Chapter

3D Printing in Pharmaceutical Sector: An Overview

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Abstract

The pharmaceutical industry is moving ahead at a rapid pace. Modern technology has enabled the development of novel dosage forms for targeted therapy. However, the fabrication of novel dosage forms at industrial scale is limited and the industry still runs on conventional drug delivery systems, especially modified tablets. The introduction of 3D printing technology in the pharmaceutical industry has opened new horizons in the research and development of printed materials and devices. The main benefits of 3D printing technology lie in the production of small batches of medicines, each with tailored dosages, shapes, sizes, and release characteristics. The manufacture of medicines in this way may finally lead to the concept of personalized medicines becoming a reality. This chapter provides an overview of how 3D printed technology has extended from initial unit operations to developed final products.

Keywords: 3D print, personalized medicines, manufacturing, drug delivery

1. Introduction to 3D printing

Gaining immense interest both in academic and industrial sector is the concept of three dimensional (3D) printing (3DP) technologies. Domains like aerospace, engineering, FMCG, architecture, military, fashion industry, chemical industry, and medical field are by no way untouched by this technology [1, 2]. 3DP has a wide range of applications like tissue design, printing of organ, diagnostics, manufacture of biomedical devices, and the design of drug and delivery systems in the medical field [3, 4]. From the data originated by various techniques like computed tomography (CT) scan and magnetic resonance imaging (MRI), complex anatomical and medical structures according to the need of patient can be fabricated [5, 6]. Replacing and repairing the defective organs like kidney, heart etc. or all together creating a new organ that mimics the same functions as that of original are some additional uses of this technology [7]. This technology is so widespread that its applications include things that are an integral part of human life like clothing, eyeglasses, jewelry, parts of cars, and drugs that can be printed in almost any geometry and shape as per the requirement of the user [8].

In this technology a concept is transformed into prototype by taking help from 3D computer-aided design (CAD) files, hence digitally controlled and customized product can be fabricated [9]. This technology utilizes a bottom-up approach in which layers of materials like living cells, wood, alloy, thermoplastic, metals etc. are placed on top of each other in order to make the required 3D object [10]. Therefore, 3D printing is also known by other terminologies such as layered manufacturing, additive manufacturing, computer automated manufacturing, rapid prototyping, or solid freeform technology (SFF) [9].

In subtractive methodology or conventional method, the product is designed from the bulk substance and due to non-advanced tools used non-standard geometries and objects made from many materials cannot be made with high quality [11, 12]. In contrast to the conventional method, 3DP technology is more automated, rapid and easy to use, customized and sophisticated and cost-effective [13–15].

2. 3D printing procedure

First, a virtual 3D design of an object using digital design software like Onshape, Solidworks, Creo parametric, Autocad, Autodesk etc. is created [2, 16, 17].

This digital model is then converted to (.STL) digital file format which stands for standard tessallation language or stereolithography [2].

Triangulated facets give information regarding the surface of the 3D model that is present in the (.STL) file [2].

The (.STL) file is converted into G file by slicing the design into a series of 2D horizontal cross-sections by the help of specialized slicer software, which is installed in the 3D printer (**Tables 1–2**).

Now the print head is moved in the x-y axis to create the base of the 3D object.

The print head is now allowed to move in the z-axis, thereby depositing the layers sequentially of the desired material, hence creating a complete 3D object [2, 9].

Maximum numbers of 3D printing technologies are compatible with (.STL) file format. Some errors might occur during the conversion of the 3D model to .STL digital file; therefore, software like Magics (Materialise) can be employed to correct the errors during conversion. File formats other than .STL like additive manufacturing file format (AMF) and 3D manufacturing format (3MF) are used as .STL does not have information regarding the type of material, its color, texture, properties, and other features [18].

3. Types of 3D printing technology

3.1 Fused deposition modeling (FDM)

The process involves the selection of the desired polymer, which is melted and forced through a movable heated nozzle. Along the entire 3 axis (i.e., x-y-z), the polymer is laid down layer by layer, which on solidification gives the exact shape as was designed by computer aided design models. Multiple dosage forms like implants, zero-order release tablets etc. that include polymer as a part of their formulation can be made by this method [9, 19–21].

