Innovative: International Multi-disciplinary Journal of Applied Technology
(ISSN 2995-486X) VOLUME 02 ISSUE 05, 2024

3D Printing in Pharmaceuticals

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Abstract:

3D printing, also known as additive manufacturing, is one of the most revolutionary technologies of contemporary life. The technology is causing a shift away from traditional mass production towards personalized 3D-printed drugs through computer-aided model design. Buy-in from healthcare professionals, including pharmacists, is vital to the integration of 3D printing into clinical settings. This paper examines the 3D printing methods and the major motivations for using 3D printing in pharmaceuticals. The benefits and challenges of employing 3D printing in large-scale manufacturing and personalized dosing are introduced.

Keywords: *3D printing (3DP), additive manufacturing (AM), 3D printing pharmaceuticals, 3D printed drug, drug delivery, personalized medicine.*

INTRODUCTION

Technological advancements have changed the face of the earth with the first and second industrial revolutions. The rapid development of 3D printing and its application in product manufacturing has been regarded as the third industrial revolution. These advancements can ease a similar impact on the pharmaceutical industry, which covers a sizeable part of world economy. The pharmaceutical industry is at the cusp of a remarkable transformation, and 3D printing technology is at the forefront of this revolution. Pharmaceutical companies are constantly reaching for new innovations in drug design, focusing on material properties, processes, and technologies. Established companies such as Roche, Pfizer, Merck, Aprecia, FabRx, and GlaxoSmithKline are taking advantage of the 3D printing technology and are transitioning 3D printing pharmaceuticals from lab to clinic.

In contrast to the traditional manufacturing techniques of "subtractive manufacturing," 3D printing is an "additive manufacturing" technology, where a model is constructed using CAD software and transferred to a printer, and the 3D product is then constructed layer by layer. The 3D printing technology is widely used in automotive, construction, aerospace, medical, and many other fields. It is transforming pharmaceuticals into more precise, effective treatments. As shown in Figure 1, 3D printing reshapes the pharmaceutical world [1]. The technology could lead to a new era of digital pharmacy, enabling electronic prescriptions to be sent to a decentralized 3D printer location for real-time personalized medicine dispensing, as depicted in Figure 2 [2].

WHAT IS 3D PRINTING?

3D printing (also known as additive manufacturing (AM) or rapid prototyping (RP)) was invented in the early 1980s by Charles Hull, who is regarded as the father of 3D printing. Since then it has been used in manufacturing, automotive, electronics, aviation, aerospace, aeronautics, engineering, architecture, pharmaceutics, consumer products, education, entertainment, medicine, space missions, the military, chemical industry, maritime industry, printing industry, and jewelry industry [3].

A 3D printer works by "printing" objects. Instead of using ink, it uses more substantive materials–plastics, metal, rubber, and the like. It scans an object–or takes an existing scan of an object–and slices it into layers, which can then convert into a physical object. Layer by layer, the 3D printer can replicate images created in CAD programs. In other words, 3D printing instructs a computer to apply layer upon layer of a specific material (such as plastic or metal) until the final product is built. This is distinct from conventional manufacturing methods, which often rely on removal (by cutting, drilling, chopping, grinding, forging, etc.) instead of addition. Models can be multi-colored to highlight important features, such as tumors, cavities, and vascular tracks. 3DP technology can build a 3D object in almost any shape imaginable as defined in a computer-aided design (CAD) file. It is additive technology as distinct from traditional manufacturing techniques, which are subtractive processes in which material is removed by cutting or drilling [4].

3D printing has started breaking through into the mainstream in recent years, with some models becoming affordable enough for home use. Many industries and professions around the world now use 3D printing. It plays a key role in making companies more competitive. The gap between industry and graduating students can be bridged by including the same cutting-edge tools, such as 3D printing, professionals use every day into the curriculum. There are 3D printed homes, prosthetics, surgical devices, drones, hearing aids, and electric engine components. As shown in Figure 3, 3D printing involves three steps [5].

3D PRINTING IN PHARMACEUTICALS

The three-dimensional printing (3DP) revolves as the new dawn in the field of pharmaceuticals. 3D-printed drug technology is ideally suited for the preparation of personalized drugs for patients with different disease states and different ages. Compared to traditional preparation technologies, 3D printing offers flexibility in the design of complex 3D structures within drugs. A typical illustration on how 3DP works in pharmaceuticals is shown in Figure 4 [6]. To date, the main 3D printing technologies used in pharmaceuticals are binder jet 3D printing (BJ-3DP), fused deposition modelling (FDM), semi-solid extrusion (SSE), and stereolithography (SLA). These 3D printing methods are briefly discussed as follows [7]:

(1) BJ-3DP is the common 3D printing technology used for drug production. The printing process of the BJ-3DP technology can be roughly divided into three steps: (1) droplet formation, (2) selective binding of droplets to powder, and (3) drying or curing of the finished product. BJ-3DP technology has been used in two main categories of preparations, namely oral solid dosage forms and subcutaneous implants.

