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A Review on Recent Selective Laser Sintering Printing of Medicines

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Abstract

Rapid Prototyping (RP) is a series of technologies for rapidly manufacturing a computer part or assembly. Computer-Aided Design (CAD) makes it possible to quickly create an intricate 3D component design. It uses a computer-aided design model that allows human interference to be reduced to an absolute minimum. It is capable of visualizing complex models as well as the way to test product efficiency. In addition, it can be used for consumer-preference research. SLS has a number of advantages that set it apart in the pharmaceutical industry. SLS' ability to create free-form 3D structures without the use of external support materials, opens up possibilities for the fabrication of a wide range of dosage types. SLS also allows the formation of objects with high porosity and pore connectivity levels. Unlike other printing technologies (such as fused deposition modeling (FDM) and stereolithography (SLA), SLS does not necessitate pre-processing of the starting material or the addition of additional excipients that may be harmful. The lack of solvents in the process improves the protection and stability of drug compounds that are susceptible to hydrolysis. As compared to other 3D printing technologies (e.g. FDM and SLA) and traditional manufacturing methods (e.g. injection molding), previous studies have shown that SLS is more cost efficient for the production of custom parts.

Background and Literature Review

Rapid Prototyping (RP) is a series of technologies for rapidly manufacturing a computer part or assembly. CAD makes it possible to quickly create an intricate 3D component design. It uses a computer-aided design model that allows human interference to be reduced to an absolute minimum. It is capable of visualizing complex models as well as the way to test product efficiency. In addition, it can be used for consumer-preference research. All here has come about because of RP's quick and simple 3D production workflows. However, the level of detail is hindered by the thickness of the sheet and to a lesser extent. Several major RP-based production processes are here: SLA, SLS, FDM, and LOM [1-4].

SLS has been used in pharmaceutics since 2001 by Low et al. in 2001 to build porous cylindrical disc matrices for use as drug delivery devices (DDD). By fine-tuning the laser power and scanning speed, the technique was first used to build porous drug delivery systems. The 3D printing platform was based on a CO2 laser, and the cubes (8*8*8 mm) were manufactured using nylon and infiltrated with a methylene blue dye. The porosity was found to be inversely proportional to the laser power but directly proportional to the scanning speed. Despite the fact that the printed devices were highly porous, the inter-layer dwell time resulted in two thick sides [5]. And, as a result, relative to the rest of the structure, drug diffusion from these sides was slowed.

Subsequent research aimed to learn more about the impact of the processing parameters [1-2]. It was discovered that a scanning length of 2 mm was all that was needed to achieve the desired porosity.

Furthermore, it was shown that the printing orientation could be used to reposition the thick walls, allowing for greater control over porosity and drug release.

In 2006, the first attempt at SLS 3D printing with biodegradable polymers was made [6]. PCL and PLLA were used as the polymers of choice. It was important to balance the laser power and scanning speed to achieve the best porosity while retaining good mechanical properties. Lowering the laser power and increasing the scanning speed were found to be the best ways to achieve the optimal porosity.

Following that, in 2007, the first attempt was made to incorporate a substance into the polymer mixture prior to sintering. The dissolution pattern unfolded with a burst release followed by a continuous drug release, resulting in a uniform drug delivery [7]. Additional exterior barrier rings formed by the laser's dwell were incorporated into the structures to minimize the initial drug burst release. The burst release was decreased as the number of circular barriers increased. It's worth noting that none of the studies mentioned above looked into the impact of the laser beam on drug stability. As a result, there were still reservations about the technology's suitability for pharmaceutical manufacturing.

The first SLS printed oral dosage forms were manufactured in 2017 [2]. For the first time in pharmaceutical science, a diode laser (= 0.445 m; P = 2.3 W) was used for SLS printing. Eudragit L100-55, which has a long release time, and Kollicoat IR, which has an immediate release time, were successfully used to make paracetamol 3D printed tablets, known as Printlets. Drug degradation from the diode laser was a major concern, but tests revealed that no such degradation

occurred. However, it was clear that using the polymer and drug combination alone would not result in sintering. This is because the diode laser absorbs visible light, and most pharmaceutical powders are white, so there would be no absorption. This necessitated the addition of a pharmaceutical-grade colorant (e.g. Candurin® Gold Sheen) to allow for diode laser absorption [1-3].

