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3D PRINTING: A Pandora Box

Mohanbir Singh[1], Harveen Kour[1], Daya Luxmi[1], Gauri [1] and Ramica Sharma[1]*

University School of Pharmaceutical Sciences, Rayat Bahra University, Mohali-140104, India

Abstract: *Three-dimensional printing (3D) is expected to be quite possibly of the developments in pharmaceutical technology. 3D printing is a fabrication technique that involves depositing materials layer by layer to create a range of designs. 3D printing might be utilized to make an extensive variety of drug dose structures, with various shapes, discharge profiles, and prescription mixes.Despite the therapeutic and commercial benefits of 3DP technology, it is limited in its usage in pharmaceutical goods due to a variety of technical and administrative issues. With 3D printing, rapid prototyping is practically endless. As a result, it's being researched for applications in a range of scientific fields, including mechanical engineering, medicine, materials science, and chemistry. 3D printing techniques are being used with increased popularity in various industries, one of the most important of which is healthcare. This paper addresses the outline on history on 3D printing, 3D printing advancements utilized in drug industry, 3D imprinting in customized medication and difficulties in 3D printing innovation in assembling industry.*

Keywords*:* Three-dimensional printing, Healthcare, Personalized medicine

Corresponding author: Ramica Sharma
e-mail: ramica@rayatbahrauniversity.edu.in

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1. INTRODUCTION

The term 3D printing is generally used to describe a manufacturing approach that builds objects one layer at a time, adding multiple layers to form an object. This process is more correctly described as additive manufacturing, and is also referred to as rapid prototyping [1,2,3]. 3D printing is a unique manufacturing philosophy that enables the flexible preparation of highly complex and precise structures that are difficult to realise using traditional fabrication methods such as casting and machining [4]. Together, 3DP and ML can use intelligence based on human learning to speed up drug product development, assure strict quality control (QC), and inspire new dosage-form design [5]. The application of 3D printing in medicine can provide many benefits, including: the customization and personalization of medical products, drugs, and equipment; cost-effectiveness; increased productivity; the democratization of design and manufacturing; and enhanced collaboration [6]. Medical 3D printing was once an ambitious pipe dream. However, time and investment made it real [7]. In the healthcare market, several factors influence global 3D printing, such as the advances in technology and improvement in the healthcare infrastructure, on the one hand, and an increase both in the percentage of the aging population and in the investment in research and development sector, on the other [8]. 3D printing technology has advanced at a breakneck pace since its inception 50 years ago, having a huge impact on both the industrial and commercial worlds. Stereolithography, selective laser sintering, and fused deposition modeling were some of the earliest widely successful 3D printing techniques, which were initially employed for industrial prototyping [9]. In the fields of agricultural, healthcare, automotive, locomotive, and aviation, 3D printing technology is increasingly being used for mass modification and production of any form of open source design[10]. Because of the rapid advancement of this technology, great inventions have been made, and 3D printing (primarily the Fused Deposition Modeling or FDM technique) has reduced the cost of manufacturing, build time, and object weight, as well as waste, when compared to some traditional manufacturing processes, making 3D printing accessible to the average consumer [11]. 3DP enables for the printing of dosage forms on demand at a cheap cost and with ease of usage. Because the dosage and release characteristics of drug delivery devices can be easily modified by adjusting the geometries of the 3D design using computer-aided design, additive manufacturing is leading to personalized medicine (CAD)[12]. 3D-printed pharmaceuticals can be produced to imitate the

immediate or sustained release profiles of traditional tablets, or even accommodate multiple medicines with varying release profiles in the same tablet, using the correct procedures [13].