Year	Major development
1980	Dr. Hideo Kodama filed first patent for RP technology
1984	Stereo lithography apparatus (SLA) was invented by Charles Hull
1986	Carl Deckard invented apparatus for producing parts by selective sintering
1989	Patent was granted to Carl Deckard for SLA
1990	Fused deposition modeling (FDM)
1992	First SLA machine was produced using 3D system
1993	3D printing patent was granted to E.M Sachs
1996	Clinical application of biomaterials for tissue regeneration
1999	Luke Massella received first 3D printed bladder which was an amalgamation of 3D printed biomaterials and his own cells
2000	MCP technologies introduced the SLM technology
2002	Miniature functional kidney was fabricated
2003	Term organ printing was coined
2004	Dr. Bowyer conceived the RepRap concept of an open-source, self-replicating 3D printer
2005	First color 3D printer was introduced by Z Corp
2007	Selective layer customization and on-demand manufacturing of industrial parts
2009	Organovo, Inc., announced the release of data on the first fully bioprinted blood vessels
2011	3D printing was applied in gold and silver World's first 3D printed car, robotic aircarft was introduced
2012	Extrusion-based bioprinting for an artificial liver 3D printed prosthetic jaw was implanted
2013	SolidConcepts produced a 3D printed metal gun
2014	Implementation of multi-arm bioprinter to integrate tissue fabrication with printed vasculature
2015	First 3D printed pill was approved by US FDA Organovo announced the release of data on the first fully bioprinted kidney

Table 1.
Historical development in the field of 3D printing (table adapted from Ref. [8]).

3D printing technology used	Formulations	API	Ref.
Semi-solid extrusion (SSE)	Bi-layered tablets (polypill)	Guaifenesin	[30]
	Multiactive tablets (polypill)	Nifedipine, Glipizide, and captopril	[31]
Stereolithography (SLA)	Hydrogels	Ibuprofen	[32]
	Facial mask	Salicylic acid	[33]
Selective layer sintering (SLS)	Tablets	Paracetamol	[34]
	Drug delivery device	Progesterone	[35]
Fused deposition modeling (FDM)	Caplets	Caffeine	[36]
	Tablets	Hydrochlorothiazide	[37]
	Oral films	Aripiprazole	[38]

3D printing technology used	Formulations	API	Ref.
Binder jet printing	Tabular devices	Methylene blue and alizarin yellow (dyes)	[39]
	Cubic tabular devices	Pseudoephedrine	[40]
	Tablets	Chlorpheniramine meleate and fluorescein	[41]
	Orodispersible tablets	Levetiracetam	[42]
Inkjet 3D printing	Implant	Levofloxacin	[43]
3D printing machine	Multidrug implant	Rifampicin and isoniazid	[44]
Inkjet 3D printing	Nanosuspension	Folic acid	[45]
Thermal inkjet (TIJ) printing	Solution	Salbutamol sulfate	[22]
Inkjet 3D printing	Nanoparticle	Rifampicin	[27]

Table 2.
Pharmaceutical preparations that were developed by 3DP technology.

3.2 Thermal inkjet (TIJ) printing

It involves the heating of ink fluid by the help of micro-resistor, thereby creating a bubble of vapor that nucleates and upon expansion forces the ink to drop out of the nozzle. Dispensing of extemporaneous preparation/solution of drug onto 3D scaffolds is an area where this technique can be employed [22, 23].

3.3 Inkjet printing

It is a powder-based 3D printing that utilizes powder as a substrate on which layer by layer different combinations of active ingredients and ink is sprayed which is of varying droplet size that eventually solidifies into solid dosage form [9, 19, 24–28].

3.4 Direct-wise

It encompasses a pattern-generating device that moves as per the guidance of computer-controlled translational stage so that layers after layers are put on in order to achieve a 3D microstructure [29].

3.5 Zip dose

This technology provides a personalized dose in additional to the delivery of a high drug-load with high disintegration and dissolution levels by manufacturing highly porous material [25].

3.6 Vat photopolymerization

It is light-induced polymerization where materials like photopolymers, radiation-curable resins, and liquid are collected in vats, which are successively cured into layers, one layer at a time by irradiating with a light source, thereby providing a 2D patterned layer. This involves techniques such as stereolithography (SLA), digital light processing (DLP), and continuous direct light processing (CDLP).

Depending on the orientation of light source and the surface where polymerization of the photoactive resin occurs, SLA can be divided into two different configurations:

1. Bath configuration (free surface approach)

2. Bat configuration (constrained surface approach) [2].

Advantages of 3D printing in the pharmaceutical field:

1. **Enhanced productivity:** 3D printing works more quickly in contrast to traditional methods especially when it comes to fabrication of items like prosthetics and implants with an additional benefit of better resolution, repeatability, more accuracy, and reliability [7].

