**3D PRINTING IN PHARMACEUTICAL SECTOR: A REVIEW**

**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 case- centric medicine product development has gained a lot of attention during the once decade. The emphasis was on innovative procedures and new lozenge phrasings. Growing demand for customized bias combined with an expansion of technological invention drives the major progress in individualized drug expressed e.g., by the product of small series of collectively- named boluses and knitter- made prostheses meet the anatomical requirements of cases.

The most honed- breaking and potent of the numerous inventions made and introduced to the medicinal and biomedical requests is allowed to be three- dimensional printing (3DP).1 This system is conceded as a flexible tool for precisely constructing a variety of bias. It functions as a technology for creating new lozenge forms, engineering apkins and organs, and modelling conditions. currently, three- dimensional printing is one of the fastest developing branch of technology, art, and wisdom, and still broadens the operations.

The term three- dimensional printing was defined by International Standard Organization (ISO) as “fabrication of objects through the deposit of a material using a print head, snoot, or another printer technology. ”2 This approach is one of the ways of cumulative manufacturing (AM), where the corridor are generated from 3D model data in the process of combining accoutrements subcaste by subcaste, in discrepancy to regularly used subtractive and constructive manufacturing methodologies.

Rapid prototyping (RP) is the name of the practical operation of cumulative manufacturing. Its benefits include the reduction of prototyping time and costs, ease of product variations at the designed position, and the capability to produce small objects, personalized product series, or structures that are insolvable to form using subtractive styles.3

With the use of 3D computer- backed design (CAD) lines, a conception 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 accoutrements like living cells, wood, amalgamation, thermoplastic, essence etc. are placed on top of each other in order to make the needed 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-fire prototyping fashion using a single ray ray.6, 7 Though he submitted a patent operation for this invention in 1980, it expired without pacing to the after stages of the Japanese patent process. In 1980 and 1981, he published papers on his trials to develop styles for automatic fabrication of three- dimensional models using UV shafts and a photosensitive resin, using a mask to control exposure of UV source. He described ways of solidifying thin successive layers of photopolymer crucial aspects of what would latterly be called stereolithography (SLA).8 In 1984, Charles Hull constructed 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 system used digital data and a computer- controlled shaft of light to produce each subcaste, one on top of the other. Housing latterly innovated 3D Systems, which ultimately produced and vended stereolithography ministry.

The first marketable 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 pupil at the University of Texas, developed the conception of the picky ray sintering (SLS) process. SLS was grounded on the picky solidification of greasepaint using a ray ray.10

Deckard went on to set up Desktop Manufacturing Corporation (DTM Corp), which produced its first SLS printers in 1992. DTM was ultimately acquired by 3D Systems. In 1993, Deckard innovated Sinterstation 2000, which launched SLS technology into the assiduity.11

S. Scott and Lisa Crump innovated the company Stratasys, and in 1989 filed a patent for a form of rapid-fire prototyping called fused deposit modelling (FDM), in which a plastic hair or essence line was hotted in a snoot and extruded. Its deposit was guided by a computer, grounded on a destined digital model. Each subcaste was kept at a temperature just below solidification point for good interlayer adhesion.12 Stratasys ultimately developed thermoplastic and printer systems for 3D printing.

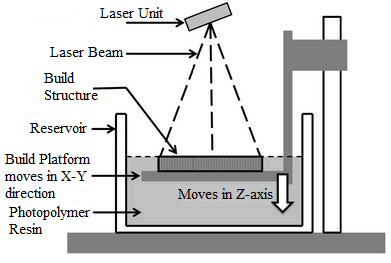


Fig. No. 1 Diagrammatic illustration of Stereolithography

Latterly in 1989, Hans Langer in Germany formed Electro Optical Systems (EOS), with a focus on direct essence ray sintering, which fabricated 3D corridor directly from computer design models. This technology used picky exposure of a ray to essence greasepaint for liquid phase sintering.13 EOS vended its first stereo system in 1994, and is honoured moment for artificial prototyping. EOS acquired the right to all DTM patents related to ray sintering in2004.14

In the early 1990s, several other 3D printing ways were being delved. Ballistic flyspeck Manufacturing, patented by William Masters, projected microdroplets of molten wax material from a spurt moving in an X-Y plane to form thin cross-sections. The stationary platform moved in the Z- axis to allow for each subcaste of the 3D object to be added.15

Michael Feygin filed a patent for laminated object manufacturing in 1995, which used automated conformation of cross-sectional slices from distance material according to a digital 3D model, also mounding and relating the layers to form a solid object. still, Feygin’s company, HelisysInc., soon went out of business due to fiscal difficulties.16

Solid ground curing was constructed by Itzchak Pomerantz, and used an optic mask system to widely expose layers of photocurable resin. The remaining liquid was also removed and replaced with wax, which was also mulled to form a flat substrate for the coming subcaste.17

