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3D Printing: A Revolution in Pharmaceutical Industry

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ABSTRACT

With the introduction of Three Dimensional (3D) Printing technology in medicines, pharmaceutical industry is set to join the fourth industrial revolution. 3D Printing technology is the most innovative and influential tool in which solid objects are constructed by depositing several layers in sequence under computer control. Three-dimensional (3D) Printed medicines may be a possible tool to understand personalized treatments adapted to the precise requirements of each and every individual patient, taking into consideration their age, weight, co-morbidities, pharmacogenetic and pharmacokinetic characteristics. 3DP technology offers a whip hand over the conventional technologies within the field of novel drug delivery system (NDDS). Novel dosage forms like microcapsules, complex drug-release profiles, nano-suspensions, and multilayered drug delivery devices can be fabricated by employing 3D printing technologies. Various sorts of 3 D Printing technologies used are inkjet printers, thermal inkjet printers, fused deposition modeling, hot melt extrusion etc. Applications of 3D Printing are widespread in pharma industries from lab grown organs to drug delivery devices, from anatomical models to personalized medicines then on. 3D Printing is now seen as a valuable, efficient and economical tool that has the potential to vary the future of general pharmacy practice and especially the pharmaceutical care.

Keywords: 3-Dimensional Printing (3DP), Drug Delivery, Novel Drug Delivery System, Thermal Inkjet Printing, Personalized Medicine.

INTRODUCTION

Efficient and safe transportation of a pharmacologically active compound i.e., the drug within the body to meet the required therapeutic efficacy is known as the drug delivery. Altering the pharmacokinetics of the drug by controlling its release profile helps in improving the efficacy and safety of the drug. [1] 3D printing has become one among the foremost technologies within the field of pharmaceutics. It offers high potential in personalized dosage form. [2] It is a completely unique novel rapid prototyping technique of fabricating solid objects by successive deposition of several layers in sequence. [1] Three-dimensional (3D) printing can be defined as a manufacturing method in which objects are made by fusing or depositing materials (such as plastic, metal, ceramics, powders, liquids, or even living cells) in layers to formulate a 3D object. [3] The rapid prototyping refers to the development of physical models using computer-aided design (CAD) in three dimensions. It is also referred to as additive manufacturing (because layer by layers of material are laid down under computer control) and solid free-form fabrication. [2]

HISTORY

3D printing technology first became visible by Hideo Kodama of Nagoya Municipal Industrial Research Institute when he invented a 3D plastic model with photo hardening polymer. But the major development was in 1984 when Charles Hull, (later became the co-founder of 3D systems) invented Stereolithography. [4]

Table 1: Historical Development in the Field of 3D Printing [5]

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)

Year	Major development
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

ADVANTAGES [1, 5, 6]

- Precise and accurate dosing of potent drugs.
- Cost of production decreases because of minimal wastage.
- Narrow therapeutic window.
- Individual and personalized medication.
- High drug loading as compared to conventional dosage forms.
- 3D printers are affordable and occupy less space.
- Manufacturing of small batches is possible.
- 3DP allows controlled size of droplets, complex drug release profiles, strength of dosage and multi dosing.

DISADVANTAGES [5-6]

- In inkjet printers, ink having high precise viscosity can only be used.
- Ink formulation material should be self binding but shouldn't bind to the other parts of the printer.
- Rate of drug release is affected when ink binds with printer materials.
- Printing of large objects is not possible.
- Limited types of raw materials can be used.

