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REVIEW ARTICLE

3D printing in pharmaceuticals: A review

SWARUPA NARAYAN SHIRKE[1], JAMEEL AHMED S MULLA[1]*, PRATIKSHA VILAS CHAVAN[2]

[1] Department of Pharmaceutics, Shree Santkrupa College of Pharmacy, Ghogaon, Karad, Dist- Satara - 415111, MS, India.

[2] Department of Quality Assurance, Alard College of Pharmacy, Hinjewadi, Pune – 411057, MS, India

***Author for Correspondence:** *Email:* jameelahmed5@rediffmail.com

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ABSTRACT

Many technologies are evolving to induce this paradigm change from traditional to personalized treatment, with three-dimensional (3D) printing being the most important. Due of its possible benefits over personalizing medications in individually tailored doses, the applications of 3D printing technology in medication conveyance system has exploded in recent years. 3D printing is the technique of building a three-dimensional item layers upon layers with the help of computer software. The ability of 3D printing drugs as an effective technique for achieving customized precision medicines and various 3D printing techniques was highlighted in this review article. Also various challenges are identified that must be overcome in order for this technology to succeed in customized medicine.

INTRODUCTION

Three-dimensional (3D) printing is a method for developing medications and formulations that uses computer-aided designs (CAD) and printing settings to provide flexibility to the product. After that, the medications are printed. In the meanwhile, conventional compounding is the method of combining, mixing, or blending medicinal ingredients adjusting the components used to make drugs in response to certain circumstances. Special dosage forms and pharmacological strengths are required in certain patient scenarios as well as excipients [1].

Additive manufacturing or 3D printing is a groundbreaking technology in pharmaceutical manufacture because it allows for the creation of an infinite number of equal dosage forms in comparison to traditional medication manufacturing methods in terms of product quality and effectiveness [2, 3]. This is a manufacturing technique in which layer by layer, an item is built [4, 5]. The International Standard Organization (ISO) defines 3D printing as the production of objects by the action of depositing a substance with the aid of a print head, a nozzle, or some additional types of printer technology.

Fused deposition modelling (FDM), direct energy deposition, thermal inkjet printing (TIJ), stereolithography (SLA) and selective laser sintering (SLS) are some of the 3D printing techniques utilized in manufacturing of pharmaceuticals [6,7]. It's been used to manufacture controlled-release tablets, orodispersible films, polypills, gastrofloating tablets, self-emulsifying drug delivery systems, microneedles, and transdermal patches, among other things, in the pharmaceutical industry [8].

The technology of 3D printing has given designers and manufacturers unparalleled flexibility in designing and manufacturing complex items, which can be used in personalized and programmed medicine. It's an effective technique to avoid some of the issues that are affecting typical pharmaceutical unit operations [9, 10].

Benefits of 3D printing technology include-

- Rapid and easy modification of design parameters is possible in the manufacturing of microparticles and nanoparticles that are coupled with functional antibodies in a continuous mixing method [11].

- High variety in developing diverse geometrical shapes and sizes, low production costs, and minimal unit-to-unit variability [12, 13].
- Compounding with 3D printing allows for more versatility in adjusting medication contents and release patterns for each patient [14].
- 3D printing technology allows for the use of fewer excipients than the mass-produced forms [15].
- It is possible to obtain great accuracy, precision, and medication consistency throughout dosage forms using 3D printing technology.

1. History of 3D Printing

The concept of 3D printing dates back to the early 1970s, when Pierre A. L. Ciraud developed a method for applying powdered material and then solidifying each layer through the action of a high-energy beam. In early 80′ Ross Housholder described an idea of sand binding by different materials. Carl Deckard invented selective laser sintering, a process of solidifying powdered beds using a laser beam called selective laser sintering (SLS). SLA was invented by Chuck Hull and was the first commercially viable technology. This technique used ultraviolet light to photopolymerize liquid resin. In 1989, Scott Crump filed a patent for fused deposition modelling, which involved extruding heated polymer filaments via a heated nozzle and depositing layer by layer onto a construction platform to solidify [16, 17]. In the early 1990s, Emanuel Sachs invented and patented pioneered 3D printing innovation within the pharmaceutical sector with a rapid prototyping strategy called "three-dimensional printing methods" [13]. Spritam (levetiracetam) tablets for oral administration were manufactured using inkjet printing, which was the first 3D printed drug approved by the Food and Drug Administration (FDA) in 2016 by Aprecia Pharmaceuticals [16].