2. History Of 3D printing

Historical Development of 3D Printing. The Battelle Memorial Institute in Ohio conducted the first study on the use of photopolymers to create 3D things in the 1960s. The researchers employed two laser beams that collided at different wavelengths to polymerize resin. By using photochemical machining with dual laser beams, WynSwainson created the first design for 3D printing, which he patented in 1971 [14]. In the same time period, Dynell Electronics Corporation invented solid photography in the late 1970s. Since the 1980s, the use of 3D printing has grown. For example, In 1983, Charles Hull became the first person to print a three-dimensional object [15]. Stereolithography (SLA) has been used to develop three-dimensional systems, as well as the first virtualization application [16]. He received a patent for 3D printing in 1984 and later co-founded 3D Systems, Inc., one of the top firms in the field of 3D technology. In the late 1980s, Charles Hull collaborated with Lisa Crump to develop fused deposition modelling through a new company called Stratasys [17]. In 1989, Hans Langer of Germany founded Electro-Optical Systems (EOS), which creates 3D objects using metal laser sintering based on a computer model. EOS acquired all dual transfer mode (DTM) patents relating to laser sintering in 2004. In the 1990s, Carnegie Mellon and Stanford proposed a novel technology of additive manufacturing based on material spraying and microcasting. In addition, during the mid-1990s, the 3D printing sector was divided into two areas: medical equipment (highly designed complicated parts) and user-friendly printers for cost-effective prototype improvement concepts. Only three original companies remained by the end of the 1990s: EOS, 3D Systems, Inc., and Stratasys [14]. By the early 2000s, most sectors had adopted three-dimensional printing technology, and it had proven to be a stable method of producing end-products. The RepRap project was started by Adrian Bowyer at the University of Bath [17]. It's interesting to learn about the history of 3D printing technology. Kodoma was the first to build a three-dimensional object that employed ultraviolet (UV) radiation to harden polymers and create solid structures in 1981. The procedure entailed using a UV laser beam to create a tangible thing from computer models. In the early 2000s, the first medical application of this technology was described [16]. Dr. Kodama is regarded highly in the field of 3D printing for his pioneering work in rapid prototyping in the 1980s. He was a pioneer in additive manufacturing, introducing stereolithography, a technology that uses

photosensitive resin polymerized with UV light [18]. Charles Hull began working with stereolithography in 1983, filing the first patent and producing the first SLA-I machine. Charles Deckard filed a patent in 1988 for a new 3D printing technique called SLS (Selective Laser Sintering), in which a laser is used to fuse powder materials together. Stratasys' founder discovered FDM (Fused Deposition Melting) technology in 1989 to bring in a new era, which was patented in 1992. Between 1993 and 1999, significant 3D printing companies developed technologies such as MIT's ZCorp binder jetting, Arcam MCP technology, and Selective Laser Melting. Engineered organs revolutionised medicine in 1999. The first 3D printed functional kidney was made in the year 2000 [15]. 3D printing has now made its way into the pharmaceutical companies, where it is being utilised to create a variety of dosage forms. The FDA authorisedSpritam (Levetiracetam), a prescription medicine for epilepsy produced by Aprecia Pharmaceuticals, as the first 3D printed drug in 2015 [17]. In 1993, MIT researchers Michael Cima and Emanuel Sachs patented the first "3D printer" device. (Gross et al., 2014). A number of other organizations have since created 3D printers for commercial applications [19]. A variety of novel technologies have evolved over the last 15 years, transforming the idea of RP to AM, where things generated by a 3D printer can be used directly for a variety of biomedical purposes. The American Society for Testing and Materials (ASTM), a new international committee dedicated to the setting of standards for additive manufacturing, was established in 2009. ASTM F42 is the name of the committee [18]. 3D printing technology has advanced at a fast pace since its beginning 50 years ago, having a huge impact on both the industrial and commercial worlds. Stereolithography, selective laser sintering, and fused deposition modelling were some of the earliest widely adopted 3D printing techniques. It was demonstrated in 2005 that 3D printed hydroxyapatite scaffolds may be constructed based on anatomical information from obtained radiologic images for a specific patient [20]. Wake Forest Institute of Regenerative Medicine employed the technology to print 3D scaffolding for organ augmentation in the 1990s, and in the 2000s, they attempted to manufacture functioning organs. When 3D printing first appeared on the Gartner Hype Cycle of Emerging Technologies in 2012, it was at the top of expectation. Furthermore, Gartner predicted that 3D printing would take five to ten years to achieve its productivity peak. The 2013 Cycle4 has improved its analysis by categorising 3D printing into three categories: enterprise 3D printing, consumer 3D printing, and 3D bioprinting [21]. Stereolithography (SLA) is a method in which photons from an ultraviolet (UV) laser light source are targeted onto the surface of a photo-curable liquid monomer

solution and scanned in multiple patterns. Because the scanned monomers are light-sensitive, they can be crosslinked with the help of a suitable light source. These monomers harden when exposed to photons, forming the essential 2D cross-sections, whereas the monomers that are not exposed remain unchanged in the bath [22].