TYPES OF 3D PRINTING TECHNOLOGIES

1. Thermal Ink-Jet Printing [5, 7]

Thermal inkjet printing involves the heating of ink fluid by a micro-resistor that converts the aqueous to vapor and expands to push the ink drop out of a nozzle. It is used in-

- preparation of drug-loaded biodegradable microspheres
- drug-loaded liposomes
- patterning microelectrode arrays coating and loading drug eluting stents

- producing biological films without compromising protein activity
- dispensing of extemporaneous preparation/solution of drug onto 3D scaffolds

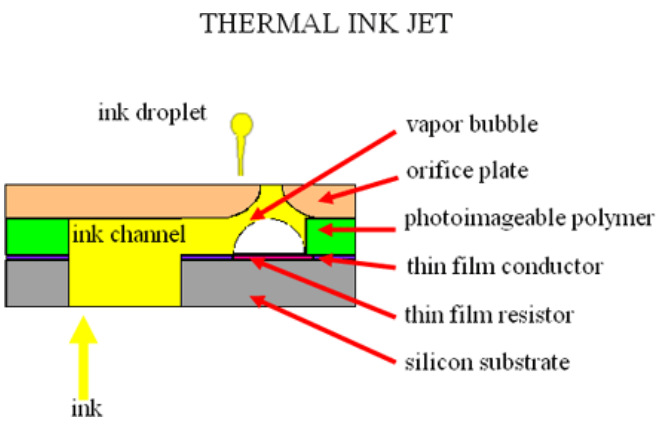

Figure 1: Thermal Inkjet Technique in 3D Printing [7]

2. 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. [5] To be used for pharmaceutical purposes, the ink is replaced with the pharmaceutical solutions containing drugs and edible sheets referred to as substrates are utilized in place of normal paper. [4, 8] Inkjet printing gives a high resolution printing capability because it deposits ink on the substrate either in the form of Continuous Inkjet printing (CIJ) or Drop on Demand (DoD) printing. Inkjet printing is additionally called as 'mask-less' or 'tool-less' approach. [7]

Advantages of inkjet printing includes- [9]

- low processing cost
- rapid processing rates
- generation of minimal waste
- it gives CAD information in a 'direct write' manner and
- it process material over large areas with minimal contamination

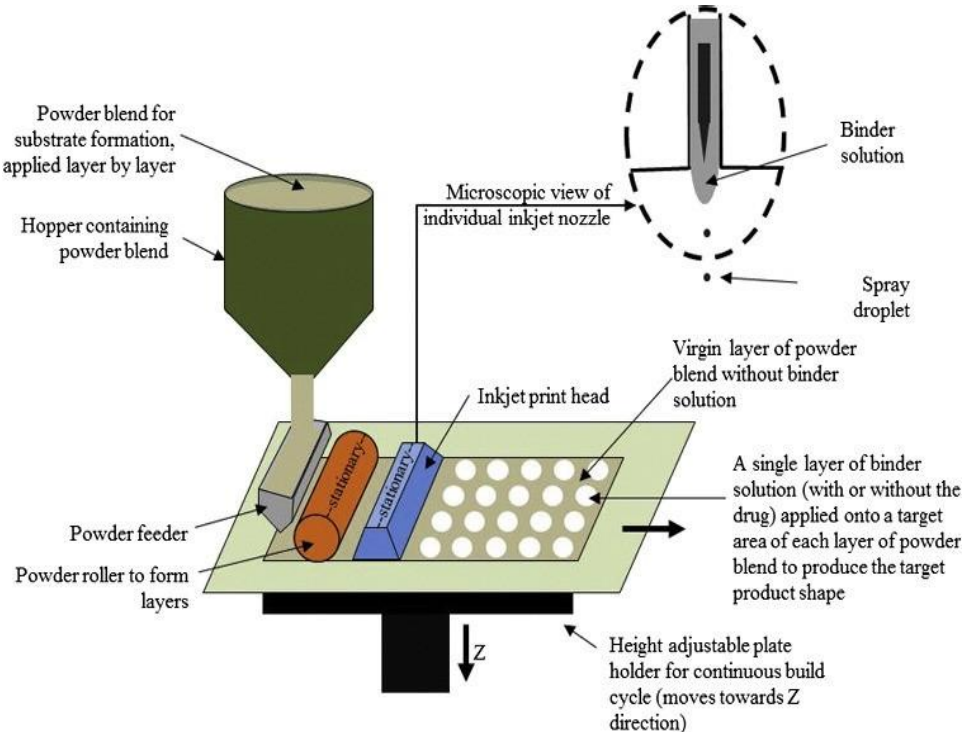

Figure 2: Inkjet Printing in 3D Printing [7]