2. 3D Printing Methods

Various 3D printing systems have been devised according on the energy supply, material source, and other mechanical features. The most common 3D printing methods for pharmaceutical applications are printing-based inkjet, nozzle-based deposition and laser-based writing systems, which are further divided into subtypes based on materials and energy sources. The following sections provide a quick overview of the overall characteristics of each 3D printing technology.

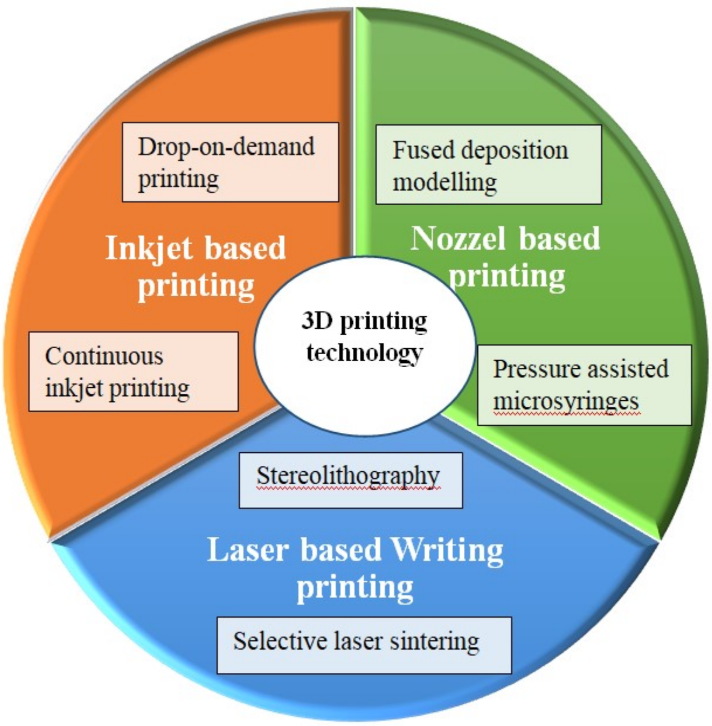

Figure 1: 3D printing technology

2.1. Inkjet Printing

The droplets of sprayed ink are sprayed onto a powdered base, which solidifies to produce a solid in the inkjet printing procedure. The active medicinal components and excipients are sprayed precisely in the form of droplets onto a non-powder substrate in various combinations [7]. Continuous inkjet printing (CIJ) and Drop-on-demand (DOD) printing are two forms of printing-based inkjet systems. CIJ printing entails the use of a high-pressure pump to discharge a continuous stream of fluid via a nozzle with a diameter of 50–80µm. This then breaks up into a flow of drops due to surface tension forces. Whereas at the DOD, only when a drop is necessary liquid is ejected from the print head: the formation of each droplet with a diameter of 10–50 µm and a volume 1–70 pL [18]. The performance of the carrier formulation during printing, which is heavily impacted by rheological characteristics such as fluid viscosity, velocity, and surface tension, is the main criterion in establishing an API formula for printing in the inkjet print system [19, 20].

2.2. Nozzle Based Printing

Nozzle-based deposition techniques combine solid materials with a binder before 3D printing and deposit the combination directly via a nozzle to generate a 3D object. Fused deposition modelling (FDM) and pressure-assisted microsyringes (PAM) are the two subtypes, depending on whether the method involves or eliminates material melting [21]. Prior to the formation of the solid dosage form, FDM involves polymer melting, extrusion and layer upon layer deposition, with the shape established by a CAD model [3, 22]. In order to expand the range of polymers that may be adapted with FDM and achieve greater drug loading, researchers have combined FDM with hot melt extrusion [23]. FDM can be used to make implants, zero-order release tablets, multi-layered tablets, and fast-dissolving tablets, among other solid dosage forms [3].

A PAM works by feeding semi-solid material into a syringe-based head, where the material is extruded continuously, layer by layer, to form a 3D printed item [24]. A mechanical, pneumatic, or solenoid piston can be used for extrusion. The viscosity, visco-elasticity, and apparent elastic limit are important characteristics that determine the technology's robustness [25].