1. Principles of Selective Laser Sintering (SLS) and Medicines

The SLS apparatus is made up of six parts: i) a building platform where the 3D object is buit and fabricated; (ii) a laser, responsible for the sintering process; (iii) Galvano mirrors, utilized to guide and project the laser beam to the correct printing positions; (iv) a powder reservoir hopper or platform to hold and dispense fresh powder onto the building platform; (v) a mechanical component in charge for spreading the powder onto the platform ; and finally vi) a material vat [1][3].

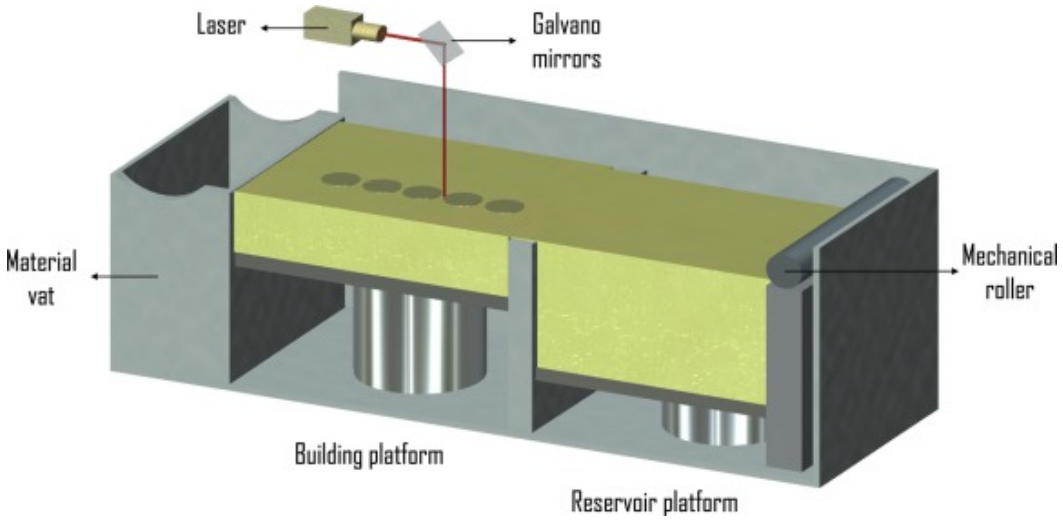

Figure 1- Different major components of SLS 3D printer [1].

The printing process begins by raising the building platform to its highest point, after which the roller spreads and flattens a fresh layer of powder. The laser beam is then activated, scanning through the powder and sintering it according to the pattern from the 3D design file. After that, the building platform is lowered to make room for a new powder layer. The reservoir platform then rises, and a new layer of powder is spread by the roller. The cycle continues until the printing job is completed. The printer is left to cool after the operation is completed. The written item is then retrieved after excess unsintered material is rubbed off or washed with compressed air. In certain cases, post-processing (e.g. painting, polishing, or surface finishing) may be needed to enhance the final object's mechanical properties (e.g. tensile strength and hardness) or appearance (e.g. dimensions and surface precision) [1].

The printing parameters that are used can have a big impact on the final product. The parameters must be optimized to fit the powder properties and the expected application in order to achieve the best results. As a result, a thorough understanding of the relationship between the processing parameters and their effect on the powder is essential. The following are the key processing parameters associated with SLS technology shown in Figure 2. The printing temperature of superficial layers of the powder in the building platform, and the chamber temperature need to be controlled. The absorbance of the laser beam depend the laser wavelength (λ), the morphology of the powder particles, the type of material utilized, the ambient gas, and the powder bed temperature. Depending upon different optical characteristics of laser beams, materials used can only absorb specific wavelengths. Therefore, proper selection laser technology should be considered in light of different range of materials. For instance, for thermoplastic polymers, superior absorption is achieved at a higher wavelength. Thus, CO2 lasers are promising

candidates for such materials due to their efficient and higher absorbance rate with lower energy [1][4] [see Figure 3].