3. Selective Laser Sintering (SLS)

Selective laser sintering is said to be a quick manufacturing process which works by the use of powder coated metal additives, a process generally used for rapid prototyping. SLS uses a continuous laser beam as a heating source to bind together the powder particles from a powder bed. During the printing, the laser is directed to draw a selected pattern onto the surface of the powder bed thereby creating a 3D structure. Laser beam sinters the powder and binds it in layer-by-layer fashion. [1, 4, 7, 10]

4. Fused Deposition Modeling

Fused Deposition Modeling Printers are common and more economic than the Selective Laser Sintering type. In Fused deposition modeling printer, beads of heated plastic are expelled from the print head in place of the ink, therefore, building the object in thin layers. [1, 11] Upon solidification, the polymer (laid down layer by layer) gives the precise shape as was designed by computer aided design models. [5]

FDM 3D printing offers several limitations such as- [7]

- lack of suitable polymers
- slow and sometimes incomplete drug release because the drug remain trapped in the polymers, and
- lack of evaluation of the miscibility of the drug and additives used with the polymers

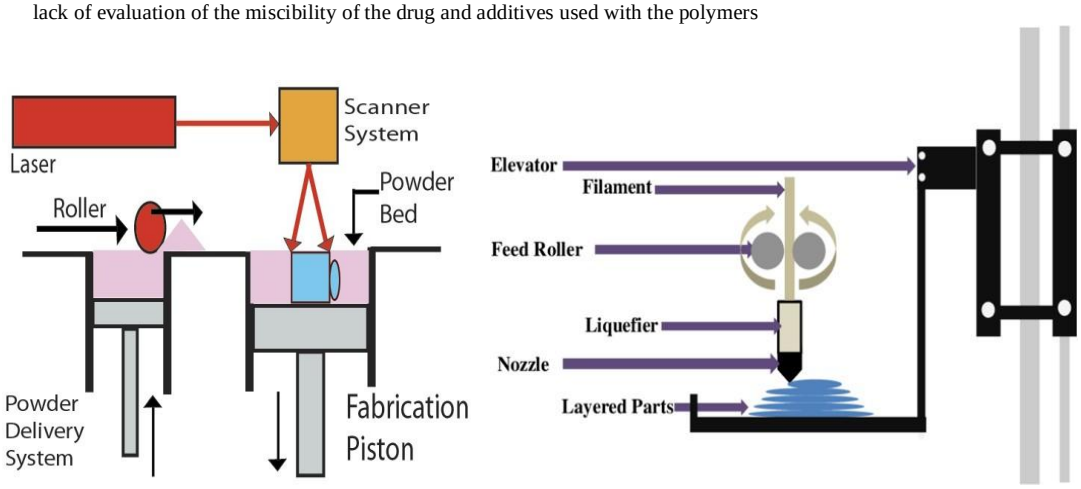

Figure 3: Selective Laser Sintering (left) and Fused Deposition Models (right) in 3D printing [7]

5. Stereo Lithography [4, 7]

Stereolithography was discovered by Charles Hull in 1988. It involves the solidification of the liquid polymer or resin by a computer aided laser beam, creating a 3D structure.

Highly accurate and detailed polymer parts are produced using this method.

6. Hot melt extrusion [4]

In this method of 3D printing, polymer and drug are melted at high temperature along with pressure for blending. It includes several operations like feeding, heating, mixing and shaping. By using hot melt extrusion technique, solubility and bioavailability of poorly soluble drugs are often improved.

7. Extrusion 3D Printing [4]

Only the ablets containing Guaifenesin as expectorant can be formulated by extrusion 3D printing. The material is extruded from the automated nozzle on to the substrate and no higher support material is needed. Molten polymers, suspensions, semisolids, pastes are the kind of materials that are extruded.

