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# ADVANCED TECHNIQUE 3D PRINTING IN THE PHARMACEUTICAL INDUSTRY WITH REGARDS TO CONVENTIONAL FORMULATION

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**ABSTRACT**

The whole world on the development in all other sectors as similar pharmaceutical have on broader development area. The recently pharmaceutical have great growth with using technique 3D Printing (3DP) as advance vehicle for the drug development and manufacturing. Three-dimensional printing (3DP) is a recent technology used to describe 3D products manufactured on a digital design platform and in a layer-by-layer fashion of the given medicinal materials. 3D printing technology has appeared as a major technological revolution of the recent years leading to the manufacturing and production of novel medical products and devices in pharmaceutical industry. The previously using this technology has gained position when the first commercial 3D tablet Spiratam® (levetiracetam) was approved by FDA in August 2015. The use of 3D printing technologies in drug delivery systems has expanded, due to its potential advantages over customizing drugs in individually adjusted doses. 3DP are precise deposition of medicaments and excipients, which might cause a change in perspective in drug configuration, production, and use. The dosage forms address the issues pertaining to on-demand manufacturing, feasibility, enhanced size, dosage and geometry, increased bioavailability with desired drug release profiles, and minimal toxicity or adverse drug reaction issues. It may help to address specific issues for various subgroups, including pediatric, geriatric, and chronic diseases. This review generally, focused on 3D Printing technology has described the advancements in manufacturing with regards the conventional dosage form (Tablet or capsule) and the futuristic potential for therapeutic approaches to bring in a vast array of useful applications and benefits to human being. As well as the compassion of the 3D Printing with the conventional manufacturing of the pharmaceutical products.

**KEYWORD:** 3D Printing, Recent Techniques, Conventional dosage form, CADD.

## INTRODUCTION

The concept of the delivery of the drug has highly shifted over the years from conventional oral dosage form towards the targeted release of the drug. A constant motivation is on the ascent, for the empowerment towards the designing of the drug, knowledge of material properties, manufacturing and processing of pharmaceutical dosage forms using a novel approach. Physicochemical and biopharmaceutical properties of the active ingredient as well as auxiliary substances needs to be considered before the development of a dosage form.[1] An increased attention is being received by personalized medicines and the dose of the drug to be administered due to their elevated chances of adverse effects. During the manufacturing of pharmaceuticals for the population, geriatrics and paediatrics have a high probability to exhibit adverse reactions. In the last few decades, the focus has highly been shifted towards the personalization of the medicines. Advancements in the novel dosage forms and technologies have risen to a considerable extent. Three-dimensional printing (3DP) is considered to be a highly revolutionized, versatile and powerful technology so as to mark its steps towards the novelty in the pharmaceutical field. It is highly helpful in engineering of medications, tissues and organs as well as in the modelling of the disease.[2] The basic flows to explains the 3D Printing in their view some steps are important for the manufacturing described in the (**Fig. 01**)-