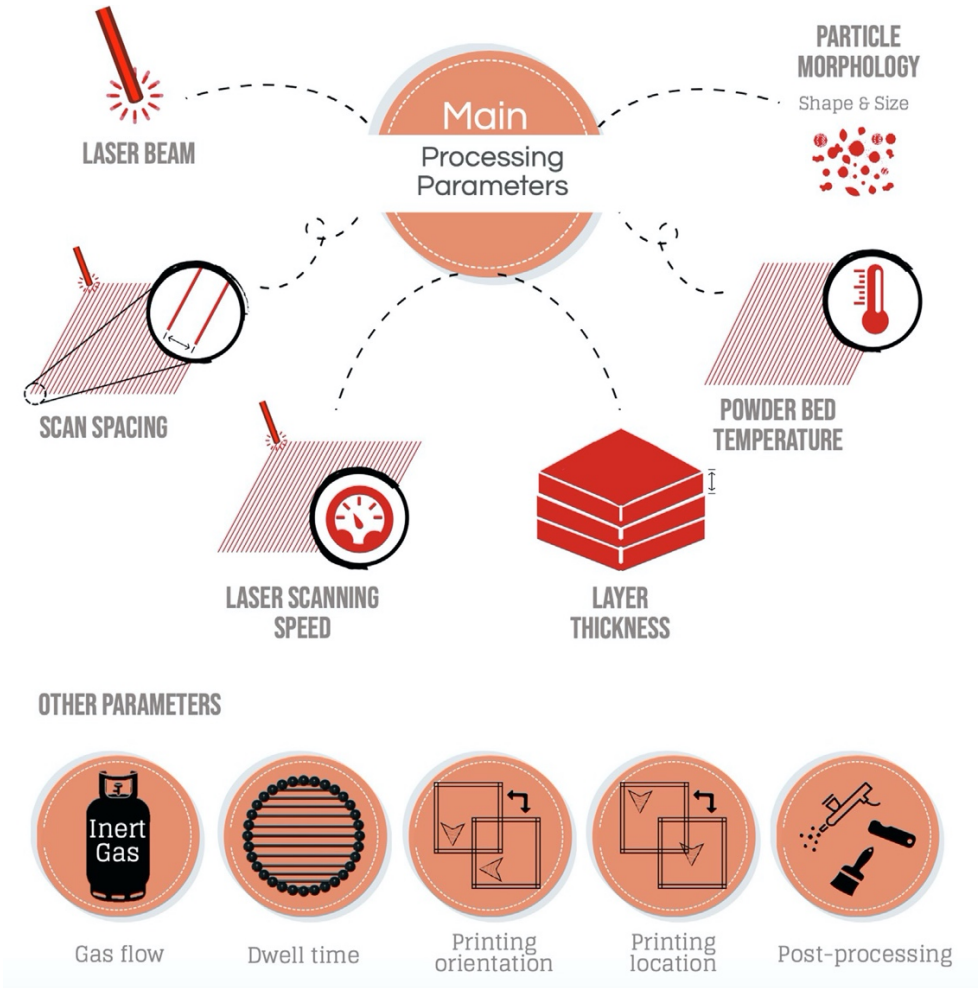

Figure 2- Major parameters affecting SLS 3D printing tailored for medicine fabrication [1].