3. 3D Printing Technologies Used in Pharmaceutical Industries

With the implementation of the 3D printing technology into the pharmaceutical industries, it is now possible to manufacture and design novel complex drug products and multiple active drug pharmaceutical ingredients (API) into a single dosage form with customised release trends and individualised design as modified for patients' specific needs. It can provide a compelling new research and developmental opportunities for the improvement of medicine formulation and administration of previously existing active pharmaceutical ingredients. This can help to increase efficacy, preciseness, individualization and decrease wastage of pharmaceutical products. Some common 3D printing technologies used in pharmaceutical industries are:

(i) Thermal Inject Printing:

It is a contactless method of depositing microscopic droplets of ink onto substrates using electromagnetic, thermal, or piezoelectric technologies in response to instructions given by the computer. In thermal injecting printer, heat is generated by using resistors and bubbles are produced by evaporation of ink. With the expansion of bubble the ink got pumped out through the nozzle [23]. In this technique ,heat is used to convert aqueous ink fluid to a vapour state, which is then expanded to force the ink drop out of the nozzle.

Use: It is utilised to make drug-loaded biodegradable microspheres and liposomes, as well as to pattern microelectrode arrays and load drug-eluting stents.It is a widely used method for making biologic films without compromising protein activity [24].Extemporaneous pharmaceutical preparations/solutions can be dispensed onto 3D scaffolds by using this method [25].

(ii) Extrusion based:

In Extrusion based 3D printing process the material is extruded from the automated nozzle onto the substrate without any additional support material.Extruded components include molten polymers, suspensions, semi-solids, and pastes.(24)By the use of Computer-aided Designs and numerous solidification methods this technology provide wide ease of use and acceptance and give good précised products [26]. S. Scott Crump invented extrusion-based printing in 1988, which is also known

asfused filament fabrication (FFF) fused deposition modelling (FDM).

(iii) Fused-deposition modelling:

Fused-deposition modelling (FDM) is a process in which two rollers extrude a molten thermoplastic polymer filament via a high-temperature nozzle and then solidify it into a build plate. The print head may move along the x and y-axes, while the platform, which can be thermostatic, can move vertically on the z-axis, resulting in layer-bilayer 3D structures.The density of the infill, speed of the extruder, height of the layers, and the temperature of both the nozzle and the construction must be controlled during FDM [27]. It is the second most commonly used commercial layered manufacturing technology for directly fabricating final products without the use of tools, dies, or moulds. It has great dimensional accuracy, is simple to operate, has a quick cycle time, and is simple to integrate with various computer-aided design tools. This method is mostly utilised in modelling, prototyping, and batch production [28].

Use: Metal printing, polymer printing, and bioprinting all use extrusion-based printing .Precision extrusion deposition (PED), precise extrusion manufacturing (PEM)), and multiple heads deposition extrusion (MHDS) are all printing processes that have recently been developed .Multiple bioprinting applications in vascular models, soft-tissue models, and bone models have been well-developed in recent years [29].

(iv) Nozzle-Based Deposition Systems:

Prior to 3D printing, medicines, polymers, and other solid ingredients are mixed in nozzle-based deposition devices. The mixture is forced into a nozzle, which creates the three-dimensional product layer by layer [30]. It allows direct writing that depends on computer-controlled manufacturing methods which deposit ink directly through a nozzle to form a 3D pattern layer-bilayer [31]. There are two types of printings according to the type of material used (a)Fused Deposition Modeling(FDM) and (b) Pressure-Assisted Micro syringes(PAM).

In FDM a liquid thermoplastic polymer filament is extruded via a high-temperature nozzle and deposited layer-by-layer onto a build plate with instantaneous solidification. It is a low-cost manufacturing technology that has a number of advantages, including the ability to produce extremely complex pharmaceuticals with difficult geometries, as well as the ability to change drug release profiles.