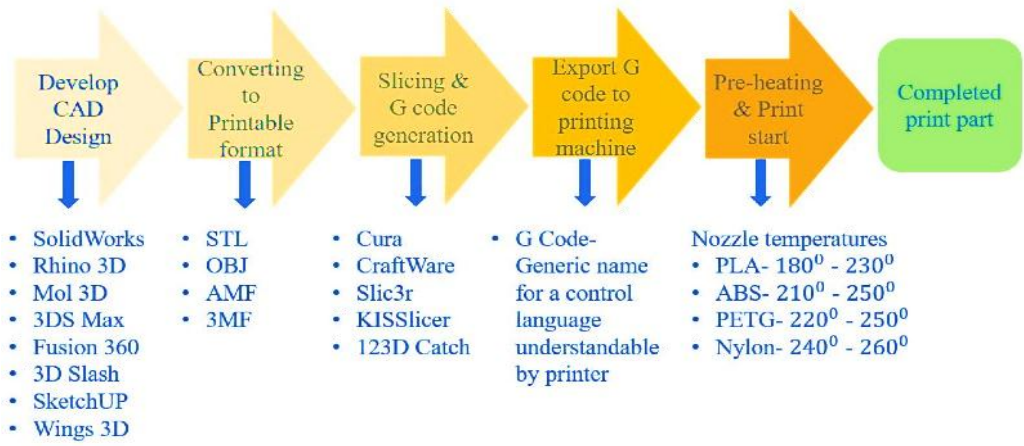


**Fig. 01: Flow Chart of 3D Printing Manufacturing.**

The process of 3D Printing has start with making a virtual design of the object you want to create. The virtual design is for instance a CADD (*Computer Aided Drug Design*) file. This CADD file is created using a 3D modeling applications or with a 3D Scanner (to copy an existing object). A 3D scanner can make a 3D digital copy of an object.

Nowadays, three-dimensional printing is one of the fastest developing branches 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''.[3] Although several conventional dosage forms and formulations have been developed over the years, they fail to cater to the individual needs of the patient or a cohort. 3DP technology addresses these issues and contributes to the upgrading and development of conventional pharmaceutical formulation techniques. 3D printing is a manufacturing process in which materials are deposited layer by layer to form an entity. Based on a pre-designed 3D digital model, it accumulates the printed layers layer by layer to complete the construction of a 3D object. In contrast to commonly used subtractive and formative manufacturing methodologies, this technique is one of the methods of additive manufacturing (AM) in which the parts are prepared from 3D model data in the process of joining materials layer by layer.[4]

**3D PRINTING IN PHARMACEUTICAL INDUSTRY:** 3D printing technology is a new chapter in pharmaceutical industry manufacturing and has gained vast interest in the recent past as it offers significant advantages over traditional pharmaceutical processes. Advance in technologies can lead to the design of suitable 3D printing device capable of producing formulations with intended drug release. The applications of 3D printers are one of the most revolutionary and powerful tools for customized and personalize of pharmaceutical formulations.[5] 3D printers have many advantages over the conventional manufacturing technology for tablet or capsules. Some requirement below-

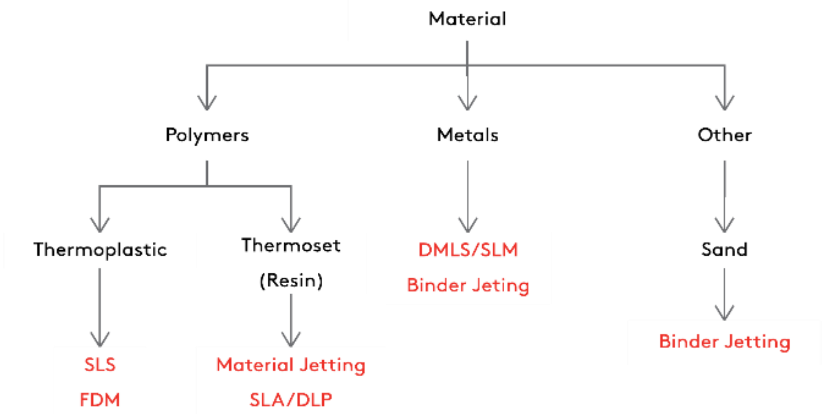


**Fig. 02: Requirements of Pharmaceutical 3D Printing Formulation.**

When all the criteria fulfill the requirements the pharmaceutical 3D Printing will initiated with good quality or therapeutic effects. Nowadays, pharmaceutical 3D printing is gaining considerable attention as a potential technology enhancing efficacy, preciseness, and individualization while reducing wastage cost. The new technology also enables creation of novel oral dosage forms and medical devices which are otherwise challenging to be produced using conventional manufacturing technologies.[6] The technology is highly disruptive and can lead to remarkable innovation in different processes of drug development. When compared to the manufacturing methods of conventional dosage form, it has a lot of advantages like high production rates owing to its fast operating systems, capability to achieve high drug loading with much desired precision and accuracy exclusively for potent drugs that are applied in small doses; reduction of material wastage can save the cost of production and pliability to more classes of pharmaceutical active ingredients comprising poorly solubility in aqueous, and narrow therapeutic index drug.[7]

