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REVIEW ARTICLES

3D Printing Technology in Pharmaceutical Delivery System: Recent Advancement in Innovative Approach

Nupur ANAND[*], Disha SINGH[**], Gurjeet SINGH[***], Lakhvir KAUR[****°], R.K DHAWAN[*****] and Narinder KAUR[******]

3D Printing Technology in Pharmaceutical Delivery System: Recent Advancement in Innovative Approach

SUMMARY

Three dimensional printing is an innovative and novel technology based on the use of computer aided drug designing to attain astonishing pharmaceutical products for its better delivery. This three dimensional printing is considered as a holistic approach in the pharmaceutical field. It has proved to be beneficial in engineering of medications, tissues, organs as well as in the modelling of the disease. The use of this technology has surged drastically and now has extended its roots in the areas of manufacturing, production, prototype formation and fabrication of drugs. A superior sustained release and the targeting effect of the medication can also be achieved easily by three dimensional printing. In this review, complete information has been gathered based on the history, use of newer technologies, materials, techniques involved in three-dimensional printing and recent advancements.

Key Words: *Three dimensional printing, drug delivery, Inkjet printing, Hot melt extrusion, Digital light processing, Stereolithography*

Farmasötik Taşıyıcı Sistemlerde 3B Baskı Teknolojisi: Yenilikçi Yaklaşımda Son Gelişmeler

ÖZ

Üç boyutlu baskı, daha iyi ilaç taşıyıcı sistemler sağlayan farmasötik ürünler elde etmek için bilgisayar destekli ilaç tasarımının kullanımına dayanan yenilikçi ve yeni bir teknolojidir. Bu üç boyutlu baskı, farmasötik alanda bütünsel bir yaklaşım olarak kabul edilir. İlaç, doku, organ mühendisliğinin yanı sıra hastalığın modellemesinde de yararlı olduğu kanıtlanmıştır. Bu teknolojinin kullanımı büyük ölçüde artmıştır ve günümüzde ilaç oluşturulması, üretimi, prototip oluşturma ve fabrikasyonu alanlarında köklerini geliştirmektedir. İlacın yüksek bir bir sürekli salım ve hedefleme etkisi de üç boyutlu baskı ile kolayca elde edilebilir. Bu derlemede, üç boyutlu baskı tarihçesi, kullanılan yeni teknolojileri, malzemeleri, geliştirilen yeni teknikler ve son gelişmeleri temel alarak bütünlükçü bir bilgi verecek şekilde derlenmiştir.

Anahtar kelimeler: *Üç boyutlu baskı, ilaç taşıyıcı sistemler, Mürekkep püskürtmeli baskı, Sıcak eriyik ekstrüzyon, Dijital ışık işleme, Stereolitografi*

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[*] ORCID: 0000-0003-2612-3212, Department of Pharmaceutics, Khalsa College of Pharmacy, Amritsar, Punjab, India
[**] ORCID: 0000-0002-5120-4148, Department of Pharmaceutics, Khalsa College of Pharmacy, Amritsar, Punjab, India
[***] ORCID: 0000-0003-4399-4693, Department of Pharmaceutics, Khalsa College of Pharmacy, Amritsar, Punjab, India
[****] ORCID: 0000-0001-8091-2365, Department of Pharmaceutics, Khalsa College of Pharmacy, Amritsar, Punjab, India
[*****] ORCID: 0000-0001-5130-327X, Department of Pharmacology, Khalsa College of Pharmacy, Amritsar, Punjab, India
[******] ORCID: 0000-0002-3465-4286, Department of Pharmaceutical Chemistry, Khalsa College of Pharmacy, Amritsar, Punjab, India

[°] Corresponding Author: Lakhvir KAUR
e-mail: lakhvir86@gmail.com

INTRODUCTION

The concept of the delivery of the drug has highly shifted over the years from conventional oral dosage form towards the targeted release of the drug. A constant motivation is on the ascent, for the empowerment towards the designing of the drug, knowledge of material properties, manufacturing and processing of pharmaceutical dosage forms using a novel approach. Physicochemical and biopharmaceutical properties of the active ingredient as well as auxiliary substances needs to be considered before the development of a dosage form (Jamroz et al., 2018). An increased attention is being received by personalized medicines and the dose of the drug to be administered due to their elevated chances of adverse effects. During the manufacturing of pharmaceuticals for the population, geriatrics and paediatrics have a high probability to exhibit adverse reactions (Jose and Christoper, 2018). In the last few decades, the focus has highly been shifted towards the personalization of the medicines. Advancements in the novel dosage forms and technologies have risen to a considerable extent. Three dimensional printing (3DP) is considered to be a highly revolutionized, versatile and powerful technology so as to mark its steps towards the novelty in the pharmaceutical field. It is highly helpful in engineering of medications, tissues and organs as well as in the modelling of the disease (Agrawal and Gupta, 2019).