2.3. Laser Based Writing Printing

It relies on the concept of photopolymerization, which involves the release of free radicals as a result of the contact between the photoinitiator and UV radiation. A laser based 3D printing technique is known as SLA that uses a photopolymerization process to control the liquid resin's solidification. This method is used to make tablets and hydrogels [16, 26]. In order to perform photo-cross-linking, the materials employed in SLA must have photo-curable properties. High resolution and reduced thermal stress are two advantages of this printing method [24]. SLS is another laser based printing technology and it is one of the latest and most advanced technology proposed for the preparation of solid dosage forms [27]. SLS is a technique that uses laser radiation to liquefy and fuse powder layers that have been spread out as thin layers [28]. This method is useful because it is a one-step, quick manufacturing procedure that does not require the use of any solvent. Due to the laser precision, it also makes high-resolution objects [29]. One of the potential applications of SLS technology is its ability to fabricate orally disintegrating tablets [30].

3. Pharmaceutical Applications of 3D Printing

3D printing is a highly valuable technique for more precise drug distribution and personalized drug release to match the particular needs of each patient. Furthermore, personalized medicine is an unprecedented opportunity of 3D printing to address the hurdles of treating diverse diseases. The applications of various techniques in pharmaceutical formulations are depicted in Table 1.

Table 1: Applications of different techniques in pharmaceutical formulations

3D printing technology used	Formulations	References
Inkjet 3D printing	Implants, nanosuspension, nanoparticle	[31, 32]
Fused deposition modelling (FDM)	Tablets, oral films	[33, 34]
Pressure assisted microsyringe (PAM)	Tablets, semisolid extrusion	[35]
Stereolithography (SLA)	Hydrogel	[26]
Selective laser sintering (SLS)	Tablets, drug delivery device	[36]

4. 3D Printing's Challenges on Formulation Development

Despite the inherent benefits of 3D printing technology in formulation creation, the availability of excipients, development of printing software and instruments and improving the mechanical qualities of products are among the technical obstacles and complications associated with 3D printing applications. Some 3D printing technologies, such as FDM and powder-based (PB), that require a nozzle mechanism to produce layers, encounter the most difficulty in maintaining a steady and reproducible flow [37]. Many studies using thermoplastic polymer demanding printers, such as FDM, have used non-pharmaceutical grade polymers because most polymers now used in conventional pharmaceutical compounding do not print effectively [38]. SLS and SLA both require the removal of manufacturing material leftovers, but FDM does not. It indicates that each printing technology needs its own set of regulations [4].

Although 3D printing techniques can considerably speed up the manufacturing process, there remains a hurdle to ensuring the printed medication’s safety, potency, and stability as compared to conventional pharmaceuticals [18]. As a result, rigorous regulatory requirements to assure the quality, safety, and efficacy of all medications manufactured are projected to have a substantial impact on a broad-based implementation of 3D printing in the field of pharmaceuticals [37]. The formulator's health and safety is also a big concern, as the heating or melting process can produce harmful vapors from polymers and organic chemicals.

With all this without a question, 3D printing has boosted the pharmaceutical industry in recent years, but there are still some challenges, that need to be resolved and constraints eliminated in order for 3D printing to achieve complete success.

CONCLUSION

The efficacy of 3D printing in pharmaceuticals is undeniable. This technology has the ability to transform formulation production, allowing for the production of extremely flexible and customized dosage forms on demand rather than in bulk. The FDA's approval of Spritam was a significant achievement in the area of 3D printing, and since then, a plethora of promising research has emerged. Rapid manufacture, cost-effectiveness, and formulation versatility are the biggest benefits of 3D printing in the pharmaceutical sector.

3D innovation is still in its infancy; this assembling technique is by all accounts an amazing tool with better flexibility in drug-producing and is likely to change medication delivery frameworks to another degree; however it requires time to improve. Even though 3D printing drug delivery systems are now facing substantial problems in terms of stability, quality, and application. Several regulatory hurdles must be addressed before 3D printing may be widely adopted.

Overall, for the pharmaceutical sector, it is more vital than ever to recognize and embrace the power of 3D printing in pharmaceuticals rather than resisting change. In the future, 3D printing will continue to develop and improve in order to be a safe and effective pharmaceutical formulation, based on regulatory requirements.

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