The advent of 3D printing technology in the pharmaceutical industry has made it possible to design and manufacture novel complex drug products, as well as multiple active drug pharmaceutical ingredients (API) into one dosage form with customized release trends and individualized design adapted to patients' specific needs. These individualized dosage forms can be directly fabricated in a pharmacy on a local 3D printer or even at home by the patient. Indeed, the main advantage of the 3D printing is its flexibility to design and fabricate diverse medical products.[8]

This review discusses 3D printing and provides an update of its contribution to drug delivery. To begin with, the principles of the different types of 3D printing that have been explored for the production of dosage forms will be defined and explained. In addition, this review discusses the future opportunities of using 3D printing for the production of personalized medicine and the challenges that limit the implementation of this technology.[9]

## HISTORY IN 3D PRINTING

3D Printing is a platform for personalized medicine from the beginning of 1990. There are major successes in 3D printed medical device, FDA's Center for Device and Radiological Health (CDRH) has revised and cleared 3DP medical devices.[25] The first 3D printing method used in pharmaceutics was attained by inkjet printing, a binder solution onto a powder bed, therefore the particles bind together. The technique was repeated until the final desired structure was obtained. This first happened in the early 90's at the Massachusetts Institute Technology developed and patented.[10] In 1989 Scott Crump filed a patent on another 3D printing technology, fused deposition modeling, to harden the surface where extruded polymer filaments heated into a semi-liquid state and extruded through a heated nozzle and deposited onto a build platform as layer by layer. Inkjet printing was the technique used to manufacture Spritam tablets (levetiracetam) for oral use, the first 3D printed drug approved by the Food and Drug Administration (FDA) in 2016 by Aprecia Pharmaceuticals. 3D printing is most advanced technique in the fields such as automobiles, aerospace, biomedical, tissue engineering and now in the pharmaceutical industry (initial phase). FDA motivates the development of advanced manufacturing technologies such as 3D printing and by means of risk-based approaches.[11]

## ADVANTAGES OF 3D PRINTED DRUG FORMUALTION

3D Printing has numbers of advantages in the manufacturing and formulation the pharmaceutical product, they are generally, described in the given below section with proper use of that particular 3D Printing. Some points discussed below-

- ✓ 3D Printing having high drug loading capability compared to conventional dosage forms.
- ✓ This manufacturing and formulation commonly, Accurate and Precise dosing of potent drugs which are administered at small doses for activity.
- ✓ Reduced production cost due to less wastage of materials in 3D Printing formulation.
- ✓ Suitable drug delivery for difficult to formulate active ingredients like poor water solubility and narrow therapeutic windows drugs.
- ✓ With the using of 3D Printing products, the treatment can be customized to improve patient adherence in case of multi-drug therapy with multiple dosing regimen.
- ✓ As immediate and controlled release layers can be incorporated owed to flexible designs, manufacturing method of dosage form and it helps in pick out the best therapeutic regimen for an individual.

Additionally, 3D Printing having, evades batch-to-batch variations met in bulk manufacturing of conventional dosage forms, Manufacture of small batch is feasible and the process can be completed in a single run and 3D printers capture minimal space and are affordable.[12]

## DISADVANTAGES OF 3D PRINTED DRUG FORMULATION

3D Printing (3DP), also known as additive manufacturing (AM), is becoming the popular with manufacturers or designing. The demand is growing due to some of the revolutionary benefits of the obtained products that it can provided.