8. Zip dose [7]

Zip dose 3D printing technology is said to be the world's first and only FDA-validated, commercial-scale 3DP for drug manufacturers. For formulating a tablet with high dose and rapid disintegration, this method offers a specific and particular digitally coded layering and zero-compression processes. Hence it helps in overcoming a issue in swallowing. Example-Spritam® is an orodispersible tablet, which is used to treat epilepsy, is marketed by Aprecia Pharmaceuticals.

Table 2: Pharmaceutical Preparations Developed Using 3D Printing Technology [5]

3D Printing Technology	Formulations	API
Semi-Solid Extrusion (SSE)	Bi-layered tablets (polypill)	Guaifenesin
	Multiactive tablets (polypill)	Nifedipine, Glipizide, and Captopril

3D Printing Technology	Formulations	API
Stereolithography (SLA)	Hydrogels	Ibuprofen
	Facial mask	Salicylic acid
Selective Layer Sintering (SLS)	Tablets	Paracetamol
	Drug delivery device	Progesterone
Fused Deposition Modeling (FDM)	Caplets	Caffeine
	Tablets	Hydrochlorothiazide
	Oral films	Aripiprazole
Binder Jet Printing	Tabular devices	Methylene Blue and Alizarin Yellow (dyes)
	Cubic tabular devices	Pseudoephedrine
	Tablets	Chlorpheniramine Maleate and Fluorescein
	Oro-dispersible tablets	Levetiracetam
Inkjet 3D Printing	Implant	Levofloxacin
3D Printing Machine	Multidrug implant	Rifampicin and Isoniazid
Inkjet 3D Printing	Nano-suspension	Folic Acid
Thermal Inkjet (TIJ) Printing	Solution	Salbutamol Sulfate
Inkjet 3D Printing	Nano-particle	Rifampicin

3D PRINTER MATERIALS [4, 12]

For pharmaceutical purposes, materials used in 3D printing are:-

1. **Acrylonitrile Butadiene Styrene**
   This is one among the foremost widely used material in 3D printing. It's very durable, slightly flexible, and lightweight and is easily extruded, thus, making it appropriate for 3D printing. Requirement of high temperature is the only limitation offered by Acrylonitrile Butadiene Styrene. 210˚ - 250˚C temperature is typically used for printing with Acrylonitrile Butadiene Styrene materials and its glass transition temperature is about 105˚C.

2. **Poly Lactic Acid**
   Poly lactic acid is biodegradable thermoplastic derived from corn and therefore, is more environment friendly than other plastic materials. Poly lactic acid is very much biocompatible with a person's body. The structure of Poly lactic acid is harder than the Acrylonitrile Butadiene Styrene material and melts at 180-220˚C which is less than Acrylonitrile Butadiene Styrene. Glass transition temperature of Poly lactic acid is between 60-65˚C.

3. **High Impact Polystyrene**
   High Impact Polystyrene filament is biodegradable and there is no adverse effect when it is in tight contact with a human or animal body. The curling and adhesion problems of High Impact Polystyrene filaments can be reduced by employing a heated bed during the printing.

APPLICATIONS

3D Printing has been used in medicines from long times for creating dental implants to its use for custom prosthetics. [4] Now a days this technology is employed in vast areas ranging from tissue and organ fabrication to various pharmaceutical researches undertaking drug discovery, delivery and dosage forms. [13]

1. **Bio printing of tissues and organs**
   Organ and tissue failure due to accidents, aging or congenital defects still remains one the main unresolved medical problem world wide. There are very less number of individuals who undergo organ transplantation because it is extremely expensive and also numbers of donors are limited. The answer to the present problem is fabrication of required tissue or organ from the patient's own body cells that significantly decreases the problem of tissue or organ rejection. [14-15]

3D printers can possibly be used for fabricating heart valves, spinal disk, knee meniscus, other types of bones and cartilages, prosthetic ears and so on. [16-17]