PAM extrudes viscous and semi-liquid materials from a micro syringe. The semi-liquid material is released by compressed air, and the syringe can move like an IJ

printer head. Microstructures of 5–10 m or smaller can be produced using PAM technology .It can also develop complicated drug delivery systems and is more efficient than other approaches because it can run continuously at room temperatures [32].

(v) Vat-polymerization:

Vat photopolymerization 3D printing technology provides an advanced way to manufacture customised medical devices and drug delivery systems by combining the advantages of high resolution and fast printing speed [33].

In vat polymerization light curing resin material and light selective hardening polymerization moulding are used. It is commonly utilised to make sophisticated devices containing functioning pieces like valves, lenses, and fluidic connections. In this technique, a vat of photosensitive polymer resin is selectively exposed to a precisely controlled beam of laser or light.

Examples of common processes used are Digital light processing (DLP), stereolithography (SLA), and multiphoton polymerization (MPP). In SLA ,a spot laser irradiates the resin in a single x-y direction, whereas in DLP, a digital illuminate irradiates the entire x-y. The print platform moves parallel to the z-axis in both SLA and DLP, while the final result is built layer by layer. With contrast, in MPP, the photosensitive polymer resin is irradiated in multiple directions by a femtosecond laser beam, hence it is not a layer-by-layer technology. Products produced using the vat polymerization method must be exposed to light after printing to improve stability [34].

(vi) Zip-Dose: Zip dosage is the world's first and only FDA-validated commercial-scale 3D printing technology for medication producers in new therapeutic areas. It uses a proprietary digitally coded layering and zero-compression technique to create a tablet with a high dosage and quick disintegration. As a result, it aids in the alleviation of swallowing difficulties. Zip Dose Technology, which was developed using Aprecia's proprietary 3DP manufacturing method, aids patients who require easy-to-administer medicines as well as caregivers, such as physicians and nurse practitioners [35]. By creating very porous material, this approach gives a tailored dose in addition to the administration of a high drug-load with high disintegration and dissolution levels [36].

(vii) Inject printing: This approach to personalised treatment is based on the same computer-assisted inkjet printing technology. It was modified for pharmaceutical use by replacing the ink with pharmaceutical solutions containing medications and the regular paper with edible sheets known as substrates [37]. If 3D printing processes works by placing liquid droplets onto a substrate in a

well-organized manner, they are considered printing-based inkjet systems. When the droplets are the main building material than this technology refers to Drop-on-Powder (DoD) deposition and when the droplets are a binder solution/suspension/polymer or other liquid used to bind the substrate together this refers to as Drop-on-Powder (DoP) deposition[38]. In inject printing to avoid clogging in the printer head, the starting materials must have a particle size of less than 1 m, a viscosity of less than 20 cP, and a surface tension of between 30 and 70 mN/m for efficient flow [39]. This method is especially useful when the starting components are liquid in nature. Based on the direction of droplets, inject printing is divided into two categories: continuous inject printing (CIJ) and drop on demand (DOD).

(a) In CIJ a transducer or a droplet loading equipment produces a constant stream of droplets. To get the desired charge, the droplets are directed to an electrically charged element. Finally, the produced droplets reach the substrate and form the three-dimensional object.

(b) In DOD printing system, by the applying a voltage to a piezoelectric crystal transducer to vibrate the materials or heating the formulation to a temperature higher than the boiling temperature, the pharmaceutical-based ink is converted to a droplet form. The dots of the solution are then pushed through an aperture to the nozzle of the printer head and solidified dropwise. Inject printing has Excellent precision and has demonstrated promising uses for producing oral dose forms such as poorly soluble and strong medicines in experimental experiments [40].

(viii) Powder based 3D printing:

It is a rapid low cost technology that has a lot of potential for making high-dose pharmaceutical formulations, controlled and immediate-release drug formulations, and multilayer tablets with diverse and appropriate active ingredients [27]. It is a widely used process because of excellent recyclability rate of powder material, faster manufacturing speed, durable functional parts, reduced cost, no or minimal support structures, various fields of application, and a vast range of suitable materials all contribute to its appeal [41]. It mainly use 3 printing methods as: selective laser sintering (SLS), selective laser melting (SLM), and binder inkjet printing (BIP).