Like almost all technologies it has its own drawbacks that need considering or manufacturing, in some of them discussed below section with the main purpose-

- ✓ Problems related to nozzle are a major challenge as stopping of the print head which affects the final products structure.
- ✓ Powder printing clogging is another hurdle, Possibility of modifying the final structure on to mechanical stress, storage condition adaptions and ink formulations effects.
- ✓ Printer related parameters and these effects on printing quality and printercost.

Limited Materials, while 3D Printing can create pharmaceutical products in a selection of raw material or API and excipients the available selection of raw materials is not exhaustive. This is due to the fact that not all material or API and excipients can be temperature controlled enough to allow 3D printing. In addition, many of these printable materials cannot be recycled and very few are human being safe.[13]

## COMMONALITIES AMONG 3D PRINTING METHODS AND COMPARISON TO TRADITIONAL MANUFACTURING

Several different 3D printing methods exist with different input materials and operating principles. There is a common denominator, though. Most 3D printing processes follow the same basic procedure for manufacturing solid products from digital designs.[14] The 3D Printing started for the pharmaceutical conventional dosage form formulation. They such as obtained the 3D Printing when the object will clarify. The steps how the 3D Printing work explained in the given (**Fig. 03**) for the well explanation.

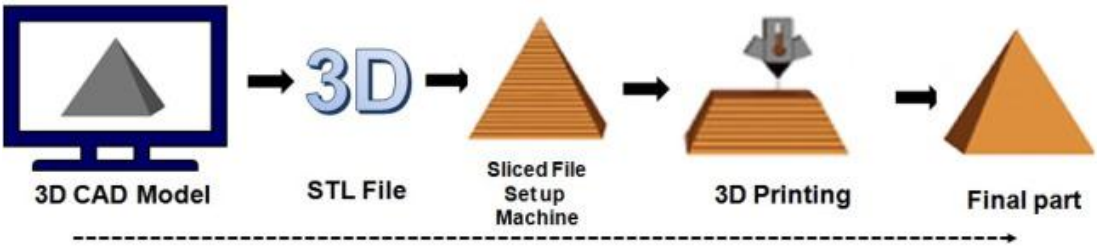


**Fig. 03: 3D Printing (3DP) Designing.**

**1. Design:** The intended product design is digitally rendered. Designs can be rendered in 3D with computer-aided design (CAD) software as a series of images corresponding to the to-be-printed layers.

**2. Conversion of the design to a machine-readable format:** 3D designs are typically converted to the STL file format, which describes the external surface of a 3D model. 3D printing programs “slice” these surfaces into distinct printable layers and transfers layer-by-layer instructions digitally to the printer.[15]

**3. Raw material processing:** Raw materials may be processed into granules, filaments, or binder solutions to facilitate the printing process.

**4. Printing:** Raw materials are added and solidified in an automatic, layer-by-layer manner to produce the desired product.

**5. Removal and Post-Processing:** After printing, products may require drying, sintering, polishing or other post-processing steps. At this stage, unprinted material may be harvested and recycled for continued use in the printing process.[16]