The 3DP depends on computer aided designing to attain flexibility, reduced efforts and time and extraordinary manufacturing of pharmaceutical products (Jassim-Jaboori and Oyewumi, 2015). Its principle is formation of layers to develop three a dimensional object using digital designs. The convergence of chemistry, optics and robotics led to the formation of this technology and facilitated the prototype formation obtained from UV-cured resins. 3DP has gained popularity due to approval of orally administered Spritam medication by the FDA in 2015 for the treatment of partial seizures, which was produced using the process layer-by-layer formation. Since then the research over 3DP has reached new heights (Norman et al., 2017). A fascinating research on the development of responsive shell capsules using the technique of 3DP was conducted by Gupta et al., 2015, which works from the stimulus obtained that would result in releasing the loaded substance of the shell to the desired site (Gupta et al., 2015). Accessibility of 3DP for public and industrial use has surged drastically. Global sales of the 3D printed materials have surged to more than 33%, raising the turnover to $4.1 billion until 2014 (Maulvi et al., 2017). The 3DP technology works in a similar manner to that of an "ink-jet" printer to design a three dimensional product in layers (Weigang et al., 2009). According to International Standard Organization, 3DP can be defined as: "fabrication of objects through the deposition of a material using a print head, nozzle, or another printer technology". Apart from the formative and subtractive methodology, additive manufacturing (AM) is one of the various methods for the layer-by-layer 3D modelling of the data. Rapid prototyping is the practical approach for AM and is highly advantageous due to its cost efficiency, reduced time, ease of product modification, small object manufacturing, personalized products and formation of structures that cannot be formed by using subtractive techniques (Jamroz et al., 2018). 3DP will attract a lot of attention in the upcoming era towards the development of solid dosage form. Solid dosage forms are highly popular due to a load of factors like painless delivery, ease of manufacturing, accuracy in dosing as well as patient compliance. But due to multi-step processing of the solid dosage forms, various challenges, have arisen, such as lengthy operation, variance between different batches, wastage of material, low levels of drug loading capacity and suitable only for limited drugs. Investigation of 3DP is at peak to advance in the development of pharmaceutical dosage forms (Jaboori and Oyewumi, 2015).

HISTORY OF 3DP

3DP technology first came into existence in 1884, during the invention of stereo lithography (based on photo-polymerization method using UV light) by Charles Hull, the maiden co-founder of 3D systems (Tariq and Mazhar, 2019). The evolution of 3DP technology was started from the early 70's by Pierre AL. Ciraud who explained the applicable method for the subsequent solidification of the powdered substance layer-by-layer by the use of high energy beam. During 1980's a patent entitles: "A molding process for forming a three dimensional article in layers", where Ross Housholder explained the use of different materials in sand binding and Carl Deckard described the technique of selective laser sintering (SLS) as one of the methods for the solidification of the powdered material by laser beam. In 1980's, Scott Crump patented fused deposition modelling (FDM) – a technique for the preparation of the object using thermoplastic material. In 1990's MIT scientist Emanuel Sachs with his peer patented "3DP techniques" for joining the powdered material by the use of binding material (Jamroz et al., 2018). A biggest advancement in 3DP was seen in the year 2005 – the launch of the RepRap project. The initiation history of RepRap project was from a British university. They designed a 3D printer to print its components and be cost effective. RepRap stands for replicating rapid prototyper using the technique of fused filament fabrication classified under the AM. In this technique, the layers of the materials are laid down. Coiling, melting and fusion of the plastic filament takes place to manufacture any of the components (https://all3dp.com/history-of-the-reprap-project/). In 2008, Darwin released, first self-replicating printer to print its own constituents. Organovo was

the first to bio-print blood vessels in 2009. Aprecia using the 3DP ZipDose technology developed Spitram that formulates high dosage oro-dispersible formulations that disintegrates at an invisibly fast rate when administered with liquid (Tariq and Mazhar, 2019).

MERITS AND DEMERITS ASSOCIATED WITH 3DP

3DP has numerous advantages and disadvantages as depicted below (Figure 1).

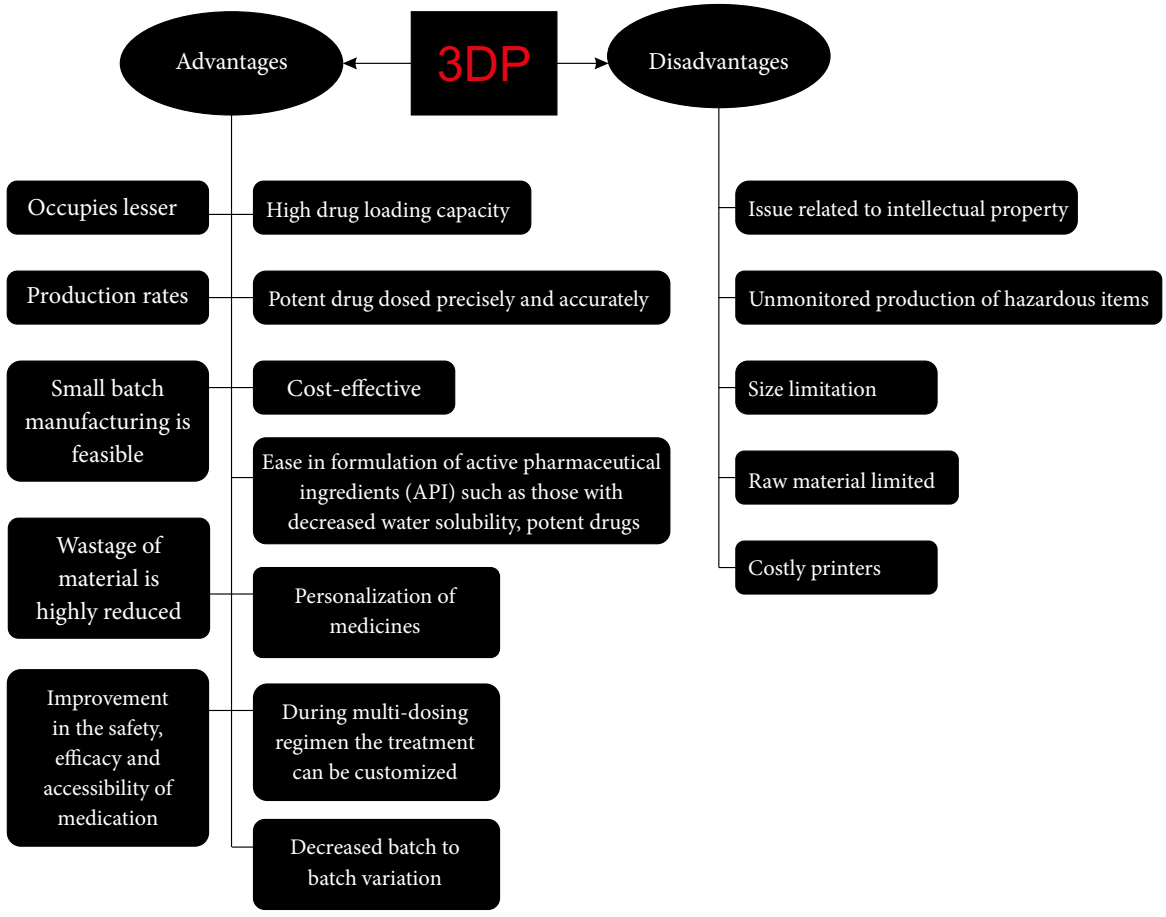

Figure 1. 3DP merits and demerits.

