**3D PRINTING IN PHARMACEUTICAL SECTOR**

**ABSTRACT**

Growing demand for customized pharmaceutics and medical devices makes the impact of additive manufacturing increased rapidly in recent years. The 3D printing has become one of the most revolutionary and powerful tool serving as a technology of precise manufacturing of individually developed dosage forms, tissue engineering and disease modelling. 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 3D printing, types of 3D printing, and its applications in various pharmaceutical sector.

**Keywords:** 3D printing, Stereolithography, Fused depositing modelling, additive manufacturing.

**INTRODUCTION**

The patient-centric drug product development has gained a lot of attention during the past decade. The emphasis was on innovative procedures and new dosage formulations. Growing demand for customized devices combined with an expansion of technological innovation drives the major progress in personalized medicine expressed e.g., by the production of small series of individually-selected doses and tailor-made prostheses meet the anatomical needs of patients. The most ground-breaking and potent of the many innovations made and introduced to the pharmaceutical and biomedical markets is thought to be three-dimensional printing (3DP).1 This method is acknowledged as a flexible tool for precisely constructing a variety of devices. It functions as a technology for creating novel dosage forms, engineering tissues and organs, and modelling diseases. Nowadays, three-dimensional printing is one of the fastest developing branch of technology, art, and science, and still broadens the applications. The term three-dimensional printing was defined by International Standard Organization (ISO) as: “fabrication of objects through the deposition of a material using a print head, nozzle, or another printer technology”.2

This approach is one of the ways of additive manufacturing (AM), where the parts are generated from 3D model data in the process of combining materials layer by layer, in contrast to regularly used subtractive and formative manufacturing methodologies. Rapid prototyping (RP) is the name of the practical application of additive manufacturing. Its benefits include the reduction of prototyping time and costs, ease of product modifications at the designed level, and the ability to produce small objects, individualized product series, or structures that are impossible to form using subtractive methods.3

With the use of 3D computer-aided design (CAD) files, a concept is turned into a prototype in this technology, allowing for the fabrication of digitally controlled and customised goods.4 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.5

**HISTORY OF 3D PRINTING**

Hideo Kodama, at the Nagoya Municipal Industrial Research Institute in Japan, was one of the first to develop a rapid prototyping technique using a single laser beam.6, 7 Though he submitted a patent application for this invention in 1980, it expired without proceeding to the later stages of the Japanese patent process. In 1980 and 1981, he published papers on his experiments to develop methods for automatic fabrication of three-dimensional models using UV rays and a photosensitive resin, using a mask to control exposure of UV source. He described techniques of solidifying thin consecutive layers of photopolymer key aspects of what would later be called stereolithography (SLA). 8

In 1984, Charles Hull invented stereolithography. He was issued a patent for stereolithography in 1986, and in the patent described a process in which liquid polymers were hardened under UV light to form cross-sections of a 3D model.9 This method used digital data and a computer-controlled beam of light to create each layer, one on top of the other. Hull subsequently founded 3D Systems, which eventually produced and sold stereolithography machinery. The first commercial SLA printer in the world was produced by 3D Systems in 1988. Around the same time as Hull’s SLA patent, Carl Deckard, at the time still an undergraduate student at the University of Texas, developed the concept of the selective laser sintering (SLS) process. SLS was based on the selective solidification of powder using a laser beam.10 Deckard went on to found Desktop Manufacturing Corporation (DTM Corp), which produced its first SLS printers in 1992. DTM was eventually acquired by 3D Systems. In 1993, Deckard founded Sinterstation 2000, which launched SLS technology into the industry.11 S. Scott and Lisa Crump founded the company Stratasys, and in 1989 filed a patent for a form of rapid prototyping called fused deposition modelling (FDM), in which a plastic filament or metal wire was heated in a nozzle and extruded. Its deposition was guided by a computer, based on a predetermined digital model. Each layer was kept at a temperature just below solidification point for good interlayer adhesion.12 Stratasys eventually developed thermoplastic and printer systems for 3D printing.