## 3D PRINTING PROCEDURE

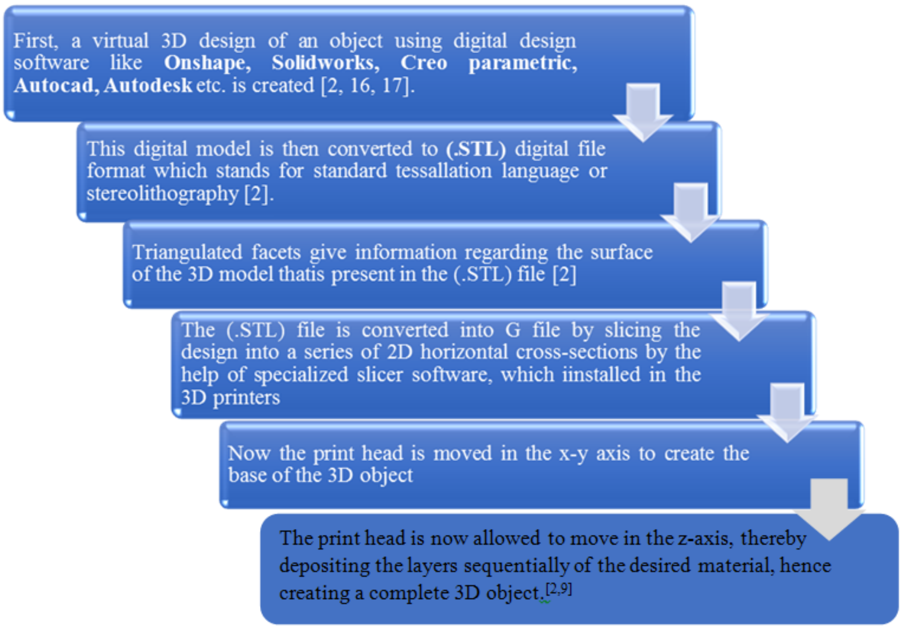


**Fig. 04: Flow Chart on Procedure of 3D Printing.**

**VARIOUS TECHNIQUES INVOLVING IN 3D PRINTING (3DP)**

Conventional methods for formulation of solid dosage form require large number of processing steps like milling, mixing, granulation etc. The number of steps involved in preparation may increase the chance of batch failure or inadequacy in quality. 3D printing can reduce number of steps involved drastically requiring lesser regulatory and quality control issues.[17] The term 3D printing encompasses several manufacturing technologies that build parts layer-by-layer. Each varies in the way they form plastic and metal parts and can differ in material selection, surface finish, durability, and manufacturing speed and cost. There are several types of 3D printing techniques used in manufacturing as discussed below (**Fig. 05**) part:

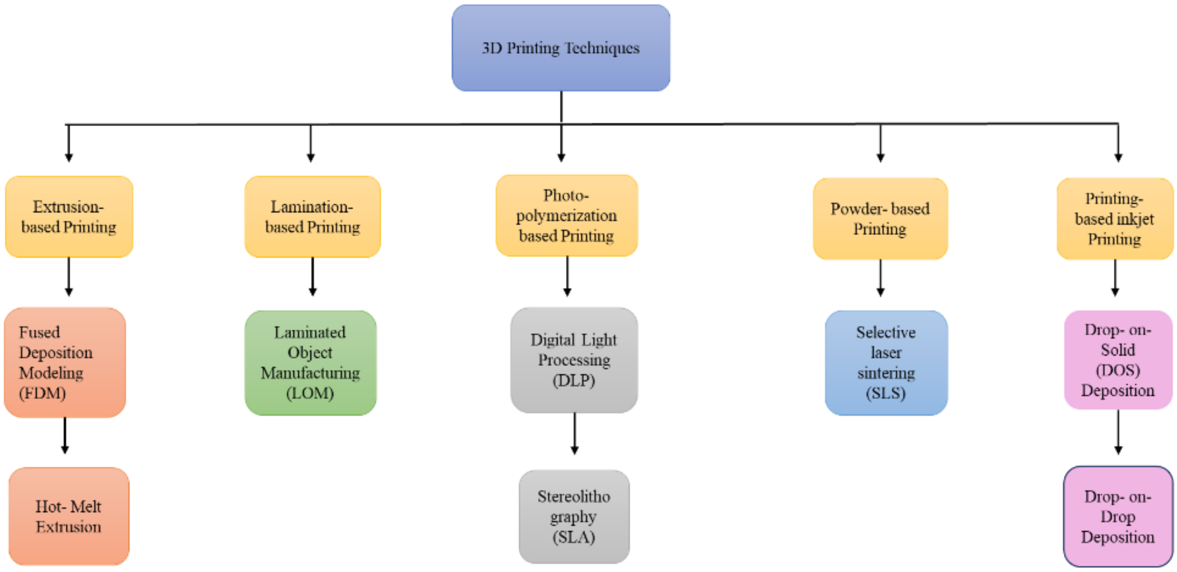


**Fig. 05: Various Techniques Involving in 3D Printing.**

1. **BINDER DEPOSITION:** This is the primary technique used in the production of pharmaceuticals by 3D printing. This technique uses binder ink such as polyvinyl alcohol, maltodextrin in small droplets which are sprayed at precise and programmed speed, movement and size on a powder bed. The ink used may contain only binder solution and the powder bed may contain a mixture of API and excipients to formulate a simplest drug product. Alternative to this API can be used along with binder in solution form or nanoparticulate suspension.[18] This technique is mostly suited for poorly soluble drugs i.e., class II and class IV of Biopharmaceutical Classification System (BCS). Pardeike et al. prepared a nanosuspension of folic acid (BCS class IV drug) and other excipients which were printed on a substrate (edible paper) to be rolled and inserted in a capsule as per required dose.

The mechanism of solidification of drug product is similar to that of wet granulation. Due to such similarities in techniques, this process has a scope of similar evaluation methods and quick regulatory approval.

2. **MATERIAL JETTING:** Powder bed is not necessarily used for inkjet printing. It can print free-form structure by ejecting drop by drop which solidifies simultaneously like stalagmites. Various jetting materials used are waxes, molten polymers, various resins, suspensions and solutions, and multi component fluids. The entire formulation is made for jetting which solidifies rapidly and the final form of formulation is determined by ejection path of droplet, droplet impact and surface wetting. Deposition of single layer and multiple layers of salbutamol sulfate on a potato starch film by thermal inkjet printing within ± 5% of theoretical dose.[19]

Nanoplexes of ciprofloxacin (BCS class IV drug) complexed with dextran sulfate and deposited the resultant nanosuspension on cellulose substrate by inkjet printing. Advantage over binder deposition is smaller layer thickness that enables formulation of micro-particles.

3. **EXTRUSION-BASED PRINTING**: The trend of using extrusion printing technology started in 1980 and became operational in 1990. Extrusion printing technique is governed by two types of printing methods including hot melt extrusion (HME) technique and fused deposition modeling. In the case of HME technique, a homogenous solid dispersion of pharmaceutical excipients such as polymeric materials and plasticizers are prepared in a molten form of polymer and a drug substance is introduced in the polymeric composition. Next, the formulation ink can be extruded directly through a die under high pressure and elevated temperature, then fused and solidified after printing, thereby generating a 3D

product of uniform shape with a high quality and drug content. The advantage of hot melt extrusion is that it is a solvent-free method which eliminates the need for a rigorous solvent selection step, making it an environmentally friendly method of production.

Concerning the fused deposition method, the drug substance is loaded in a thermoplastic polymeric filament for example via passive diffusion from solutions and used as starting materials. The fused deposition technique is also known as fussed filament (FF) in the literature. In comparison with the hot melt extrusion printing, in fused deposition modeling, the mechanical properties of 3D products and the drug load are lower. Further, the fused filament method can be efficiently used as a 3D printer for local or home-fabricated products for personalized medicine at the point of use.

The main advantage of the 3D extrusion printing technique is its high flexibility to develop a novel formulation of solid oral dosage forms with a different geometry, complexity and hallow structure product and various drug release profiles, and the ability to print a different range of polymers. Also, the extrusion technique is a promising way to printing materials in an amorphous form which enhances the dissolution rate thereby improving the bioavailability of poorly soluble drugs.[20]

