduced the first drug product using the ZipDose technique for the treatment of epilepsy. FDA approved the drug product SPRITAM levetiracetam for oral use for the treatment of partial seizures, primary generalized tonic clonic seizures, myoclonic seizures in adults and children. Spritam was formulated by ZipDose technology that produced a porous formulation that disintegrates rapidly. Spritam was designed to fill the needs of the patients who have problems with the current medication therapy. ZipDose technology enables the incorporation of large doses upto 1000 mg in single dosage form. This technology enhanced the patient compliance by easy administration of drug. ZipDose technology combines the drug formulation science with unique manufacturing capabilities of 3D printing. Aprecia pharmaceuticals have the FDA approved licence for developing the pharmaceutical dosage form worldwide [10].

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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AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

Declared none

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