 Fig. No. 1 Diagrammatic illustration of Stereolithography

Later in 1989, Hans Langer in Germany formed Electro Optical Systems (EOS), with a focus on direct metal laser sintering, which fabricated 3D parts directly from computer design models. This technology used selective exposure of a laser to metal powder for liquid phase sintering.13 EOS sold its first stereo system in 1994, and is recognized today for industrial prototyping. EOS acquired the right to all DTM patents related to laser sintering in 2004.14 In the early 1990s, several other 3D printing techniques were being investigated. Ballistic Particle Manufacturing, patented by William Masters, projected microdroplets of molten wax material from a jet moving in an X-Y plane to form thin cross-sections. The stationary platform moved in the Z-axis to allow for each layer of the 3D object to be added.15

Michael Feygin filed a patent for laminated object manufacturing in 1995, which used automated formation of cross-sectional slices from sheet material according to a digital 3D model, then stacking and bonding the layers to form a solid object. However, Feygin’s company, Helisys Inc., soon went out of business due to financial difficulties.16 Solid ground curing was invented by Itzchak Pomerantz, and used an optical mask system to selectively expose layers of photocurable resin. The remaining liquid was then removed and replaced with wax, which was then milled to form a flat substrate for the next layer.17

In the mid-1990s, the 3D printing industry split into 2 areas of focus: high end for highly engineered complex parts (e.g., medical) and printers for concept development and functional prototyping user-friendly, cost effective. By the end of the 1990s, only three original companies remained: 3D Systems, Statasys, and EOS.

**Advantages of 3D printing in the pharmaceutical field**:

* 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.18
* 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.18
* 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.19, 20 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.21
* 3DP allows controlled size of droplets, complex drug release profiles, strength of dosage and multi-dosing. 22, 23, 24

**Disadvantages of 3D Printing:**

* In inkjet printing, proper flow of ink can only be achieved with ink that has precise viscosity.25
* 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. 26
* Rate of drug release may get affected due to binding of ink with other printer materials. 27

**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.28-30

This digital model is then converted to (.STL) digital file format which stands for standard tessallation language or stereolithography.28

Triangulated facets give information regarding the surface of the 3D model that is present in the (.STL) file.28

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.

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.28, 5

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 colour, texture, properties, and other features.31

**TYPES OF 3D PRINTING**

**FUSED DEPOSITION MODELLING (FDM)**

Since this method is by far the most used and in many ways the simplest of the choices, most people interpret 3-D printing to be fused deposition modelling (FDM). The most common polymers used in FDM are PLA (polylactic acid) and ABS (acrylonitrile butadiene styrene), which have a range of melting points and can fuse when melted and resolidified. Because it uses standard Cartesian coordinates (X, Y, and Z) to produce the printed items, the most typical configuration for an FDM printer is known as a Cartesian print engine. Even within this broad category, there are many kinds of printers, but two are more popular than others: the MakerBot style, which uses a fixed plane X and Y printhead and movable Z print bed, and the so-called "RepRap" style, which uses a fixed plane X axis while the Y axis is controlled by moving the print bed itself and the Z axis is achieved by moving the entire printhead system vertically upwards.

There is at least one other significantly different geometry for an FDM printer, the layout that is called a delta printer. In this instance, the printhead is suspended from three arms that are controlled along vertical supports while the print bed is completely stationary. This arrangement allows the printhead to “float” above the print bed and be located at any physical point in three dimensions simply by altering the relation of each of the three arms to the other. This is the same sort of control geometry at work in the flying cameras used in NFL games, applied to a robot.32

**STEREOLITHOGRAPHY (SLA)**

Healy et al. developed oral dosage forms including aspirin and paracetamol in concentrations of 2.5% and 5% using SLA as the AM method. Drugs were manufactured using a photopolymerisable resin and a SLA 3D printer. The possibility for mass production of oral dosage forms using SLA was demonstrated by Healy et al., who were able to create 28 pharmacological dosage forms in one print cycle. The dimensions of printed dosage forms varies from the design, and this study also highlighted the impact of drug addition on those dimensions. This draws attention to a subject that will need further study: the impact of adding materials on printed goods.33

Robles-Martinez et al., were able to construct a novel SLA printing method that allowed the production of multi-layered tablets (polypills) that had flexible drug content and shape. The drugs chosen for the work were paracetamol, caffeine, naproxen, chloramphenicol, prednisolone and aspirin. Three different tablets shapes were printed: cylinder, ring, and ring with a soluble filler. Raman microscopy confirmed the spatial separation of the drugs but also showed the ability of certain drugs (naproxen, aspirin, and paracetamol) to diffuse between the layers due to its solid-state characteristics. Dissolution tests showed that the polypill geometry and the type of excipient affected the drug release allowing distinct release profiles for each of the six drugs. This study showed the possibility to use SLA 3DP for fabricating multi-drugs tablets to improve personalisation for patients.34, 35

**SELECTIVE LASER SINTERING (SLS)**

Similar to SLA, this form of additive manufacturing uses lasers, however instead of using resin like SLA does, powder materials are fused together. For the first time, SLS 3DP was used by Awad et al. to create tiny oral dosage forms with altered release characteristics. They created dual miniprintlets using paracetamol and ibuprofen as well as single miniprintlets using paracetamol as a model medicine. Ethyl cellulose (EC) was used as the primary polymer matrix for the individual miniprintlets. Dual miniprintlets were used, with the first layer having EC for prolonged release and the second layer having Kollicoat IR (a graft copolymer made of PEG: PVA, 1:3) for immediate release.36