2. **Customization and personalization:** One of the pioneer benefits of this technology is the liberty of fabrication of customized medical equipment and products. Customized implants, prosthetics, surgical tools, fixtures can be a great boon to patients as well as physicians [7].

3. **Increased cost efficiency:** Objects produced by 3D printing are of low cost. It is an advantage for small-scale production units or for companies that produce highly complex products or parts because almost all ingredients are inexpensive [46, 47].

By eradicating the use of unnecessary resources, manufacturing cost can also be reduced. For instance, 20-mg tablets could be potentially formulated as 1-mg tablets as per need [19].

4. 3DP allows controlled size of droplets, complex drug release profiles, strength of dosage and multi-dosing [44, 48, 49].

Disadvantages of 3D Printing:

1. In inkjet printing, proper flow of ink can only be achieved with ink that has precise viscosity [50].

2. Ink formulation material should have the property of self-binding but should not bind to other printer elements. In some formulation when the ink does not possess adequate self-binding property or it binds with other elements of printer then the resultant formulation does not have required hardness [51].

3. Rate of drug release may get affected due to binding of ink with other printer materials [52].

4. Medical applications of 3D printing

4.1 Bioprinting of tissues and organs

One of the critical medical issues is the failure of organs and tissues as a result of accident, congenital defects, aging etc (**Figure 1**) and the current resolution for this problem is organ transplant from dead or living donors. However, only few

Figure 1.
Different medical applications of 3D printing technology.

fortunate people receive organs and the rest die due to donor shortage. Moreover, the procedures for organ transplants are so expensive that it is out of reach of common people. Another problem with transplant surgery is that donors with tissue match are difficult to find [7, 53].

The solution to this problem lies in the fact that the required tissue or organ should be fabricated using the patient's own body cells, which would decrease the risk of tissue or organ rejection; moreover, the requirement for immunosuppressant will also be greatly reduced [7, 54].

In the conventional method of tissue engineering from a small tissue sample, stem cells are isolated, amalgamated with growth factor, and then multiplied in the laboratory. Then the cells are seeded onto scaffolds that direct cell proliferation and differentiation into a functioning tissue.

Placement of cell with accuracy, digitally controlled speed, drop volume, resolution, concentration of cells and diameter of printed cell are some of the additional advantages that 3D bioprinting offers over traditional tissue engineering [2, 54].

Depending upon the porosity, the type of tissue, and required strength, various materials are present to make the scaffolds. Among all materials, hydrogels are said to be the most suitable for building soft tissues [2, 55].

No doubt that organ printing is still in the phase of development but several researches have demonstrated its concept with proof. Scientists have built an artificial ear, cartilage and bone, and heart valve by the help of 3D printers [2, 47, 55]. Wang et al. used 3D bioprinting technology to deposit different cells within various biocompatible hydrogels to produce an artificial liver [54].

As with the increasing interest of researcher and academician and with vast potential of this technology it can possibly unfold new potential therapeutic drugs thereby greatly cutting research cost and time [7].

4.2 Unique dosage forms

Infinite dosage forms can be created using 3D printing. Inkjet-based 3D printing and inkjet powder-based 3D printing are the two main printing technologies employed in the pharmaceutical industry. Microcapsules, antiobiotic printed micropatterns, mesoporous bioactive glass scaffolds, nanosuspensions, and hyaluronan-based synthetic extracellular matrices are some of the novel dosage forms formulated using 3D printing [53] (**Table 3**).

Active pharmaceutical ingredients	Inactive pharmaceutical ingredients
Vancomycin	Glycerin
Ofloxacin	Methanol
Folic acid	Acetone
Dexamethasone	Surfactants (likeTween 20)
Theophylline	Kollidon SR
Acetaminophen	Ethanol-dimethyl sulfoxide
Paclitaxel	Propylene glycol
Tetracycline etc.	Cellulose etc.

Table 3.
List of active and inactive ingredients used in 3D printing.

4.3 Personalized drug dosing

Increasing the efficacy of drugs and at the same time reducing the chances of adverse reaction should be the aim of drug development, which can be achieved by using 3D printing to fabricate personalized medications [7, 26, 53].

Oral tablets are prepared by mixing, milling, and dry and wet granulation of powder ingredients, which are eventually compressed to form tablets; till today, tablets are the most popular dosage form because of the ease of preparation, good patient compliance and accurate dosing and because they are painless. However, no method is available that can prepare personalized solid dosage forms like tablets.

In the traditional way of preparing tablets, drugs can easily undergo degradation if proper guidelines are not followed, leading to altered therapeutic value of the final product. Moreover, these conventional methods cannot be used to prepare customized dosage forms that possess long-lasting stability, novel drug release profile, and detailed geometries [26].