TERMINOLOGIES USED IN 3DP

Table 1 below enlists all the terms used in the 3DP technology and describes the process followed in each of the following.

Table 1. Terminologies along with its description used in 3DP.

S. No.	Terminology	Description
1.	AM	This process mainly deals with joining of the materials for fabrication and designing of objects using 3D data, layer-by-layer preferably. Precisely speaking of which, in 2010, the American Society for Testing and Materials (ASTM) group set some standards to classify AM according to Standard terminology into seven different categories as described below:
	• Material Jetting	It is a challenging method to be implemented. It is advantageous than the others due to its resolution. The diameter of inkjet droplet is 100μm and thickness being smaller than the diameter of the droplet. Molten polymers, waxes, complex multi-component fluids, UV- curable resins are various materials to be jetted.
	• Binder Jetting	Inkjet deposition is the primary 3DP technique used in the production of pharmaceuticals. Small droplets of binders and drugs are sprayed onto the powder bed at precise motion, speed and sizes from inkjet printers. In some cases, the drug may be incorporated in the powder bed and the binder in the liquid to be sprayed and vice versa. The active ingredient in the form of nano-particulate suspension can be jetted onto the powder beds.
	• Material Extrusion	The extrusion of the material in this process is through robotically actuated nozzles. It can print on a variety of substrates. FDM is a common extrusion printing type, enabling the use of various thermoplastic polymers like poly-lactic acid (PLA), acrylonitrile butadiene styrene and polyvinyl alcohol (PVA).
	• Powder Bed Fusion	In this process high melting point particles bind to low melting point particles through sintering (partial surface melting and congealing). It is a fast, complex and useful for heat-labile materials like PLA.
	• Photo-polymerization	Another term used for this process is stereo-lithography. In this, induction of polymerization reaction occurs by the use of photo-polymerizable material and unveiling of liquid resins to high energy or ultraviolet light source. Its example includes photo-polymerizable hydrogels.
	• Directed Energy Deposition	In this process, by the use of focused energy source such as, laser or electron beam the raw materials are melted and simultaneously been deposited. Used mainly for those substances those cannot be extruded.
	• Sheet Lamination	It is a highly rapid process and cost-effective but is disadvantageous in the context of waste generation and low-resolution. In this technique, it utilizes automatic laser cutting system and assembling of the product layer-by-layer (Marzuka and Kulsum., 2016).
2.	Computer-aided Design (CAD)	It deals with the use of computers to create, modify and optimize the 3D designs for a particular API. A number of industries use CAD modelling. This technique is useful in designing and engineering of 2D or 3D models.
3.	Rapid Prototyping	It is also termed as solid freeform fabrication. This is the process of complex shape building without the use of any tools. It helps in the fabrication of any physical part by the use of 3D computer aided designing prototype models these physical objects are produced.
4.	Resolution	It deals with the degree of conformity between the electronic model and the 3D printed substance. It generally determines the Planar dimensions and a 3D dimension i.e., the Z dimension. Thus, resolution needs to be tackled differently in 3D printing and determines the conformational studies.
5.	Solidification of Powder	In this process, the selective layers of powders are joined using liquid binders. The laser beam is one of the main components that helps in enhancing the binding properties of the powder and hence, solidifying the powdered drug or material in a layered fashion.
6.	Subtractive Manufacturing	The formation of the 3D structure by cutting off the excess material from the solid block (Agrawal and Gupta, 2019). Computer numerical control is the tool utilized that performs the mobility and the cutting of the excess material to obtain the required shape and size. Laser cutters and electrical discharge machine are another method used to obtain this.

FUNCTIONING OF 3DP TECHNOLOGY

The initial step for the 3DP is the designing of the 3D model using various software programs available such as 3D CAD in case of industrial use, ZPrint and some simpler software for use in various other fields. Further, slicing of the model into layers is done to convert it into a 3D printer readable file. These layers are then arranged in accordance with the design and process. There is a wide variance in the technologies used for the 3DP for creation of the different objects. An exceptional number of substances can only be used in the processing of such substances and further ongoing research is also being performed to identify more materials to be used in 3DP (Bhusnure et al., 2016).

3DP MATERIALS

The materials used in the technology of 3DP have come a long way from being unidentified for such use to a bulk of materials. Here the emphasis has been given to the substances being efficiently used for the processing and the designing of the product via 3DP (Figure 2).

Plastics

The different plastics used in the 3DP technology mainly include nylon, polyamide, Acrylonitrile butadiene styrene (ABS), PLA. Nylon is a flexible, long lasting and strong material which when combined with aluminium powder converts to another 3DP useful material i.e., alumide. But polyamide is a durable and flexible material, white in colour but can fur-

ther be coloured before or after its processing. However, ABS is a strong material, available in different colours. Used mainly in the technique like FDM. PLA is a bio-degradable material, but has low durability and flexibility than the others. It is used in techniques like Digital light processing and FDM.