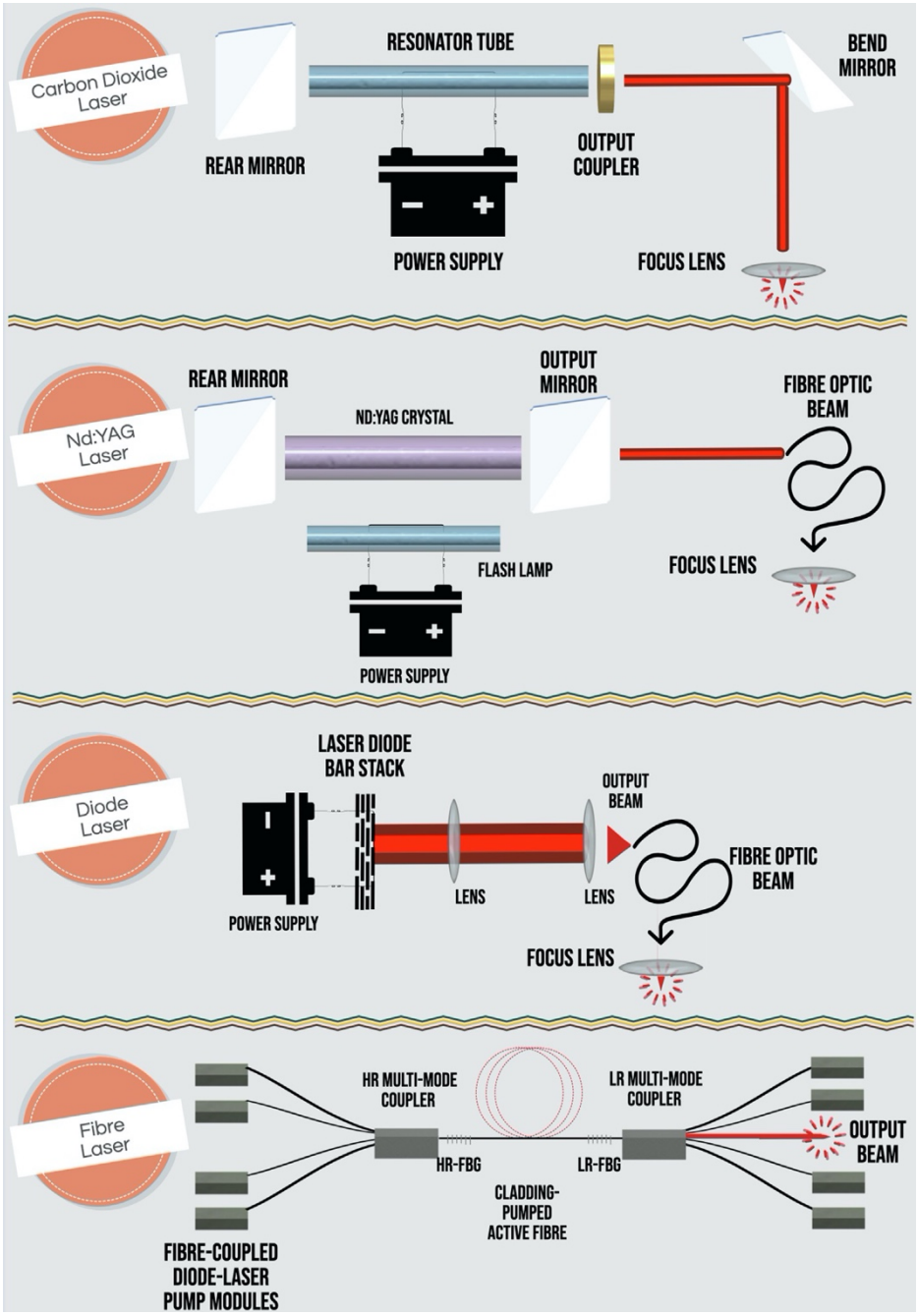

Figure 3- Graphical schemtics of differences between carbon dioxide (CO2), neodymium-doped yttrium aluminum garnet (Nd:YAG), diode and fibre lasers [1].

2. Advantages and Disadvantages

SLS has a number of advantages that set it apart in the pharmaceutical industry. SLS' ability to create free-form 3D structures without the use of external support materials, for example, opens up possibilities for the fabrication of a wide range of dosage types. SLS also allows the formation of objects with high porosity (e.g., the percentage of void spaces in the total volume of the object) and pore connectivity (e.g., the average volume of pores inside an object) levels (Leong et al., 2003). Unlike other printing technologies (such as fused deposition modeling (FDM) and stereolithography (SLA), SLS does not necessitate pre-processing of the starting material or the addition of additional excipients that may be harmful. The lack of solvents in the process improves the protection and stability of drug compounds that are susceptible to hydrolysis. As compared to other 3D printing technologies (e.g. FDM and SLA) and traditional manufacturing methods (e.g. injection molding), previous studies have shown that SLS is more cost efficient for the production of custom parts [1-2].

Furthermore, printed items can be stacked on top of one another, expanding the building platform's capability and increasing efficiency, making it ideal for scale-up and mass production. SLS also provides the option of recycling and reprocessing feed content, which helps to reduce waste while also promoting green pharmaceuticals [1].

SLS has a number of drawbacks, one of which is its impact on laser-sensitive materials, such as natural polymers and medications. As a result, materials and medications are limited in their suitability. Furthermore, in terms of technical aspects, printing large amounts of powder is needed to ensure consistent layer height and proper powder flow, which may not be feasible in all cases

[1]. This is especially critical when dealing with expensive or limited-quantity medications. Furthermore, while unsintered powders can be recycled, due to concerns about chemical consistency and physical changes, they can only be used for a limited number of prints. As a result, when large amounts of powder are required, a portion of the material can be wasted if the process is not optimized. Similarly, since the procedure may entail post-treatment (e.g., sieving and brushing printed dosage forms), it may necessitate an additional time-consuming step and incur additional costs [1-2].