4. **POWDER-BASED BINDING METHOD:** Rapid prototyping with a powder-based method is of particular interest to the pharmaceutical industry as it has many parallels with current manufacturing processes and may offer a more efficient longer-term printing solution. Multilayers of 3D printing products are constructed by spraying a solution of binder or drug with additional excipients in small droplets from an X-Y print head (in two-dimensional manners) over a powder bed on a built platform. Then, it is lowered along Z-axis based on the height of layers until the subsequent layer is constructed. The layers could be bonded via adhesion or welding in a liquid solution or suspension. Finally, the residual of the solvent and unbound powder is removed under appropriate conditions, allowing for the 3D product to develop properly (post-printing step). Powder bed 3D printing method is fast and compatible for printing a wide range of pharmaceutical substances. Further, the quality of fabricated 3D products is high and contributes to a considerable reduction in the production cost. The method has great potentials for fabricating high dose formulations of drug substance, controlled and immediate release drug formulation, and multilayer tablets containing different and precise active substances.

These advantages have led to wide adoption of this technique in pharmaceutical applications. Selecting a suitable binder and concentration can result in the appropriate integrity of 3D drug products. Further, the particle size of the powder is another major factor which affects the quality of the final 3D products.[21]

4.1 **Powder-based printing:** Powder-based printing technologies include selective laser sintering (SLS), direct metal laser sintering (DMLS), selective laser melting (SLM) and electron beam melting (EBM). Powder-based printing technologies all rely on localized heating to fuse the powdered materials, yet differ in the energy source and powder materials. SLS, DMLS and SLM utilizes laser beams directed by mirrors, whereas EBM uses a high-energy electron beam precisely directed by electromagnetic coils, which require vacuum conditions, thus increasing the production cost. DMLS is essentially the same process as SLS, but exclusively utilizes metal alloys. SLS can use a wide range of materials, including polymer and ceramic based powders. SLM and EBM fully melt the materials using a high-energy laser and electron beam, respectively. They primarily use metal alloys and ceramics. There are some subtle but distinct differences between products produced by sintering and melting. In addition, the SLM (or EBM) melting process requires that the candidate materials exhibit similar properties in terms of laser absorption and flow behavior of the liquid phase in order to obtain the desired properties. However, one major advantage of the melting process is that it is capable of producing nearly fully dense parts, thus eliminating lengthy post-processing steps such as thermal treatments or infiltration, which is usually required for the SLS (or DMLS)-printed products.[22]

5. **PHOTOPOLYMERIZATION:** It is (also known as *stereolithography*) involves exposing liquid resins to ultraviolet or other high-energy light source to induce polymerization reactions. The primary limitation of this technique is the need for photopolymerizable raw materials, which are relatively uncommon in pharmaceutical manufacturing. Also, residual resin can represent a toxicology risk because the uncured material is chemically distinct from the printed product and may contain functional groups that are plausible structural alerts for genotoxicity. In terms of potential advantages, photopolymerization systems tend to be among the fastest and highest resolution 3D printers available. An example drug delivery application is 3D printing of photopolymerizable hydrogels.[23]

6. **PRINTING-BASED INKJET SYSTEMS:** In printing-based inkjet system, the ink is deposited onto the substrate mainly in two forms as listed below: -

6.1 **Continuous inkjet printing-** In this type, due to the counter mechanisms the drops are continuously driven as needed thereby expelled only when necessary. this method continuous flow of ink is desired during the process. The processing occurs in such a manner that the vibration in the piezoelectric crystals helps in releasing the liquid continuously. The droplet obtained are charged electrostatically and thus, directed towards the substrate. It is mainly useful in printing of packaging.[24]

**6.2 Drop On Demand (DOD)-** In the DOD printing system, the pharmaceutical-based ink is converted to a droplet form by applying a voltage to a piezoelectric crystal transducer to vibrate the materials or heating the formulation to the temperature higher than the boiling temperature thereby creating droplets. Then, the dots of the solution are driven from an orifice to the printer head's nozzle and solidified dropwise. The main criterion in developing a formula of API for printing in the inject print system is the performance of the carrier formulation during printing, which is strongly influenced by rheological parameters such as fluid viscosity, velocity, and surface tension. Likewise, the release profile of the formulation can be modified given the deposition pattern of droplets onto the substrate. The main advantage of inject printing method in the pharmaceutical application is its high accuracy in creating 3D drug products. The technology also opens up new possibility for usage of new active pharmaceutical ingredients and personalisation in drug discovery.[25-28]