Metals

A variety of metals like aluminium (widely used at industrial scale), cobalt derivatives, stainless steel, gold, silver, titanium and ceramics are also being used in this technology. The cobalt derivatives are the mostly used composites for the production of the end product in the industries. Stainless steel is the strongest material and is sometimes plated with gold and bronze. Gold is a very strong material and is used mainly in the works of jewellery. Silver is available in the powder form and is strong in nature. Titanium is highly used in industries due to its strength and is also available in powder form. Ceramics is a newly identified metal that can be used in 3DP technology and is highly successful in its use.

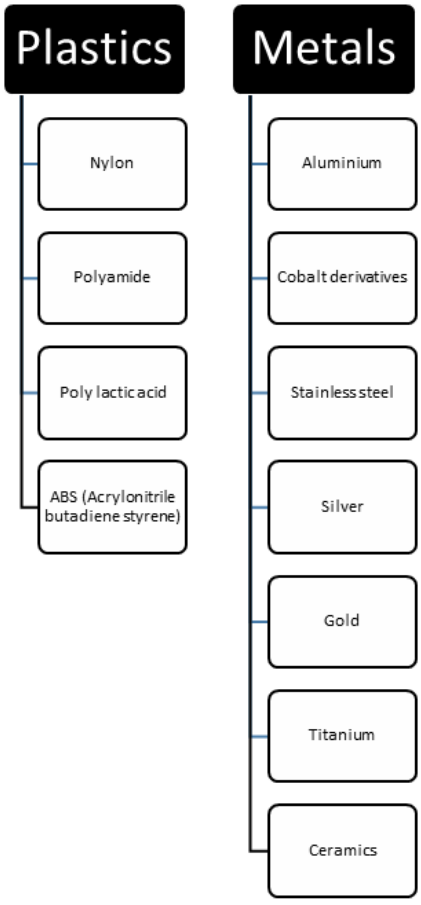

Figure 2. Metals used in 3DP technique.

THE PRINTING CYCLE

3DP technology broadly includes three major steps of its working which are described below (Figure 3):

1. Preparation

In this step, the printer follows an in-built mechanism that starts to warm the air of the printer thereby creating an appropriate environment. Simultaneously, the build chamber of the machine gets filled with the powder layers. The automatic process further prints, reads and aligns the pattern formed.

2. Printing

After the completion of the in-built process with the help of the software, the printing is initiated and the layers start to build up by the material through the hopper. Further, the movement of carriage enhances the binder deposition in a specific pattern. The solidification of the powder takes place and recycling the rest of it. At this stage, the piston of the machine lowers down to prepare another such layer to repeat the cycle.

3. De-powdering or Finishing

At the end of the cycle the excess powder is removed from the area using vacuum pressure or vibration method. The powder removed is recycled to be used for another round. Further, opening the de-powdering chamber, compressed air is sprayed to remove any traces if left. No powder is being waste as the loop cycle of loading, removing and recycling continues. In some other cases, where there is no de- powdering step, the printed material is lacquered or painted, as one cannot directly use it. An example of this includes the inkjet printing.

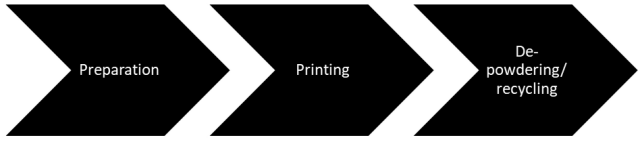

Figure 3. Steps followed for the processing of printing cycle.

TECHNIQUES USED IN 3DP

1. Printing-Based Inkjet Systems

In printing based inkjet system, the ink is deposited onto the substrate mainly in two forms as listed below:

- Continuous inkjet printing

In this type, due to the counter mechanisms the drops are continuously driven as needed thereby expelled only when necessary. this method continuous flow of ink is desired during the process. The processing occurs in such a manner that the vibration in the piezoelectric crystals helps in releasing the liquid continuously. The droplet obtained are charged electrostatically and thus, directed towards the substrate. It is mainly useful in printing of packaging (Figure 4).

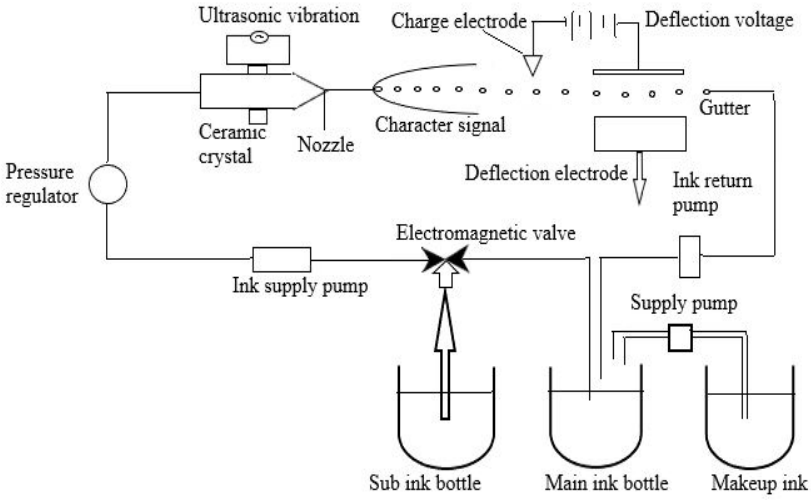

Figure 4. Continuous inkjet printing

- Drop on demand

In this case, the liquid passes through the small orifice with the use of a piezoelectric crystal in one case that helps in the breakdown of the liquid into small droplets. In the piezoelectric process application of electric field distorts the stream, creating pressure in the ink chamber where finally the drops are pushed over the substrate. The droplets are used in accordance with the needs. In the second process thermal technology is utilized where heating and a film creation of the resistive element occurs. A growing bubble is formed that initiates the entry of the ink in the nozzle which move towards the substrate (Konta et al., 2017).