3. Applications of SLS and Medicine Applications

3D printing is commonly used in industrial production to help streamline a more sustainable and reliable manufacturing process. SLS can be used in a variety of fields due to its combination of material flexibility and design independence. SLS, for example, has been commonly used in electronics production to replace conventional micro-patterning methods. Also, SLS has been used in the automotive and aviation industries to produce light-weight parts while reducing energy consumption during manufacturing. The military has looked into the possibility of using SLS in different incidents such as creating explosives in a safe manner. Also, SLS has been used in the medical sector to fabricate patient-specific implants as well as surgical tooling [8-11]. For instance, SLS has shown promise in tissue engineering as a means of restoring or regenerating tissues. Also, in dentistry, SLS has been used to make prosthetics and dental appliances [1].

With regards to pharmaceutical industry and medicine, the approval of the first 3D-printed tablet (Spritam®) by the US Food and Drug Administration (FDA) marked a significant landmark in the history of 3D printing, setting a benchmark for pharmaceutical manufacturing (Aprecia Pharmaceuticals, 2018). Since then, 3D printing has continued to advance at a breakneck pace,

with cutting-edge research demonstrating the technology's many novel applications. As a result, researchers are looking at and exploring more 3D printing methods to see if they are suitable for pharmaceutical applications. In comparison to other 3D printing technologies, SLS has taken a long time to gain traction in pharmaceutical science. This is due to initial concerns about drug and excipient degradation caused by the laser beam and the lack of pharmaceutically approved materials commercialized for SLS use [1-3].

4. Research Improvement Issues

Although most 3D printing methods are still focused on tailoring doses, there are a number of other possibilities that have yet to be explored. For example, SLS 3D printing's unique laser features can provide a novel and sophisticated approach to creating dosage forms tailored to particular patient groups, such as those with visual disability.

In Awad et al. 2020 studies, orally disintegrating Printlets, in particular, have Braille (Figure 4A) and Moon patterns on their surfaces, allowing patients to recognize drugs after they've been removed from their original packaging [1]. Since all of the Printlets disintegrate in less than 5 seconds, they eliminate the need for water and thus make self-administration of medications easier (Figure 4B). Printlets with unusual shapes were also made, including a sun, a moon, a heart, a caplet shape, a pentagon, and a square (Figure 4C). These shapes provide patients with additional drug details, such as the medication indication and/or dosing regimen. Since many commercialized paracetamol products are marketed in caplet form, a caplet shape may reflect paracetamol. Similarly, because of its similarity to the organ being treated, a heart shape may reflect cardiovascular medications. The shapes of the sun and moon could indicate morning and evening dosing, respectively. In addition, the number of edges in the pentagon and square forms could be

used to match the time of medication intake. A caplet with three Braille letters can be developed, expanding the technology's capabilities and demonstrating that three-letter abbreviations could be printed on larger-sized formulations (Figure 4D). Overall, this lowers drug errors and increases medication adherence in visually impaired patients.