Drugs with narrow therapeutic index can easily be prepared using 3D printing; and, by knowing the patient's pharmacogenetic profile and other characteristics like age, race etc., optimal dosage can be given to the patient [53].

Preparation of entirely new formulation is another vital potential of 3D printing for instance fabrications of pills that have a blend of more than one active pharmaceutical ingredient or dispensed as multi-reservoir printed tablets. Hence patients suffering from more than one disease can get their formulation ready in one multi-dose form at the healthcare point itself, thereby providing personalized and accurate dose to the patient with better or best compliance [26].

4.4 Complex drug release profile

In most conventional compressed dosage forms, a simple drug release profile which is a homogenous mixture of active ingredients is observed. Whereas in 3D printed dosage forms, a complex drug release profile that allows fabrication of complex geometries that are porous and loaded with multiple drugs throughout, surrounded by barrier layers that modulate release, is found [55]. One example is the printing of a multilayered bone implant with a distinct drug release profile alternating between rifampicin and isoniazid in a pulse release mechanism. 3D printing has also been used to print antibiotic micropatterns on paper, which have been used as drug implants to eradicate *Staphylococcus epidermidis* [53].

In a research concerning drug release profiles, chlorpheniramine maleate was 3D printed onto a cellulose powder substrate in amounts as small as 10–12 moles to demonstrate that even a minute quantity of drug could be released at a specified time. This study displayed improved accuracy for the release of very small drug doses compared with conventionally manufactured medications [53].

5. Customized implants and prostheses

By the support of MRI, CT scan, and X-ray and its translation into .stl 3D print files, implants and prostheses of any possible shape can be made [1, 7, 55].

Standard as well as complex surgical implants and prosthetic limbs can be made as per need in time as less as 24 hours. Spinal dental and hip implants have been fabricated so far but their validation is a time-consuming process. Previously, in order to achieve a desired shape and size that fits perfectly, surgeons had to craft metal and plastic pieces and perform bone grafting or use drill machines to modify the implants [2, 7]. This also stands correct in neurosurgery cases due to the irregular shape of the skull whose standardization is a complex procedure.

Some examples of commercially and clinically successful 3D printed implants and prostheses are as follows:

a. First 3D printed titanium mandibular porsthesis was implanted successfully at BIOMED Research Institute in Belgium [1].

b. Dental, orthopedic, maxillofacial, and spinal implants are manufactured by a company named Layer Wise [55].

c. Invisalign braces is another successful commercial use of 3D printing.

By using silver nanoparticles, chondrocytes, and silicon, a prosthetic ear was made out of 3D printing technology that was able to detect electromagnetic frequencies. The impact of this technology is so extensive in the field of hearing aids that today 99% of customized hearing aids are made using 3D printers, because, as everyone's ear canal has a different shape, this technology is able to provide perfect fit for each receiver and, moreover, the devices can be produced efficiently and cost effectively [7].

6. Anatomical models for surgical preparations

In order to have successful medical procedures, knowledge about patients' specific anatomy before medical surgery is essential due to variations in individual and complex human anatomy. 3D printed models have helped extensively in this respect, making them a vital tool for surgical methods [1, 55].

One of the most complicated structures of human body is the head, whose 3D printed neuro-anatomical models are of great help to neurosurgeons. Sometimes, it is very difficult to gain detailed information about the connections between skull architecture, cerebral structure, cranial nerves, and vessels from radiographic 2D images only and even a slight error in the medical procedure can be fatal. Here comes the role of 3D models, which are more realistic and provide in detail comparison and contrast between a normal brain structure and a brain with deformity or lesions, which suggest the surgeons more safe procedures to follow.

- For liver transplant, Japan's Kobe University Hospital had used 3D printed models by using replica of patients' own organ, to find out how to precisely craft a donor liver with least tissue loss [1].
- 3D printed model of calcified aorta for surgical planning of plaque removal was used by surgeons [55].
- To study aerosol drug delivery to lungs, airways of premature infants was reconstructed using 3D printing technology [55].

7. Conclusion

3D printing technology is a valuable and potential tool for the pharmaceutical sector, leading to personalized medicine focused on the patients' needs. It offers numerous advantages, such as increasing the cost efficiency and the manufacturing speed. 3D printing has revolutionized the way in which manufacturing is done. It improves the design manufacturing and reduces lead time and tooling cost for new products. This chapter has summarized different fabrication methods and some notable applications of 3D printing in the healthcare sector, especially in pharmaceutical sciences.

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