I. Piezoelectric jet

This process works by applying varying voltage to a piezoelectric element which is connected to the fluid and results in a volumetric change in the reservoir of fluid. Due to this, a pressure is generated between the nozzle and the reservoir therefore, releasing the droplet of the desired substance (Rahmati et al., 2009).

II. Thermal Ink-Jet Printing

In this printing technique, with the help of heat, the liquid ink is converted to the vapours and is forced to push the ink out of the nozzle or the orifice. Biodegradable drug loaded microspheres, liposomes, coating of microelectrode array and eluting stents loaded with drug are prepared using this technique. Biologic films are also produced practically and efficiently by thermal inkjet printing (Srinivas et al., 2019) (Figure 5).

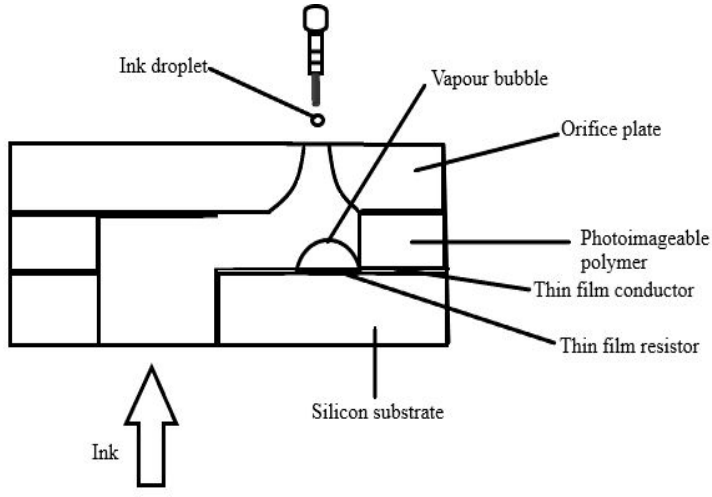

Figure 5. Thermal Ink-Jet Printing

These both techniques are capable of high resolution printing. "Mark-less" and "tool-less" are the other terms to describe inkjet technology. This is described using these terms due to its nozzle movement for the formation of the required model without the requirement of any special tool. This technique is cost-effective in the context of processing; rate is rapid, low waste production, delivers CAD knowledge and minimum contamination over large areas.

2. Nozzle-Based Deposition Systems

This technique involves the prior mixing of the API, polymer and other elements. It produces 3D structure layer-by-layer after passing the mixture through the nozzle. The printing method for this technique is further divided into two major types:

- FDM

a) Hot melt extrusion

This is a pre- step of FDM. In this method the polymer and the API are molten at high temperature and pressure. Hot melt extrusion is a continuous manufacturing process performing several functions like heating, mixing, feeding and shaping. Solubility and bioavailability of poorly soluble drugs are the other parameters that are enhanced by using this technique.

b) FDM main processing

It is an AM technology. This deals with the prototyping, modelling and production of the 3D printed product. The principle of working of FDM is production of layer-by-layer system. The working is initiated by turning the flow on and off the material through the extrusion nozzle using a plastic filament or metal wire. It is controlled by computer-aided manufacturing software. In this the substance is melted by heating the nozzle that can move in both the directions i.e., horizontally and vertically. By extruding the thermoplastic material through the nozzle it forms layers and the model is developed. FDM mainly uses stepper motors for initiating the extrusion head movement. It is most prominent and considerably inexpensive prototyping method.

- Pressure-assisted micro syringes

In this the deposition of viscous materials is enhanced by pressurized air piston linked to syringe extruder. Viscosity, visco-elastic nature and elasticity are the parameters that determine the robustness of the technology and hence help in the formation of an appropriate product which are arranged in layers. This technique is mainly used in printing of soft tissues.

3. Laser-Based Writing System

Photo polymerization is the basic principle being followed in this technique. In this due to the interaction between the UV light and photo-initiator, free radicals are generated (Jose et al., 2018).

- Stereo-lithography

In this technique the solidification of the liquid substance is performed by laser beam controlled by computer thus, the formation of a 3D model occurs. It is the AM technique. The first layer formed shows polymerization and the next ensures adhesion thereby forming a layer. The printers of this technique mainly compose of UV light beam that passes through the liquid where the transfer of energy occur finally forming 3D product layer-by-layer.

- Multi- photon polymerization

Multi- photon polymerization is also known as direct laser writing. This technique was discovered in 1931 by Maria Goppert- Mayer. This 3DP technology helps in assembling the structures which are below the particle range of 100nm. In this process an ultra-fast laser beam is directed towards the material resulting in absorption of the laser and exciting the photons from ground state to the excited state. Thus, obtaining non-linear absorption pattern by the polymers and polymerizing it locally. Finally, fabricating the finished model by following the designed path (Selimis et al., 2014).

- SLS

In this technique the powdered particles are joined using laser. Further, during the process of printing a specific pattern is drawn by the laser onto the powder bed surface which finally forms the 3D structure. It is also an AM technique that uses laser of high power to easily join the particles. Plastic, ceramic and metallic objects have been known to be developed using the technique of SLS. It has been proved a method for the production of orally disintegrating tablets (Fina et al., 2018).

4. Continuous Layer Interface Production

This technique was designed to enhance the speed of printing but it does not produce the end product in a layered fashion. Oxygen is the main component for increasing its speed that enhances photo-polymerization. This shows similar action as that of the material jetting and solidifies at a very high rate. In this technique, the image projection on surface occurs by digital light projector using UV radiations. The oxygen is permeable and a dead zone is formed just below it. Thus, it passes the same image for platform building.

- Powder Based 3DP

The figure below describes the structure of this technique (Figure 6). The powder in this technique is thinly spread by using a powder jet and simultaneously the liquid binder is applied. Finally, the ink is sprinkled to produce layered end product. It is easily acceptable technique to be used in pharmaceutical field.