2. Unique dosage forms

Inkjet based or inkjet power based 3D printing technologies are the two sorts of technologies mainly utilized in pharma industries. Novel dosage forms like nanosuspensions, microcapsules, mesoporous bioactive glass scaffolds, hyaluronan based synthetic extracellular matrices, multilayered drug delivery devices, and antibiotic printed micro patterns are often produced using 3D printing technology. [15, 18]

3. Hearing aids

Hearing aids can be manufactured by using 3D printing technology in three steps: scanning, modeling, and printing. 65 hearing aid shells or 47 hearing aid moulds can be printed by printers within 60 to 90 minutes. The printing speed helps manufacturers to adjust demand to supply. [3]

4. Anatomical Models

Anatomical variations differ from individual to individuals. Therefore, appropriate knowledge about the patients' specific anatomy is very vital before an operation.

3D printed models have helped extensively in this respect, making them an important tool for surgical method. [13, 19] For example;

- Neuro-anatomical models generated by 3D-printing assist neurosurgeons by providing a representation of some of the most complicated structures in the human body. [19]
- Japan's Kobe University Hospital utilized 3D printed models by using replica of patients' own organs to find a donor liver with least tissue loss. [5]
- Airways of premature infant were re-build to study aerosol drug delivery to lungs.[5]

5. Personalized medicine

3D printing of personalized medications offers the benefits of increasing the efficacy of drugs reducing the chances of adverse reaction. Drugs having narrow therapeutic index can fabricated using 3D printing, and by knowing the patient's pharmaco-genetic profile and other characteristics optimal dosage can be given to the patient. [14, 15, 20]

Personalized medicine is considered as tailoring medical treatments that suits the needs and preferences of each single patient. It involves purposely run diagnosis, therapy and follow-up. It can also include pre-emptive medicine aimed at reducing the risk of diseases a subject has shown susceptible to, by changing his lifestyle, diet and habits and by advising him on the use of peculiar supplements or drugs. [21]

CHALLENGES

3D printing technology has shown encouraging results in the field of pharmaceutical drug development and delivery, but still the technology is under the developing stage. There are many hurdles in the form of optimization process, including improving the performance of device for versatile use, selections of appropriate excipients, post treatment method to enhance the performance of 3D printed products' and to widespread the application range in novel drug delivery systems. [7, 22]

Many of the important parameters like printing passes, printing rate, line velocity of the print head, interval time between two printing layer, distance between the nozzles and therefore the powder layer need to be properly optimized to attain quality of 3D products. [23- 24] The chemistry of binder and formulation need to be properly highlighted to achieve quality 3D printed products. The selected binder in 3D Printing process should be compatible with the printer head components. [22] To extend the drug loading capacity in 3D printing processed tablet, uniaxial compression and suspension dispersed methodologies are utilized, but there are certain drawbacks including increased complexity and clogging of spray nozzle. [4, 22]

CONCLUSION

3D printing technology has proven to be vital and potential tool for the pharmaceutical sector, resulting in personalized medicine focused on the patients' needs. The versatility of 3D printing as highlighted, offers numerous advantages including increasing the cost efficiency and the manufacturing speed.

Although the development of 3DP pharmaceutical industry is only in its infancy, but in the near future 3DP approach will be utilized to fabricate and engineer various novel dosage forms, to achieve optimized drug release profiles, develop personalized medicines, avoid incompatibilities between multiple drugs, design multiple release dosage forms, limit degradation of biological molecules and many more. However, a significant hurdle is still to be overcome to ensure that 3D printed medicines have the same efficacy, safety, and stability as the pharmaceuticals conventionally manufactured by the pharmaceutical industry.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

ABBREVIATIONS

3D: Three Dimensional; 3DP: Three Dimensional Printing; SLA: Stereo Lithography Apparatus; FDM: Fused Deposition Modeling; SLM: Selective Laser Melting; CIJ: Continuous Inkjet Printing; Dod: Drop on Demand; CAD: Computer Aided Design; SLS: Selective Laser Sintering; FDA: Food And Drug Administration

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