(a) Selected laser sintering (SLS) and selective laser melting (SLM) are two laser-based printing techniques (SLM). Stereolithography (SLA) or also known as laser-based writing system was the first laser-based liquid resin polymerization technology widely used in rapid prototyping. This uses a computer-controlled laser beam

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to turn a liquid polymer/resin into a solid, resulting in a three-dimensional structure.It is suitable for thermolabile medicines since it avoids heat procedures and has great resolution [42]. Selective laser sintering (SLS) was developed recently by ASTM (American Society for Testing Material) under the Powder Bed Fusion category to eliminate the need for liquid photo-reactive substrates [43]. The material powder is rolled to the fabrication platform on a powder supply platform with a pre-set powder bed temperature below the melting point during the SLS process. The scanner will scan and sinter each layer once one layer of powder has been deposited on the platform, utilising CO2 and Nd in a YAG laser with varying operating powers.The main difference in SLS and SLM is that, the material powder is fused but not entirely melted in the SLS process, whereas in SLM the temperature is high enough to totally melt the powder and fuse it into one metal block with higher mechanical compliance [44]. SLM can also refers to as direct metal laser melting or laser powder bed fusion (LPBF).SLM can be more suitable for manufacturing dense metal parts,print glass like materials and recently micro-SLM 3D printing has been formed for microscale printing [45].

(b) Binder jetting: It is a 3DP approach that uses a physical mixture of APIs and excipients as starting materials, often known as "drop-on-powder" printing. With the help of a roller, a powder layer is put to the supporting bed, and a liquid binder is laid onto the powder in the designated area by an inkjet nozzle. The bed is then lowered, and a new layer of powder is deposited over the previously produced one. This technique is repeated until the entire item is printed [46]. This is an additive manufacturing method where the powder material is dispersed into a layer and precisely linked into the desired shape with a binder that is a polymeric liquid.It has recently been used for electro - chemical energy storage electronic devices, food technology, solid oxide fuel cells, moulds for sand casting waveguide circuits and antennas, concrete construction, renewable bio-based materials , ceramic scaffolds, biopolymers, sand stone production, and biomedical applications and drug delivery [47].

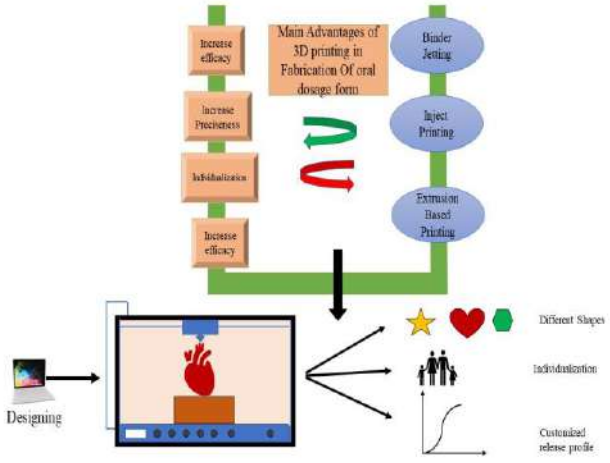

Fig.

4. Challenges in 3D printing technology

In this section challenges faced by the 3D printing has been discussed. The main project confronted is computational cost, general for qualification and facts acquisition techniques [48].In addition, the size distribution and shape of powder is a challenge in the manufacture of 3D printed biomedical products [49]. There are some restrictions that can prevent it from launching. These include the inability to print large amounts of material, slow printing times, limited availability of materials, inaccurate operation, expensive printers, and the inability to print more materials on the same printer [50]. Despite the advantages of 3D printing technology, many technical difficulties and obstacles need to be urgently overcome in order to promote widespread adoption of drug delivery systems [51]. In addition, the current drawbacks of 3D printing are additive research, printing software and equipment development, optimization of the mechanical properties of pharmaceuticals, and the status of related regulatory conditions [52].