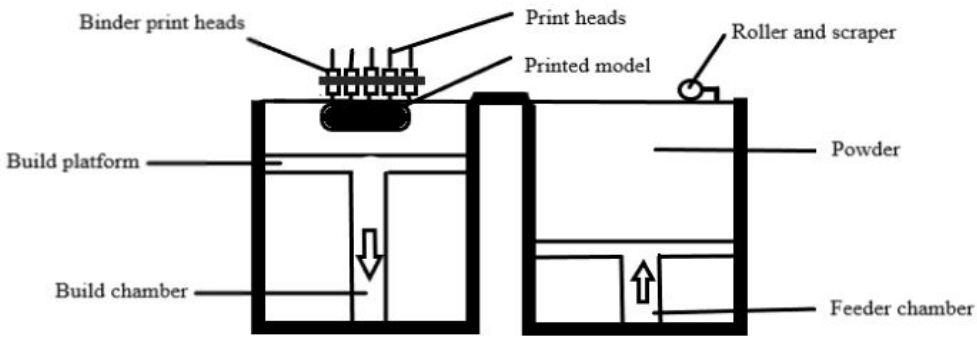

Figure 6. Powder Based 3DP

5. Digital light processing

This works in similar action to stereo-lithography by using photo-polymers. But the difference here relies on the light source that is mainly an arc lamp, incorporated with deformable mirror device or liquid crystal display panel (Figure 7). It is the technique with excellent resolution and is rapid in action than stereo-lithography. The advantage of this method is that it produces very less amount of waste.

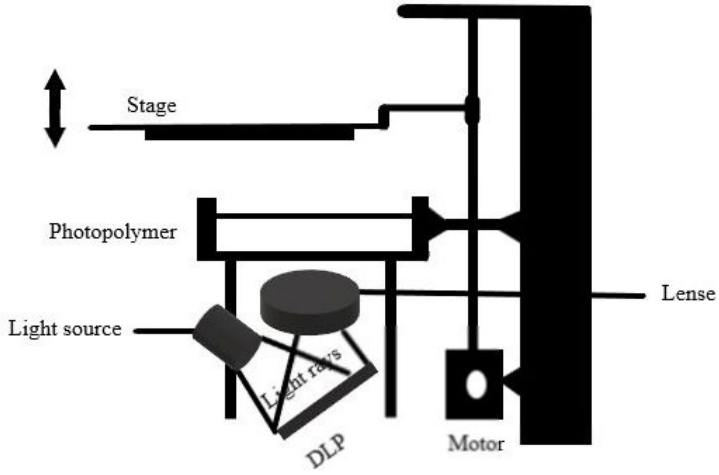

Figure 7. Digital light processing

7. Selective Deposition Lamination

Mcor technologies was the first to process and develop this technique. By the use of standard copier paper, layer by layer parts of the 3DP are being built. Each layer is positively joined to the next one using an adhesive. High density of adhesive is used in the main product and low density used in the surrounding area that provides support.

8. Electron beam melting

Arcam, a Swedish company developed this technique. This is a metal printing method. It is highly similar to laser sintering method; the only difference is in the source of heat. The heat source here is electron beam rather than a laser. Its major necessity is the presence of vacuum.

9. Semi-solid Extrusion 3DP

In this technique a syringe is used to extrude out the semi solid product and arrange it in layers. The semi solid is a combination of solvent and polymer. It can either be in the form of a gel or a paste. During its drying deformation and shrinking may occur. The layer should be of appropriate hardness to bear the other formed layers' over it which otherwise can lead to collapsing of the delivery system while printing, if it is not in accordance with the specifications.

These are the various 3D techniques which are used in the development of an appropriate and ideal dosage form. The table below enlists the different techniques used in the development a particular dosage form (Table 2).

Table 2. Utilization of 3DP technology in development of different pharmaceutical dosage forms