(2) FDM is popular 3D printing technique that is widely employed for manufacturing a wide variety of products. It is widely used in pharmaceuticals due to the advantages of simple equipment, low cost, and high product strength. In FDM the hot melt extruded filament is used as primer for printing where drug loaded filament is passed through the nozzle. Based on the properties of FDM technology, it has been widely used for variety of preparations. FDM printers can be equipped with multiple nozzles to print compounded preparations containing different materials.

(3) SSE is an additive manufacturing technology that deposits semisolid material layer by layer. It is based on FDM, with the difference that the print material used in this technology is in a semisolid form at room temperature. The main difference between SSE and other material extrusion technologies (such as FDM) is the material. The technology uses semisolid or semi-molten materials, which require a high level of material stability to prevent material precipitation.

(4) MED 3D printing is a material extrusion technology that combines both hot melt extrusion and fused deposition modeling technologies. It consists of feed and mixing modules, material delivery modules, and multiple print stations, each of which prints one material. Compared to FDM or SSE, the MED technology process has no need to prepare filaments or semisolid materials in advance, and there is no secondary heating of materials.

(5) SLA technology is more precise than any other 3D printing technology. The first commercially available technology created by Chuck Hull in 1980 was SLA. It is based on the principle of photopolymerization and uses laser scanning to harden liquid resin to manufacture 3D-printed objects layer by layer. In this technique, the laser is used to photopolymerize resin for preparation. Depending on the printer setup, printing can be performed from the top down or the bottom up. SLA products generally require post-curing after printing. The purpose of post-curing is to improve the mechanical properties of the product.

Figure 5 shows 3D printing methods applied for drug formulation [8], while Figure 6 shows some 3D printed drugs [9].

PERSONALIZED MEDICINE

A major benefit of 3D-printing medicines is the potential to adjust the individual dose. The idea of more individualized pharmacotherapy has been developed for many years, but it has only recently begun to gain widespread adoption. The need for developing personalized medicine by rational use of drugs by the patients in right dose has been a subject of intensive discussion. The 3D printing procedure is an elegant solution to personalized drug dosing. There is value in 3D printing formulations that require personalization to improve therapeutic outcomes.

Personalized 3D printed medicines can be adjusted by their therapeutic value, so doctors can treat their patients rather than the numbers pharmaceutical companies find convenient. Personalized medications are already being manufactured for both customized dosages and formulations. The ability to produce medicines with personalized dosage, flavor, shape and size can provide many benefits to pediatric populations. In the near future, pharmacists will be able to print medications unique to every patient. However, the idea that patients will print their medicines in their own houses is rather faraway perspective.

BENEFITS

As an emerging technology in the pharmaceutical industry, 3D printing has many benefits. 3D printing offers an eco-friendly method of medicines manufacture, producing mass customized or personalized medicines. It may improve medicines independence. Medicines can also be produced on demand, reducing wastage of medicines liable to degradation upon storage. Compact and user-friendly nature, 3D printers could be easily integrated into community and hospital pharmacy settings. 3D printing can be relatively easily introduced into the pharmaceutical compounding in the pharmacies. Other benefits of pharmaceutical 3D printing include [10]:

1. *Personalized Medicine:* A major benefit of 3D printing medicines is the ability to truly personalize a treatment based on a patient's therapeutic or individual requirements. The 3D printing allows to individualize medicine to the patient body weight and lifestyle by dose and dosage form adjustment. As mentioned earlier, personalized medications are already being manufactured for both customized dosages and formulations. Personalized drugs are suited for special populations such as the elderly and children.
2. *Dosage-Specific Parameters:* The 3D printing technology tackles one of medicine's most prominent issues: targeted therapies. Three-dimensional printing technology is highly flexible and can be used to print targeted medicines by adjusting model parameters such as size, shape, or fill rate.
3. *Micro-Dosing Without Oxidation:* Breaking up tablets can oxidize ingredients. 3D-printed options can offer unique dosage forms that deliver microdoses without oxidation risk.
4. *Increased Solubility:* Thermal inject printing TIJ has been used to manufacture Miconazole, which has notoriously low solubility in aqueous environments. Researchers are currently looking into what hot-melt extrusion and drug geometry changes will do for drug release.
5. *Faster Trials:* Medical engineers have used vat photopolymerization and other 3D technologies to create pre-clinical medications for trials. This process is much faster than has ever been possible before.
6. *Unique Dosage Forms On-Demand*: Unique dosage forms can be achieved through authorized blueprints. This gives pharmacists the power to shorten the supply chain.
7. *Non-Contact Processing:* Inkjet printing can process up to 100 pl droplets into 3D structures through a micrometre-scale nozzle. This technology has been used to create prednisolone solid dosage forms with the help of heat and extra polymorphs.
8. *Repeatable Accuracy:* 3D printed methods offer more resolution, accuracy, and repeatability. This will become a great equalizer in the pharmaceutical industry as small businesses gain the ability to create complex products on tight budgets.
9. *Rapid Production:* A very high production capacity is needed for pharmaceutical companies to meet the global demand for traditional drugs. The 3D printing technology can integrate rapid manufacturing, with compact equipment and the ease of changing the variety of drugs produced.

Some of these benefits are portrayed in Figure 7 [10].

CHALLENGES

Despite the advancements and benefits of using 3D printing in the pharmaceutical field, several challenges remain, such as the need for clear regulatory guidance on the integration of novel point-of-care (POC) manufacturing technologies for the production of personalized medicines. As an emerging technology, intellectual property rights, drug regulations, and other policies are still breaking new ground. The printable products must comply with the current manufacturing and control standards for the medical products and devices. Other challenges of 3D printing in pharmaceuticals include the following [11,12]:

1. *Complex Structure:* The 3D printing of commercial products requires tight control over the quality and consistency of the product, since the product may involve complex tablet structures that could be challenging to produce with quality and consistency. As the complexity of the structure of a dosage form increases, the modelling and slicing software used to design and inform its production must be continuously updated.

2. *Quality Control:* When the production of personalized medicines by 3D printing is carried out, the issue of quality control arises. These issues include assuring that the right drug substance is being printed and assuring the right amount of tablets is printed. This becomes particularly important if the drug product is to be printed at the patient's private home.
3. *Safety:* 3D printing in healthcare involves the production of medical devices, implants, and medications, which raises regulatory and safety concerns. The challenge of ensuring the safety and effectiveness of these products is significant. To ensure that 3D-printed healthcare products satisfy the necessary quality, safety, and performance requirements, regulatory bodies must establish clear guidelines and standards
4. *Regulation:* No regulatory body has issued guidelines for 3D-printed preparations, and there is an urgent need to establish regulatory standards for them. Regulatory approval from agencies can bring the 3DP product into the market. In March 2021, the Medicines and Healthcare Products Regulatory Agency (MHRA) released a proposal for a new regulatory framework to enable the development of point-of-care (POC) manufacturing and supply, including 3D printing technologies for personalized medicine production.
5. *Standardization:* This is indispensable to the healthcare industry. Variability is introduced into the manufacturing process by 3D printing, which can affect the quality and efficacy of printed objects. It is essential to standardize the processes, materials, and quality control measures of 3D printing in healthcare to ensure reliable and reproducible results.
6. *Intellectual Property:* 3D printing permits the duplication of objects, which raises concerns about the infringement of intellectual property rights and copyrights. The ubiquitous availability of 3D printing technology makes it more difficult to safeguard the intellectual property of medical devices and pharmaceuticals. Developing appropriate legal frameworks to resolve these concerns is necessary to ensure that the technology is used fairly and ethically.
7. *Expertise:* The operation of 3D printers and the design of printable objects require training and specialized knowledge. It is essential to train healthcare professionals, including clinicians, pharmacists, and technicians, to utilize and benefit from 3D printing technology.

CONCLUSION

3D printing is an emerging technology with great potential in pharmaceutical applications. It is causing a paradigm shift in pharmaceuticals, transitioning away from the traditional mass production of drugs towards tailored drug products that are personalized and customized to each individual. This requires the engagement and support of healthcare staff, including pharmacists, doctors, nurses, and pharmacy technicians to enable the widespread translation of the technology into clinical practice. Growing demand for customized pharmaceutics and medical devices makes the impact of 3D printing increase rapidly in recent years. 3D printing has become a successful method especially in personalized medicine.