In themid-1990s, the 3D printing assiduity resolve into 2 areas of concentrate high end for largely finagled complex corridor (e.g., medical) and printers for conception development and functional prototyping stoner-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 snappily in discrepancy to traditional styles especially when it comes to fabrication of particulars like prosthetics and implants with a fresh benefit of better resolution, repetition, further delicacy, and trustability.18
* Customization and personalization: One of the colonist benefits of this technology is the liberty of fabrication of customized medical outfit and products, tailored implants, prosthetics, surgical tools, institutions can be a great boon to cases as well as croakers.18
* Increased cost effectiveness: Objects produced by 3D printing are of low cost. It's an advantage for small- scale product units or for companies that produce largely complex products or corridor because nearly all constituents are affordable.19, 20 By eradicating the use of gratuitous coffers, manufacturing cost can also be reduced. For case, 20- mg tablets could be potentially formulated as 1- mg tablets as per need.21
* 3DP allows controlled size of driblets, complex medicine release biographies, strength of lozenge and multi-dosing. 22, 23, 24

**Disadvantages of 3D Printing**

* In inkjet printing, proper inflow of essay can only be achieved with essay that has precise density.25
* Essay expression material should have the property of tone- list but shouldn't bind to other printer rudiments. In some expression when the essay doesn't retain acceptable tone- binding property or it binds with other rudiments of printer also the attendant expression doesn't have needed hardness.
* Rate of medicine release may get affected due to list of essay with other printer accoutrements.27

**3D PRINTING PROCEDURE**

First, a virtual 3D design of an object using digital design software like Onshape, Solidworks, Creo parametric, Autocad, Autodesketc. iscreated.28-30 

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



Triangulated angles give information regarding the face of the 3D model that's present in the (. STL) train.28



The (. STL) train is converted into G train by slicing the design into a series of 2D verticalcross-sections by the help of technical slicer software, which is installed in the 3D printer.



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



The print head is now allowed to move in the z- axis, thereby depositing the layers successionally of the asked material, hence creating a complete 3D object.28, 5

Maximum figures of 3D printing technologies are compatible with (. STL) train format. Some crimes might do during the conversion of the 3D model to. STL digital train; thus, software like wizardries (Materialise) can be employed to correct the crimes during conversion. train formats other than. STL like cumulative manufacturing train format (AMF) and 3D manufacturing format (3MF) are used as. STL doesn't have information regarding the type of material, its colour, texture, parcels, and other features.31

**TYPES OF 3D PRINTING**

**FUSED DEPOSITION MODELLING (FDM)**

Since this system is by far the most habituated and in numerous ways the simplest of the choices, utmost people interpret 3- D printing to be fused deposit 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 equals (X, Y, and Z) to produce the published particulars, the most typical configuration for an FDM printer is known as a Cartesian print machine. Indeed within this broad order, there are numerous kinds of printers, but two are more popular than others the MakerBot style, which uses a fixed aeroplane X and Y printhead and portable Z print bed, and the so- called" RepRap" style, which uses a fixed aeroplane 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 overhead.

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

**STEREOLITHOGRAPHY (SLA)**

Healy etal. developed oral lozenge forms including aspirin and paracetamol in attention of 2.5 and 5 using SLA as the AM system. Medicines were manufactured using a photopolymerisable resin and SLA 3D printer. The possibility for mass product of oral lozenge forms using SLA was demonstrated by Healy etal., who were suitable to produce pharmacological lozenge forms in one print cycle.28 The confines of published lozenge forms varies from the design, and this study also stressed the impact of medicine addition on those confines. This draws attention to a subject that will need farther study the impact of adding accoutrements on published goods.33

Robles- Martinez etal., were suitable to construct a new SLA printing system that allowed the product of multi-layered tablets (polypills) that had flexible medicine content and shape. The medicines chosen for the work were paracetamol, caffeine, naproxen, chloramphenicol, prednisolone, and aspirin. Three different tablets shapes were published cylinder, ring, and ring with a answerable padding. Raman microscopy verified the spatial separation of the medicines but also showed the capability of certain medicines (naproxen, aspirin, and paracetamol) to diffuse between the layers due to its solid- state characteristics. Dissolution tests showed that the polypill figure and the type of excipient affected the medicine release allowing distinct release biographies for each of the six medicines. This study showed the possibility to use SLA 3DP for fabricating multi-drugs tablets to ameliorate personalisation for cases.34, 35