S. No.	Active ingredient	Dosage form	3DP technique used	Reference
1.	Chlorpheniramine maleate and Diclofenac sodium	Tablet	Inkjet 3D printer	Rowe et al., 2000
2.	Fluorescein	Tablet	3D printer (Solid free form fabrication)	Katstra et al., 2000
3.	Captopril	Tablets	Powder solidification drop on solid	Lee et al., 2003
4.	Pseudoephedrine hydrochloride	Capsule and tablet	3D printer and Powder bed inkjet	Wang et al., 2006
5.	Levofloxacin	Implant	Inkjet 3D printer and Fused deposition modelling	Huang et al., 2007
6.	Tetracycline, Vancomycin and Ofloxacin	Microporous bio ceramics	3D powder direct printing technology	Gburenk et al., 2007
7.	Dye	Implant	FDM	Masood et al., 2007
8.	Fenofibrate, Zotarolimus, Rapamycin	Coated Stent and Tablet	Inkjet printer and Fused deposition modelling	Tarcha et al., 2007
9.	Rifampicin	Implant	Powder bed inkjet	Wu et al., 2007
10.	Acetaminophen	Tablet	Powder bed inkjet	Yu et al., 2007
11.	Prednisolone	Solid dosage form	Thermal inkjet printing	Melendez et al., 2008
12.	Rifampicin, Levofloxacin, Isoniazid and Salicylic acid	Implant and Patch	Powder bed inkjet and Stereo lithography printer	Weigang et al., 2009
13.	Paracetamol	Tablet	Powder bed inkjet 3DP	Yu et al., 2009
14.	Acetaminophen	Capsule	FDM	Yu et al., 2009
15.	Felodipine	Solid dispersion	Thermal inkjet technique	Scoutaris et al., 2011
16.	Folic acid	Nanosuspension and Microneedle	Thermal inkjet printing and FDM	Pardeike et al., 2011
17.	Polyvinyl pyrrolidone	Microneedle	Inkjet printing	Scoutaris et al., 2011
18.	Salbutamol sulphate	Oral films	Thermal inkjet printing	Buanz et al., 2011
19.	Rifampicin and calcium phosphate	Nanoparticles, Implant and Nanocomposite structure	Commercial Inkjet 3D printer	Gu et al., 2012
20.	Dexamethasone	Encapsulation of drug in PLGA (Poly(lactic-co-glycolic acid)) and PVA	3D Extrusion printer	Rattanakit et al., 2012
21.	Paclitaxel/ Fluorescein 5-isothiocyanate	Microparticles	Inkjet printing	Lee et al., 2012
22.	Terbutaline sulphate	Solution	Thermal inkjet technique	Sharma et al., 2013
23.	Loperamide/ Caffeine	Tablet/ Capsule	Thermal inkjet technique	Genina et al., 2013
24.	Peroxicam	Capsule	Inkjet printer	Raijada et al., 2013
25.	Rasagiline mesylate	Oral dosage	Inkjet printer	Genina et al., 2013
26.	Isoniazide and Poly L lactic acid	Implant	Powder solidification drop on solid	Wu et al., 2014
27.	Fluorescein	Tablet	Fused-filament 3DP	Goyanes et al., 2014
28.	Nitrofurantoin	Catheter	FDM	Sandler et al., 2014
29.	Levetiracetam	Tablet	Powder bed inkjet	Jacob et al., 2014
30.	Guaifenesin	Tablet	FDM	Khalid et al., 2014
31.	Ketoprofen	Tablet	Inkjet printing	Marizza et al., 2014
32.	Prednisolone	Tablet	FDM	Skowyra et al., 2015
33.	5-Aminosalicylic acid, Budesonide and 4- Amino salicylic acid	Tablet	FDM	Goyanes et al., 2015
34.	Aspirin/ Atenolol/ Ramipril	Tablet	3D extrusion printer	Khaled et al., 2015
35.	Felodipine	Solid dispersion	Inkjet printer	Melocchi et al., 2015
36.	Indomethacin	Subcutaneous rods and intrauterine system	FDM	Genine et al., 2015
37.	Gentamicin sulphate/ Methotrexate	General device	FDM	Weisman et al., 2015
38.	Nitrofurantoin	Implant	FDM	Water et al., 2015
39.	Captopril/ Nifedipine/ Gupizide/ Pravastatin	Tablet	FDM	Khaled et al., 2015
40.	Insulin	Microneedle	Inkjet printing	Ross et al., 2015
41.	5-flurouracil/ Curcumin/ Cisplatin	Microneedle	Inkjet printing	Uddin et al., 2015

42.	Atenolol	Sprays	Inkjet printing	Alomari et al., 2015
43.	Voriconazole/ Itraconazole	Microneedle	Inkjet printing	Boehm et al., 2015
44.	Nitroglycerin	Injection	Inkjet printing	Daly et al., 2015
45.	Amino salicylate	Tablet	FDM	Goyanes et al., 2015
46.	Acetaminophen and Furosemide	Capsule	FDM	Melocchi et al., 2015
47.	Saline solution	Microfluidic pump	FDM	Thomas et al., 2016
48.	Domperidone	Tablet	FDM	Chai et al., 2017
49.	Budesonide	Tablet	FDM	Okwuosa et al., 2017
50.	Enalapril maleate/ Hydrochloride thiazide	Tablet	FDM	Sadia et al., 2018
51	Itraconazole	Tablet	Powder extrusion	Goyanes et al., 2019
52	Theophylline	Tablet	Digital light processing	Kadry et al., 2019
53	Paracetamol, Naproxen, Caffeine, Chloramphenicol, Aspirin and Prednisolone	Multilayer constructs (Polypills)	Stereolithographic 3DP	Martinez et al., 2019
54	Levofloxacin	Vaginal meshes	FDM	Robles et al., 2020
55	Ibuprofen	Implant	FDM	Stewart et al., 2020
56	Theophylline	Tablet	FDM	Dumpa et al., 2020

APPLICATIONS OF 3D PRINTING

3DP depicts bulk use in the pharmaceutical field in the areas of research and development, safety, efficacy and availability of medications. The major applications included are:

1. Personalization of medicine is a trending topic in today's era. 3DP is considered to be useful and a successful approach in personalizing the medicine at affordable and easy costs. 3DP is now on the verge of extending its roots in the areas of manufacturing, production, prototype formation and fabrication of drug. Personalized medicine deals with the tailoring of medicine according to the individual needs based on his preferences, diagnosis and needs. In Personalized therapy**,** the 3DP was emerged as a technique to model human parts and study its anatomy. In this therapy the organs or the required tissue is modelled so as to deliver the medication to the specific area and identify its activity;
2. Tailored medication in this 3DP technique is a simple and flexible method for producing medicines according to the patient's needs. It is widely adopted by paediatrics, due to dose variation and shape variation for those affected by swallowing difficulty;
3. Complex shapes, where the formation of difficult shapes is possible with precise dosing of the drug thereby reducing the adverse effects. The shapes of dosage form also affect its release studies;
4. Sustained release controls the release rate and the targeting of the medication that can be easily performed by 3DP. This is achieved by addition of the binder to the layers;
5. Unique dosage form where the extraordinary, novel and unlimited dosage forms are produced using this technique;
6. Mini/small dispenser unit, in this the printers require less space, low in cost, handled by software and helps in personalization;
7. Integrated with Health Care Network that deals through this technology, the health needs of the patient can be improvised, accessibility increased and further shortening of the time to obtain results by a specific medication;
8. Accelerated disintegration of medication deals in the 3DP where the strength of binding in tablets is low at centre and high at the edges thus fast disintegration of the medication seen;
9. Less usage of tools and cost-effective;
10. Sustainable/eco-friendly;
11. Decreased production time;
12. Ease of manufacturing due to less waste generation, less time consuming process and pocket friendly;
13. The setup is flexible and cost effective designing of products;
14. The on demand production of materials has been initiated that cuts down its costing (Agrawal et al., 2019). This 3DP is also useful in various other fields like automotive, art, design, sculpture, fashion and food (Bhusnure et al., 2015).