5. 3D Printing in Personalised Medicine

3D printing may be used to make a wide range of pharmaceutical dosage forms, with different shapes, release profiles, and medication combinations. Modularizing the dose, controlled release, and combining various medications in a polypill demonstrate its promise in personalisedmedicine [53]. 3DP has a number of advantages, including the ability to streamline the manufacturing process and generate personalised treatments. In the pharmaceutical field, the main medicinal and technological benefits of 3DP are related to customiseddrugs [54]. The current state of 3D printing in healthcare (including themes like dentistry, surgery, and biomaterials of patient-specific organs), and also the possibility of recent advancements like 4D printing to decide the future of delivery of drugs and enhancing treatment paths [55]. The aim of 3D-printed personalised medicine is laudable, but the difficulties of such production must be considered. For example, present technology has a low throughput, needing a large amount of time to create a single dose[53]. Due to the variety and ease of changing the design and dosage of the products, 3DP will allow for a wider acceptance of personalised medicine. This will allow devices to be made specifically for the individual, with the flexibility to alternate the medications added to the product [56]. 3D printing offers the ability to create personalised medicines in wholly new formulations, such like pills with numerous active components in a single blend or as complicated multi-layered or multireservoir printed tablets [57]. Fused deposition modelling 88 (FDM), one of the commercially accessible 3D printing methods, is likely the most commonly employed in pharmaceutics. FDM is easy to use and inexpensive, and it has been proved to be exceedingly adaptable in the production of drug

delivery systems particularly 90personalized medicines [58]. The introduction of 3DP into the clinic will significantly improve personalised medicine, in which patients are prescribed and given bespoke formulations based on their unique needs [59]. 3DP tablets dissolve, whereas a normal tablet of the same high-dose does not,3DP is also well-suited to the production of multi - component polypill formulations [60]. The benefits of 3D printing include that it allows for the manufacturing of small quantities of medications with custom dosages, shapes, sizes, and release characteristics. Medicines made in this manner may eventually lead to the concept of personalisedmedicine [61]. The challenges, risks, and benefits of personalised medicine (PM) are reviewed, with a focus on the prospects provided by the arrival of 3D printing technologies, as well as the requirements for success in terms of both healthcare effectiveness and cost [62]. The combination of machine learning and three-dimensional printing, both of which are digital processes, may make it easier to move away from "one-size-fits-all" treatments and toward data-driven omics and the production of personalised medications [60, 63]. Fused deposition modelling (FDM is easy to use and affordable, and it has proven to be incredibly adaptable in the development of drug delivery systems, particularly personalised medications, and medical devices [64]. The next step in personalised medicine is molecular 3D printing. In addition to anatomical (tissue- and organ-based) indicators, this technology will enable patient-specific therapies guided by molecular biomarkers [65]. it is clear that one dose does not suit all; requirements can differ depending on a patient's genetic profile, illness condition, and other characteristics (such as gender, age, and weight). This insight gave rise to the discipline of personalised medicine, which entails adapting treatments to a patient's unique features, needs, and preferences[66]. With their a bility to produce medication forms upon within small production quantities, 3D printers have proved particularly disruptive [67]. This 3D printing technology has the potential to be used in digital healthcare for point-of-care production of individualised medicines at a patient's home, in an emergency, or in resource-constrained circumstances. This type of technology could be crucial in the future for setting a new standard for efficient and cost effective mobile-health solutions [68]. The majority of progress in this area has so far been limited to basic oral dosage forms (i.e., tablets), in which single or multiple medications were included and spatial and temporal control over drug release was demonstrated through polymer content modifications [69, 70, 71].

6. Conclusion

Future applications for 3D printing are widely anticipated. The time it takes for designers and engineers to conceptualize, produce, and evaluate prototypes has decreased thanks to new 3D printing techniques. But in order for the quickly

evolving manufacturing sector to adopt 3D printing, businesses will need to start viewing it less as an amazing technological advancement and more as a routine business choice. The medical industry offers 3-D printing perhaps the most room for expansion from useful prostheses to the therapy of birth defects and cancer. The goal of 3D printing-based inventions in medicine is to give patients a good quality of life and a longer lifespan. A brief overview of 3D printing technologies and study trends is given in this paper. A number of cutting-edge technologies and applications are also presented.

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