3D printing has the potential to revolutionize the pharmaceutical industry by enabling the production of customized and personalized products that are tailored to the specific needs of individual patients. While the opportunities for 3D printing are still being explored, the integration of 3D printing into the pharmaceutical industry will require a shift in business model and approach. To date, globally, pharmacists have been the driving force behind 3D printing in pharmaceuticals. They have recognized the true potential of this technology for medicines production. The individualization of medicines with patient centric dosage form will become reality in upcoming future. More information about 3D printing technology in pharmaceuticals can be found in the book [13] and the following related journals:

- ✓ *Pharmaceuticals*

- ✓ *Pharmaceutical Research*
- ✓ *The Pharmaceutical Journal*
- ✓ *The International Journal of Pharmaceutics*
- ✓ *Future Journal of Pharmaceutical Sciences*

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Figure 1. 3D printing reshapes the pharmaceutical world [1].

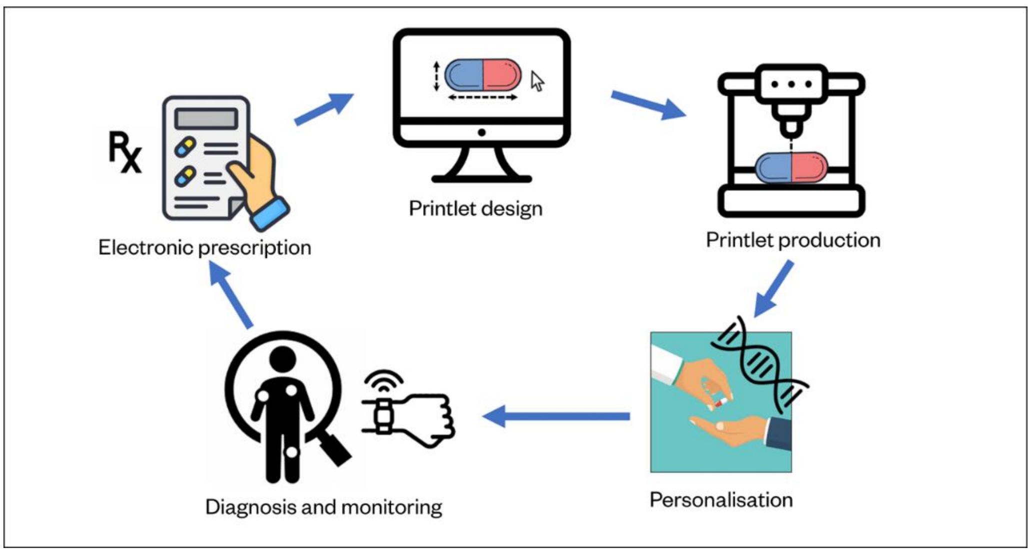

Figure 2. The five components of a digital pharmacy era [2].

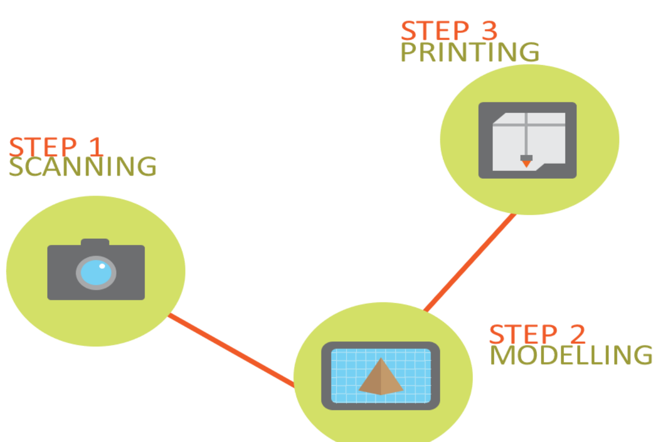

Figure 3. 3D printing involves three steps [5].