Miniprintlets of two different diameters, 1 mm and 2 mm, have been developed in order to evaluate the impact size has on dissolving qualities. When the diameter was increased, the sluggish paracetamol release seen in the single miniprintlets was sped up. The diameter has no impact on the release profile of paracetamol for the twin miniprintlets. This work demonstrates how numerous Active Pharmaceutical Ingredients (APIs) with various release qualities can be combined using SLS 3D printing to create a single dosage form.36

**DIGITAL LIGHT PROCESSING (DLP)**

Another 3DP approach that is comparable to SLA is DLP. is a resin-based technique, however DLP employs UV light from a projector to cure each layer of the 3D printed product rather than a laser-focused UV beam. Ibuprofen pills were made by Madzarevic et al. using DLP 3DP technology. Eleven formulations were created using Design Expert software's D-optimal mixture design. It has been observed that adding more water lengthens the printing process. The effects of the components and printing settings on the release of ibuprofen were assessed using two artificial neural networks (STATISTICA 7.0 and MATLAB R2014b). The data obtained from these two software were compared with the one obtained experimentally. The drug release predicted with STATISTICA 7.0 was quite similar to the one obtained experimentally. This study described that suitable ANN allows to recognise the input–output relationship in DLP printing of pharmaceutics.27

**STENCIL PRINTING**

Wickstrom et al. suggest a brand-new printing technique that hasn't been applied to the production of pharmaceuticals. The purpose of this study was to determine whether it was possible to develop drug-containing polymer inks that could be used to create flexible dosage forms and produce goods with acceptable homogeneity and mass content. Using a prototype stencil printer and polyester as the stencil material, haloperidol (HAL) discs were manufactured. The dose was determined by the geometry of the stencil, and doses were changed by varying the aperture areas and stencil heights. The therapeutic HAL, which met the requirements for homogeneity in both mass and substance, was successfully developed for the treatment of children aged 6 to 17. Using 16% hydroxypropyl methylcellulose (HPMC) and 1% lactic acid, the HAL dosage was attained. The outcomes demonstrate that the medication was amorphous upon printing and that the pH stayed above pH 4. Disintegration tests revealed that the printed orodispersible discs had disintegration times under 30 s. As a result, it was determined that the unique technique of batchwise stencil printing might be employed as a practical way for producing medicines.38

**EMBEDDED 3D PRINTING (E-3DP)**

In an innovative use of additive manufacturing (AM), a viscoelastic ink is extruded into a reservoir that is hardening using a deposition nozzle along a predetermined path. One of the earliest examples of creating chewable oral dosage forms employing e-3DP in the pharmaceutical industry was presented by Rycerz et al. by loading two drugs. Paracetamol and ibuprofen, the two drugs, were suspended in a locust gum solution and an embedding medium made of a matrix substance based on gelatin. These were solidified at room temperature after being printed at a high temperature of 70 C. The printed dosage forms were given different doses by specifically changing the printing patterns. We looked at the rheology, printing speed, and needle size of the embedding phase. This proof-of-concept study demonstrated the potential for e-3DP to be used to print innovative paediatric oral dose forms with individualised dosing and geometry, which might incorporate a variety of materials.39

**SEMISOLID EXTRUSION PRINTING (EXT) AND INKJET PRINTING (IJP)**

Blom et al. compared two cutting-edge printing techniques, semisolid extrusion 3D printing (EXT) and inkjet printing (IJP), with the traditional manufacturing method to produce patient-tailored doses of the anticoagulant drug warfarin at Helsinki University Hospital (HUS) Pharmacy, Finland's largest hospital pharmacy. Printed orodispersible films (ODFs) displayed higher uniformity, thickness, and flexibility than oral powders in unit dosage sachets (OPSs). OPSs and ODFs were suitable for administration to the patients via a naso-gastric tube after remaining stable for a month. A Quick Response (QR) code was printed using IJP onto the ODFs in order to give more details about the dosage form and decrease medicine administration errors. The study demonstrated how printing technologies are promising techniques for the development of patient-specific dosage forms.40

**MEDICAL APPLICATIONS OF 3D PRINTING**

**Bioprinting of tissues and organs**

The failure of organs and tissues due to trauma, congenital flaws, ageing, etc. is one of the most serious medical problems, and the current treatment for this issue is organ transplantation from deceased or living donors. Only a select few fortunate individuals obtain organs, and the majority pass away from lack of donors. Additionally, the costs associated with organ transplant treatments put them beyond the means of the average person. The difficulty in finding tissue-matched donors is another challenge with transplant surgery. The essential tissue or organ should be created using the patient's own body cells to reduce the danger of tissue or organ rejection. Additionally, this will reduce the need for immunosuppressants, which is the solution to this problem.41