**SELECTIVE LASER SINTERING (SLS)**

Analogous to SLA, this form of cumulative manufacturing uses spotlights, still rather of using resin like SLA does, greasepaint accoutrements are fused together. For the first time, SLS 3DP was used by Awad etal. To produce bitsy oral lozenge forms with altered release characteristics. They created binary miniprintlets using paracetamol and ibuprofen as well as single miniprintlets using paracetamol as a model drug. Ethyl cellulose (EC) was used as the primary polymer matrix for the individual miniprintlets. Binary miniprintlets were used, with the first subcaste having EC for prolonged release and the alternate subcaste having Kollicoat IR (a graft copolymer made of PEG PVA, 13) for immediate release.36 Miniprintlets of two different compasses, 1 mm and 2 mm, have been developed in order to estimate the impact size has on dissolving rates. When the periphery was increased, the sluggish paracetamol release seen in the single miniprintlets was sped up. The periphery has no impact on the release profile of paracetamol for the binary miniprintlets. This work demonstrates how multitudinous Active Pharmaceutical constituents (apis) with colorful release rates can be combined using SLS 3D printing to produce a single lozenge form.36

**DIGITAL LIGHT PROCESSING (DLP)**

Another 3DP approach that's similar to SLA is DLP. is a resin- grounded fashion, still DLP employs UV light from a projector to cure each subcaste of the 3D published product rather than a ray- concentrated UV ray. Ibuprofen capsules were made by Madzarevic etal. using DLP 3DP technology. Eleven phrasings were created using Design Expert software's D- optimal admixture design. It has been observed that adding further water lengthens the printing process. The goods of the factors and publishing settings on the release of ibuprofen were assessed using two artificial neural networks (STATISTICA7.0 and MATLAB R2014b). The data attained from these two software were compared with the one attained experimentally. The medicine release prognosticated with STATISTICA7.0 was relatively analogous to the one attained experimentally. This study described that suitable ANN allows to honour the input – affair relationship in DLP printing of pharmaceutics.27

**STENCIL PRINTING**

Wickstrom etal. suggest a brand-new printing fashion that hasn't been applied to the product of medicinals. The purpose of this study was to determine whether it was possible to develop medicine- containing polymer inks that could be used to produce flexible lozenge forms and produce goods with respectable unity and mass content. Using a prototype stencil printer and polyester as the stencil material, haloperidol (HAL) discs were manufactured. The cure was determined by the figure of the stencil, and boluses were changed by varying the orifice areas and stencil heights. The remedial HAL, which met the conditions for unity in both mass and substance, was successfully developed for the treatment of children progressed 6 to 17. Using 16 hydroxypropyl methylcellulose (HPMC) and 1 lactic acid, the HAL lozenge was attained. The issues demonstrate that the drug was unformed upon printing and that the pH stayed above pH 4. Decomposition tests revealed that the published orodispersible discs had decomposition times under 30 s. As a result, it was determined that the unique fashion of batchwise stencil printing might be employed as a practical way for producing drugs.38

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

In an innovative use of cumulative manufacturing (AM), a viscoelastic essay is extruded into a force that's hardening using a deposit snoot along a predetermined path. One of the foremost exemplifications of creating chewable oral lozenge forms employinge-3DP in the pharmaceutical assiduity was presented by Rycerz etal. by loading two medicines. Paracetamol and ibuprofen, the two medicines, were suspended in a locust goo result and an embedding medium made of a matrix substance grounded on gelatin. These were solidified at room temperature after being published at a high temperature of 70º C. The published lozenge forms were given different boluses by specifically changing the printing patterns. We looked at the rheology, publishing speed, and needle size of the embedding phase. This evidence- of- conception study demonstrated the eventuality fore-3DP to be used to publish innovative paediatric oral cure forms with individualised dosing and figure, which might incorporate a variety of accoutrements.39

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

Blom etal. compared two slice- edge printing ways, circumfluous extrusion 3D printing (EXT) and inkjet printing (IJP), with the traditional manufacturing system to produce case- acclimatized boluses of the anticoagulant medicine warfarin at Helsinki University Hospital (HUS) Pharmacy, Finland's largest sanitarium drugstore. published orodispersible flicks (ODFs) displayed advanced uniformity, consistence, and inflexibility than oral maquillages in unit lozenge sachets (OPSs). OPSs and ODFs were suitable for administration to the cases via a naso- gastric tube after remaining stable for a month. A Quick Response (QR) law was published using IJP onto the ODFs in order to give further details about the lozenge form and drop drug administration crimes. The study demonstrated how printing technologies are promising ways for the development of case-specific lozenge forms.40