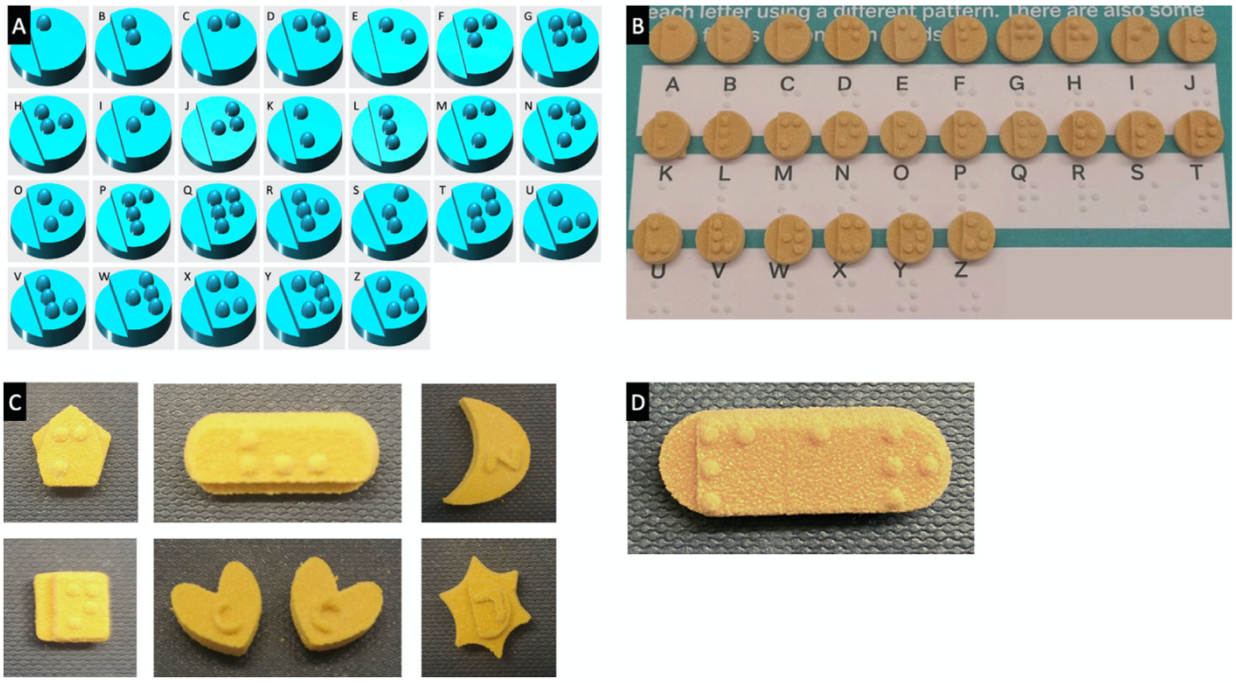

Figure 4- (A) 3D CAD designs of Printlets showing the 26 Braille alphabets.; Cylindrical Printlets showing the 26 (B) Braille alphabets, (C) Printlets with different shapes of Braille or Moon patterns and (D) Printlet with three Braille letters of P, A, and R (from left to right) [1].

5. Creative Thinking and Discussion

Selective laser sintering (SLS) 3-dimensional printing is currently used for industrial manufacturing of plastic, metallic and ceramic objects. The use of SLS 3D printing methods was first reported in 2017 to fabricate oral drug loaded products. In this report, novel works in the field of SLS 3D printing of medicines are explored to discuss the opportunities and suitability of SLS printing for medicine manufacturing. Selective laser sintering (SLS) 3D printing method

benefits medicine fabrication with high printing precision, allowing customized and unique medicines tailored for different application in drug delivery discussed in the previous sections.

The SLS process is an ingenious method for fabricating almost any material including thermoplastic polymers and FDA approved materials. In comparison to other RP processes, it is simple to plan a complex 3D geometry, it needs no help during the process, and it is capable of producing the toughest and delicate components. However, before starting the operation, the machine must be preheated to just below melting temperature. SLS also enables the development of objects with high porosity (the percentage of void spaces in an object's total volume) and pore connectivity (the average volume of pores within an object). SLS, unlike other printing technologies like fused deposition modeling (FDM) and stereolithography (SLA), does not require pre-processing of the starting material or the inclusion of potentially harmful excipients. Since there are no solvents in the process, drug compounds that are prone to hydrolysis are better protected and stabilized. Previous studies have shown that SLS is more cost effective than other 3D printing technologies (such as FDM and SLA) and conventional manufacturing methods (such as injection molding).

As one the limitation of this method for medicine fabrication, researchers need to explore more on its impact on laser-sensitive materials, such as natural polymers and medications. However, SLS allows the engineering of delicate dosage forms that can be customized to suit the needs of specific patient groups. In future studies, different patient groups and customized need of the patients based on SLS printing method and different printing environments and material and polymer selection and their effect on the mass production of SLS printed medications, as an

alternative way of manufacturing, could be realized. Additionally, concerns about drug and excipient degradation caused by the laser beam and the lack of pharmaceutically approved materials commercialized for SLS use need to be studied. And finally, the potential of SLS 3DP to produce commercial personalized medicines to deliver intricate immediate-release and modified-release of drugs should be explored as a promising and novel 3DP technology in pharmaceutical industry.

6. Conclusion

SLS 3D printing has been predicted to pave the way for a new pharmaceutical revolution since its inception. SLS is the most capable of being scaled up for mass production of all the 3D printing techniques, and because its starting materials are the most similar to existing pharmaceutical production technologies, it has the greatest potential for adoption as a novel and scalable manufacturing method for pharmaceutical fabrication. SLS allows the engineering of complex and delicate dosage forms that can be customized to suit the needs of specific patient groups due to the high resolution of its laser beam. Complex dosage forms can be achieved without the use of external support material or methods, unlike other technologies. Although technological and quality control issues have hampered the implementation of such novel technologies, preliminary results appear promising.

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