## COMPARISON TO CONVENTIONAL MANUFACTURING TECHNIQUE

3D printing in pharmaceuticals demonstrates more complexity in dosage forms using layer-upon-layer process. This can be differentiated for personalization in medicine as it is digitally designed and on-demand manufactured using automated and cheap operational methods. The rationales supporting the increasing research in 3D printing for drug manufacturing are noteworthy. In general, there is a demand for adaptability, a feature that is not often seen in pharmaceuticals.[29] This includes the ability to fabricate dosage forms with complex geometries and architectures, which directly correlates to increased complexity and control over release characteristics. The adaptability of 3D printing may also be applied for the precise and unique dosing of drugs, whereby drug doses can be printed with the safety of digital control. Additionally, multiple doses or multiple drugs can be printed together in a singular dosage form. Finally, and importantly, 3D printing allows for drug products to be adapted for on-demand, prescription specific production. The ability of on-the-spot drug fabrication will have major implications in emergency medicine and for medications with limited shelf-life.[30-32] Furthermore, 3D printing of drugs means that they can be manufactured for patients on an individualized basis. This capacity directly responds to the demand for individualized medicine and healthcare.[33] Patient-specific medicine entails the modification of drug dosing and combinations to meet the individual's needs. Conventional drug manufacturing methods lack the ability to fulfill this necessity, as they focus on large-scale batches.[34] There is little flexibility in the typical manufacturing process, requiring several steps which would be too difficult to tailor for a small batch. Conversely, 3D printing-based fabrication of drug products can be changed between prescriptions, also showing promise to transform pharmacy compounding.[35]

## FUTURE ASPECTS OF 3D PRINTING

With continued research, we believe personalized medicine will reach new levels of possibility, and pharmacies will be revolutionized by this particular application of 3D printing. Even Though this technology is still in its infancy, it seems to be a revolutionary tool that offers more flexibility in drug manufacturing and is expected to transform drug delivery systems to a different level, in near future. The use of 3D Printing in medical applications has great promise for the future; however, significant barriers exist to successful implementation, regardless of scientific knowledge. The goal of research is to successfully 3D Prinitng organs for transplant, and soon there might be breakthroughs that allow autologous 3D printed organs that use a patient's cells. However, 3D printing the complex cytoarchitecture of organs remains difficult. Furthermore, 3D printing could b used more as a teaching tool. For pharmacology, research into 3D printed patients specific medicine is expected to expand, and companies, such as Curifylabs have developed an automated digital technology (***CURIFY MiniLab***) to 3D print medicines; however, the potential of multiple formulations in on tablet is unknown. For medical companies, research into modifying existing products to facilitate 3D printing, and expanding the range of materials that can be 3D printed, would be a logical direction for research, in addition to improvements in the efficiency and speed of 3D printing.

## CONCLUSION

3D printing for drug manufacturing represents the future of pharmaceuticals. While diverse industries across all of society are adopting 3D printing as a method for manufacturing, medicine and healthcare have yet to fully harness the capabilities of 3D printing for the direct-write fabrication of medications. Current advances in technology and increased research in this field can assure more safe and effective treatment. Since conventional pharmaceutical manufacturing is a large batch process and generally does not support personalized therapy the idea of tailored medication for therapy has achieved wide attention these days. Current advances in technology and increased research in this field can assure more safe and effective treatment. The purpose of the 3D Printing well explained in the given review article with proper manner. All steps and recent techniques well simplify with the review such as stereolithography, fused deposition, and binder jetting etc. are the recent techniques in the formulation or manufacturing of pharmaceutical products.

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