**MEDICAL APPLICATIONS OF 3D PRINTING**

**Bioprinting of tissues and organs**

The failure of organs and apkins due to trauma, natural excrescencies, ageing,etc. is one of the most serious medical problems, and the current treatment for this issue is organ transplantation from departed or living benefactors. Only a select many fortunate individualities gain organs, and the maturity pass down from lack of benefactors. also, the costs associated with organ transplant treatments put them beyond the means of the average person. The difficulty in chancing towel- matched benefactors is another challenge with transplant surgery. The essential towel or organ should be created using the case's own body cells to reduce the peril of towel or organ rejection. also, this will reduce the need for immunosuppressants, which is the result to this problem.41 In the conventional system of towel engineering from a small towel sample, stem cells are insulated, composite with growth factor, and also multiplied in the laboratory. The cells are also sown onto pulpits that control cell division and proliferation to develop a functional towel. fresh benefits of 3D bioprinting over conventional towel creation include accurate cell placement, digitally controlled speed, drop volume, resolution, cell attention, and published cell periphery. The accoutrements used to make the pulpits vary depending on their porosity, the type of towel they're intended to support, and their needed strength. According to some, hydrogels are the stylish accoutrements for creating soft apkins.42 Organ printing is really still in the early stages of development, but multitudinous studies have handed substantiation to support the idea. Using 3D printers, scientists have created artificial heart faucets, cartilage, and bone. In order to produce an artificial liver, Wang etal. used 3D bioprinting technology to deposit different cells inside different biocompatible hydrogels. Due to the immense eventuality of this technology and the growing interest of academics and experimenters, it may be suitable to reveal new possible medicinal specifics, drastically reducing the cost and time of exploration.43

**Unique dosage forms**

horizonless lozenge forms can be created using 3D printing. Inkjet- grounded 3D printing and inkjet greasepaint- grounded 3D printing are the two main printing technologies. Different medical operations of 3D printing technology employed in the pharmaceutical assiduity. Microcapusles, antiobiotic published micropatterns, mesoporous bioactive glass pulpits, nanosuspensions, and hyaluronan- grounded synthetic extracellular matrices are some of the new lozenge forms formulated using 3D printing.41

**Personalized drug dosing**

Adding the efficacity of medicines and at the same time reducing the chances of adverse response should be the end of medicine development, which can be achieved by using 3D printing to fabricate substantiated specifics.43 Tablets are the most extensively used lozenge form due to their simplicity in medication, high case compliance, precise dosing, and lack of discomfort. Oral tablets are made by mixing, mulling, and dry and wet granulating greasepaint constituents, which are also compressed to form tablets. still, there's presently no means for creating individualised solid lozenge forms like tablets. However, drugs can readily degrade, changing the end product's remedial utility. If suitable procedures aren't followed when making tablets the traditional system. Also, these traditional ways cannot be utilised to produce customised lozenge forms with new medicine release biographies, long- lasting stability, and intricate shapes.43 Medicines with narrow remedial indicator can fluently be prepared using 3D printing; and, by knowing the case’s pharmacogenetic profile and other characteristics like age, raceetc., optimal lozenge can be given to the case. Preparation of entirely new expression is another vital eventuality of 3D printing for case fabrications of capsules that have a mix of further than one active pharmaceutical component or allocated asmulti-reservoir published tablets. Hence cases suffering from further than one complaint can get their expression ready in onemulti-dose form at the healthcare point itself, thereby furnishing substantiated and accurate cure to the case with better or stylish compliance.

**Complex drug release profile**

In utmost conventional compressed lozenge forms, a simple medicine release profile which is a homogenous admixture of active constituents is observed. Whereas in 3D published lozenge forms, a complex medicine release profile that allows fabrication of complex shapes that are pervious and loaded with multiple medicines throughout, girdled by hedge layers that modulate release, is set up. A multilayered bone implant published with a different drug release profile that alternates between rifampicin and isoniazid in a palpitation release medium is one illustration. Antibiotic micropatterns published on paper using 3D printing have also been employed as drug implants to get relieve of Staphylococcus epidermidis. Chlorpheniramine maleate was 3D published onto a cellulose greasepaint substrate in situations as bitsy as 10 – 12 intelligencers in a study on medicine release biographies to show that indeed a little quantum of medicine could be released at a predetermined period. This study showed that the release of veritably small pharmacological boluses was more accurate than when routinely synthesised medicines were used.43

**Wound Dressing**

Growing demand for knitter- made functionalized accoutrements has come a driving force for the development of additively manufactured structures. Nanotechnological approaches address numerous of challenges faced by ultramodern drug, still the safety of their use is still under ferocious disquisition. Although similar approaches give operation of antibacterial nanoparticles and carriers of factors perfecting the crack mending, they're delicate for artificial operation. It opens a new grueling field for cumulative manufacturing as a fashion sufficient to produce substantiated and d safe accoutrements of complex armature and functionalities.44 Muwaffak described the product of PCL- grounded case-specific antibacterial crack dressings that contain added zinc, bobby, and tableware. Hot melt extrusion was used to produce the essence- homogeneously loaded fibers, which were also used to publish 3D performances of the nose and cognizance. The antibacterial and colourful essence released from the crack 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

AM – Additive manufacturing

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