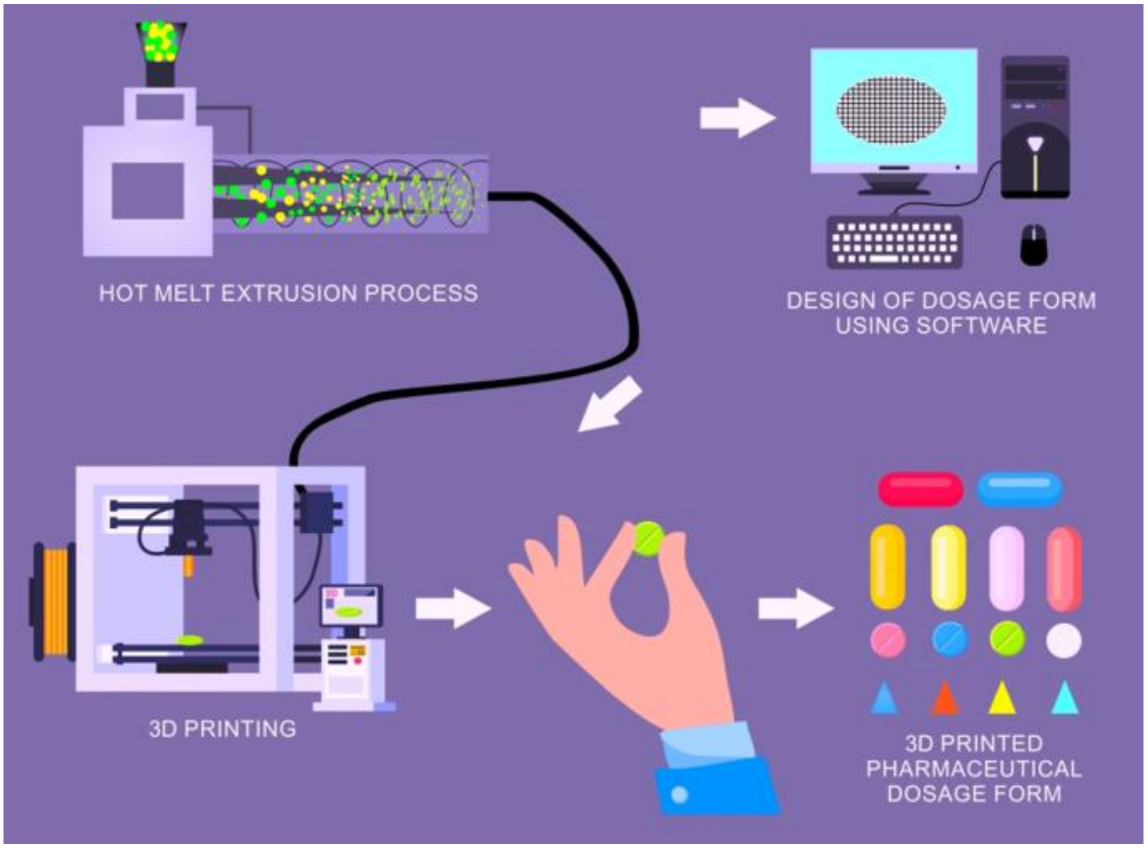

Figure 4. How 3DP works in pharmaceuticals [6].

Figure 5. 3D printing methods applied for drug formulation [8].

Figure 6. 3D printed drugs [9].

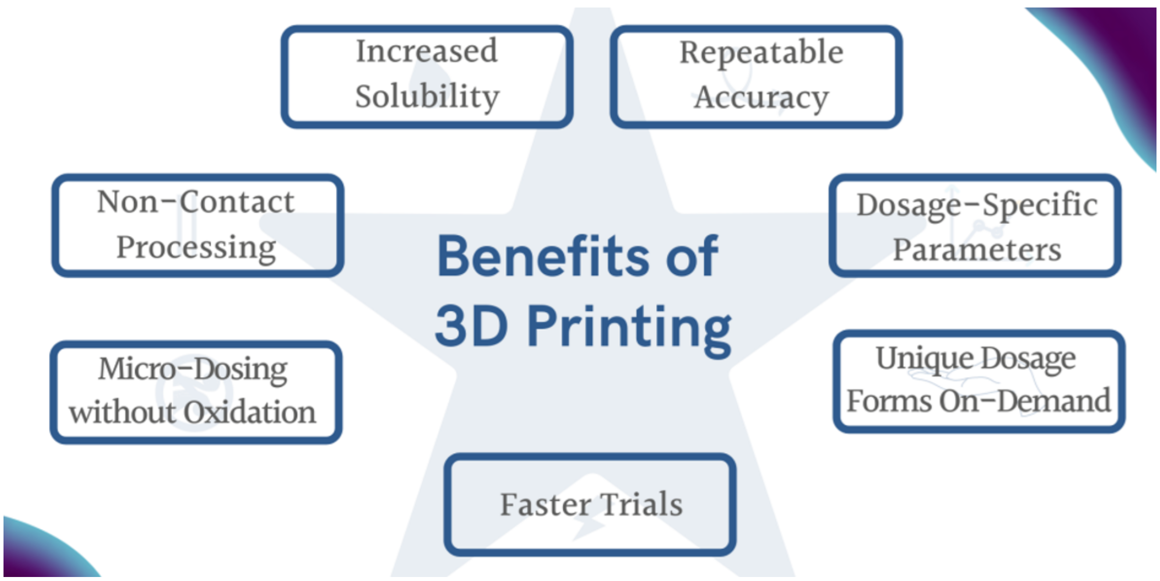

Figure 7. Benefits of pharmaceutical 3D printing [10].