3DP has become the topic of interest in the pharmaceutical field and a number of companies are leaning towards the development of 3D printed medications. Until date, a large number of researches have been carried out for developing different drug formulations. There are a variety of dosage forms developed that show extended release of the desired drug to the site of action, most of which are the oral dosage forms. However, the research conducted and ongoing in the advancement of this field for the development of medicinal substances, would significantly benefit all of

the health industry. Highlighting some of the examples here includes the development of pharmaceutical co-crystals. These solid substances having crystal lattice helps in improving and enhancing the activity of an API. They help in increasing the bioavailability, solubility, permeation and various pharmacokinetic parameters of the API (Arnum, 2013). Similarly, the University of Seville in collaboration with University of Nottingham, developed 3D printed gold nanoparticles, which follow the characteristic of being highly biodegradable, biocompatible and stable. This is a great advancement as it can be helpful in designing the biocompatible biosensors which are proven efficient for the diagnosis of carcinogenic and tumour cells (https://www.eurekalert.org/pub_releases/2020-01/uos-3pw011720.php). In the year 2017, Shao et al, using the 3DP techniques developed bioactive ceramics that helped in repairing any tissue damage related to bones or any bone defects. (Shao et al., 2017).

Later, in the year 2020, Stewart et al., developed a biodegradable implant of Ibuprofen, which was targeted towards obtaining the prolonged release of the drug so that it prevents the occurrence of adverse effects in the body and releases small dose at a time. During its development, five models of different dose were prepared which were further tested for the drug release and finally by adding the rate controlling membrane, the drug release was controlled (Stewart et al., 2020). The research on 3DP is advancing day by day. Similarly, in the year 2020, Robles et al., developed vaginal meshes using 3DP technology. These meshes were developed for treating urinary diseases such as stress urinary incontinence, pelvic organ prolapse, etc. The material used for developing the mesh accounts for thermoplastic polyurethane, as it is safe to use due to its elasticity and softness. The drug was found to be uniformly distributed and the bacteriostatic activity was determined on different bacterial strains by the meshes resulting in no infection risk after its insertion into the body cavity (Robles et al., 2020). Apart from this, there are myriad of studies where 3DP technology has shown astonishing results. Hence, this 3DP technique soon in future will prove to be a widely used technique in designing of the drugs and medical substances.

LIMITATIONS AND CHALLENGES OF 3DP TECHNOLOGY AND ITS DOSAGE FORMS

There are bunch of limitations that needs to be overcome before advancing the 3DP technology for its use worldwide. The process challenges that we need to surmount includes the following:

1. Selection of raw materials in which all the properties of the material to be used must be thoroughly studied and known;
2. Mechanism of nozzle, where the nozzle is the main part that deals with the formation of layers of a substance and thus requires continuous flow and no clogging;
3. Mechanical resistance, in which the resistance to friability in 3DP should be enhanced especially for powdered substances;
4. The imperfections on the surface of the finished product occur because of the layer stacking, the drying rate and methods thereby causing surface imperfections;
5. Manufacturing process, in this the thermo-labile drugs might show printing resistances at high temperatures.

We visualize the activities for creating 3DP clinically, that incorporate software performance which must be optimized and improved, testing and production of excipients to be used in 3DP, manufacturing process optimization, production for variety of API and thorough human studies to test safety, efficacy and stability of newly produced formulation. Even after great use of 3DP it is still undergoing development. Hence, a variety of challenges has to be overcome so as to enhance the performance and application. The challenges include process of optimization, performance improvement, choice of excipients and post treatment method. The developing cost or re-designing of formulation using 3DP, the main liability of safety is its in-built flexibility. For obtaining highly optimized product various specifications such as rate of printing, printing passes, print head velocity, interval time of two layers, nozzle distance and layer of powder must be optimized.

FUTURE PROSPECTS

The gateway for whole new research and application of 3DP in the pharmaceutical field has been opened. In the present scenario and the approaching future, the technology of 3DP will reach great heights in the context of fabrication of variety of dosage forms, optimization of release kinetics of the API, development of excipients, eliminating multiple drug incompatibility, support delivery and the degradation of biological moieties is limited. The pharmaceutical 3DP technique has high level of versatility regarding areas of work that includes the association of software and hardware expertise, pharmaceutical expertise, polymer expertise and persons excelling in biological and medical sciences. Though this technology may not become universal method but might be accepted as the primary method for development of certain drugs and certain therapies (Dumitrescu et al., 2018). The approach of personalized medicine would be greatly affected positively and led to its advancement by 3DP. The major concern of scientists in this case is to formulate 3D printed tablets. Depending on the shelf life of the API on demand printing of the medication may be done in accordance with the patient specifications. Due to the novelty of the process there is lack of regulation, security and safety concern which are required to overcome in near future (Srinivas et al., 2019). As

stated by Global pharma news and resources, it is estimated that by the end of 2020 3D printed market would gross $278 million rising upto $ 522 million by the year 2030 (https://www.pharmiweb.com/press-release/2020-02-11/3d-printed-drugs-market-projected-to-improvement-of-growth-in-the-coming-years).

Concluding to the study, the gateway of advancement for 3DP has been wide open following its in-built flexibility for individualization of the medication. The 3DP will revolutionize safe and efficient new product development with our sustained patience and perseverance (Jassim-Jaboori and Oyewumi, 2015; Kumar et al., 2019).

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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