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. The cells are then sown onto scaffolds that control cell division and proliferation to develop a functional tissue. Additional benefits of 3D bioprinting over conventional tissue creation include accurate cell placement, digitally controlled speed, drop volume, resolution, cell concentration, and printed cell diameter. The materials used to build the scaffolds vary depending on their porosity, the type of tissue they are intended to support, and their required strength. According to some, hydrogels are the best materials for creating soft tissues.42

Organ printing is undoubtedly still in the early stages of development, but numerous studies have provided evidence to support the idea. Using 3D printers, scientists have created artificial heart valves, cartilage, and bone. In order to create an artificial liver, Wang et al. used 3D bioprinting technology to deposit diverse cells inside different biocompatible hydrogels. Due to the immense potential of this technology and the growing interest of academics and researchers, it may be able to reveal new possible medicinal medications, drastically reducing the cost and time of research.43

**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. Different medical applications of 3D printing technology employed in the pharmaceutical industry. Microcapusles, 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. 41

**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. 43

Tablets are the most widely used dosage form due to their simplicity in preparation, high patient compliance, precise dosing, and lack of discomfort. Oral tablets are made by mixing, milling, and dry and wet granulating powder ingredients, which are then compressed to form tablets.

However, there is currently no means for creating individualised solid dosage forms like tablets. If suitable procedures are not followed when making tablets the traditional method, medicines can readily degrade, changing the end product's therapeutic usefulness. Additionally, these traditional techniques cannot be utilised to create customised dosage forms with new drug release profiles, long-lasting stability, and intricate geometries. 43

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. 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.

**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.

A multilayered bone implant printed with a different medication release profile that alternates between rifampicin and isoniazid in a pulse release mechanism is one illustration. Antibiotic micropatterns printed on paper using 3D printing have also been employed as medication implants to get rid of Staphylococcus epidermidis. Chlorpheniramine maleate was 3D printed onto a cellulose powder substrate in levels as tiny as 10–12 moles in a study on drug release profiles to show that even a little amount of drug could be released at a predetermined period. This study showed that the release of very small pharmacological doses was more accurate than when routinely synthesised drugs were used. 43

**Wound Dressing**

Growing demand for tailor-made functionalized materials has become a driving force for the development of additively manufactured structures. Nanotechnological approaches address many of challenges faced by modern medicine, however the safety of their use is still under intensive investigation. Although such approaches provide application of antibacterial nanoparticles and carriers of factors improving the wound healing, they are difficult for industrial application. It opens a new challenging field for additive manufacturing as a technique sufficient to produce personalized and d safe materials of complex architecture and functionalities. 44

Muwaffak described the production of PCL-based patient-specific antibacterial wound dressings that contain added zinc, copper, and silver. Hot melt extrusion was used to create the metal-homogeneously loaded filaments, which were then used to print 3D versions of the nose and ears. The antibacterial and various metals released from the wound dressings over an extended period of time. It was determined that the anatomically adaptive dressings were more affordable than traditional flat dressings. 45

**CONCLUSION**

The 3D printing of drug delivery systems and medical devices serves as an attractive tool to produce customized product. Since few years the concept of 3D-printed drug formulation quickly evolved and was directed to enhance therapy by patient-centric medicine. This promising technology offers formulation flexibility that is difficult to achieve with the conventional technological processes. Additional manufacturing allows to prepare different kind of dosage forms with high precision of API-excipients ratio, in totally new manner with comparison to traditional pharmaceutical manufacturing. The added value of the 3D printing is also opportunity to create multifunctional drug delivery systems, multidrug devices, and drug formulations for personalized therapy with accelerated release characteristic. This chapter has summarized different fabrication methods and some notable applications of 3D printing in the healthcare sector, especially in pharmaceutical sciences.

**ABBREVIATIONS**

3DP – 3D printing

ISO – International Standard Organization

RP – Rapid Prototyping

CAD - computer-aided design

UV - Ultraviolet

SLA - Stereolithography

SLS – Selective Laser Sintering

DTM Corp - Desktop Manufacturing Corporation

FDM – Fused Deposition Modelling

EOS - Electro Optical Systems

PLA - polylactic acid ABS-acrylonitrile butadiene styrene

EC - Ethyl cellulose

APIs - Active Pharmaceutical Ingredients

DLP – Digital Laser Printing

HAL - Haloperidol

HPMC - Hydroxypropyl Methylcellulose (HPMC)

AM – Additive manufacturing (AM)

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