3D printing: principles and pharmaceutical applications of selective laser sintering

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Abstract

Pharmaceutical three-dimensional (3D) printing is a modern fabrication process with the potential to create bespoke drug products of virtually any shape and size from a computer-aided design model. Selective laser sintering (SLS) 3D printing combines the benefits of high printing precision and capability, enabling the manufacture of medicines with unique engineering and functional properties. This article reviews the current state-of-the-art in SLS 3D printing, including the main principles underpinning this technology and highlights the diverse selection of materials and essential parameters that influence printing. The technical challenges and processing conditions are also considered in the context of their effects on the printed product. Finally, the pharmaceutical applications of SLS 3D printing are covered, providing an emphasis on the advantages the technology offers to drug product manufacturing and personalised medicine.

Keywords:

Powder bed fusion; 3D printed drug products; printlets; additive manufacturing; personalized medicines; digital health; gastrointestinal drug delivery systems.

1. Introduction

Three-dimensional (3D) printing is a type of additive manufacturing technology that has provided fresh opportunities to rethink manufacturing paradigms in various sectors which require the design and fabrication of products (Basit and Gaisford, 2018; Capel et al., 2018; Ong et al., 2020); its use in preparing medicines is particularly promising (Charoo et al., 2020; Hsiao et al., 2018; Liang et al., 2019; Tan et al., 2018; Trenfield et al., 2019) and it has the potential to be a disruptive technology, moving the pharmaceutical sector away from mass production of fixed-dose units towards the flexible manufacture of individual units with dose or other properties tailored to the patient (personalised medicine) (Alhnan et al., 2016; Capel et al., 2018; Goole and Amighi, 2016; Goyanes et al., 2019b; Melocchi et al., 2020; Zhang et al., 2018). In addition, because objects are fabricated in a layer-by-layer manner from a computer-aided design (CAD) model, 3D printing permits the creation of constructs which would otherwise be impossible to produce with conventional manufacturing processes (Chen et al., 2020; Ghosh et al., 2018; Goyanes et al., 2019a; Pandey et al., 2020). In the pharmaceutical sector, this allows the design and evaluation of novel drug-eluting devices which were not previously able to be created (Aho et al., 2019; Gioumouxouzis et al., 2019; Liang et al., 2019; Mohammed et al., 2020; Mohtashami et al., 2020; Xu et al., 2020).

Many types of 3D printing process have been developed (Jamróz et al., 2018; Mukhopadhyay and Poojary, 2018; Trenfield et al., 2018a). Each technology has its own distinct attributes, so a unique range of applications (Jennotte et al., 2020), and each requires specific feedstock materials. The American Society for Testing and Materials (ASTM) classifies 3D printing technologies in seven main categories; vat

polymerisation, binder jetting, material jetting, direct energy deposition, sheet lamination, material extrusion and powder bed fusion (ASTM International, 2016). Within these categories, there are subsets of printer types, broadly grouped in terms of the method they use to consolidate the printer feedstock into a solid object.

One of these, selective laser sintering (SLS), is a subset of powder bed fusion 3D printing; it uses a laser beam to create solid objects by heating powder particles, fusing them together at their surfaces (Fina et al., 2018a). The SLS technology was developed by Carl Deckard in 1984, and was based on a neodymium-doped yttrium aluminum garnet (Nd:YAG) laser, which had a power of 100 W (Beaman and Deckard, 1990). The printer feedstock material was a powder of acrylonitrile butadiene styrene (ABS), a thermoplastic polymer used in many prototypes (Shellabear and Nyrhilä, 2004).

Currently, the majority of commercially available SLS printers employ carbon dioxide (CO_2) lasers, which provide higher power at lower cost, permitting the use of a wide array of powdered thermoplastic materials. As such, applications of SLS span many fields, including the aerospace, automotive, military, medical, dentistry, engineering and electronics industries (Di Giacomo et al., 2016; George et al., 2017; Hettesheimer et al., 2018; Jiba et al., 2019; King and Tansey, 2003; Revilla-León and Özcan, 2017; Theodorakos et al., 2015; Williams and Revington, 2010). In the pharmaceutical sector, therapeutic products can be fabricated using SLS printing if the feedstock material is a powder blend of a drug and thermoplastic polymer. This means that, compared with other 3D printing technologies, the feedstock material of SLS printing has the closest resemblance to that of traditional tabletting. As such, it has been

anticipated that SLS is more amenable for pharmaceutical use. Whilst other 3D printing technologies, such as binder jetting, are also based on powdered materials, being a solvent-free process makes SLS a faster process, wherein the need for additional drying steps to evaporate any residual binder is avoided.

This article reviews the current state-of-the-art in SLS 3D printing, including the main principles underpinning the technology. The technical challenges and processing conditions are considered in the context of their effects on the printed product. Finally, pharmaceutical applications of SLS 3D printing are highlighted, providing an emphasis on the advantages the technology offers to drug product manufacturing and personalised medicine.

2. Technological stratification

Powder bed fusion is one of the seven main 3D printing classifications assigned by the ASTM (Chatham et al., 2019). It refers to the selective consolidation of powder particles into 3D objects using a heat source focused onto specific areas. Powder bed fusion currently has four subset technologies; SLS, selective laser melting (SLM), electron beam melting (EBM) and multijet fusion (MJF) (Gibson et al., 2015). The technologies differ by the type of materials they employ and by the type and amount of light utilised to transmit energy to the powder bed. In all cases, objects are built layer-by-layer through the use of thermal energy resulting from the combination of increased temperature and the use of a light source (Goodridge and Ziegelmeier, 2017) and all use powders as their feedstock materials. One immediate benefit of this is that it permits fabrication of overhanging and/or intricate structures, without the need

for a secondary support material, because the loose powder particles inside the bed act as a support, maintaining the integrity of the object during printing.

Thermoplastic polymers are used as the main feedstock material in SLS printing. The laser beam melts the surface of the powder particles, fusing them together, a process termed ‘sintering’ (Kruth et al., 2003a). Because a relatively low-power laser is used, the printer itself heats the feedstock powder, so the laser needs only to provide a small increase in surface temperature of the powder to induce sintering. When the feed materials are metals or alloyed powders, the technology is normally called selective laser melting (SLM) or direct metal laser sintering (DMLS) (Spears and Gold, 2016).

EBM also uses metal and alloyed powders as its main feed material (Murr et al., 2012; Rafi et al., 2013), although the energy required to sinter the particles is provided with an electron beam instead of a laser beam. The high intensity of the electron beam renders the powdered materials completely melted during the printing process. MJF utilises only one feedstock, nylon (for instance, PA 12), and it employs an infrared (IR) lamp as the energy source. Two additional components are needed in MJF (Sillani et al., 2019); (i) a fusion agent, which is precisely deposited by an ink-jet head onto the printing regions, and (ii) a detailing agent, which is responsible for absorbing heat from the edges of the object. As such, only the regions coated with the fusion agent will melt, enhancing the printing efficiency and speed. The addition of the detailing agent decreases thermal bleeding (e.g. the spreading of heat across neighbouring regions) and enhances printing resolution and accuracy.

Of these printing technologies, SLS is most well suited for use within pharmaceutical research, because it is able to sinter pharmaceutical-grade powders. Thus, it offers a novel and versatile approach for the rapid tailoring of medications.

3. Fundamentals

The SLS apparatus is comprised of six parts; (i) a build platform, upon which the 3D object is fabricated; (ii) a laser, responsible for the sintering process; (iii) Galvano mirrors, which are used to project and direct the laser beam to the correct printing positions; (iv) a powder reservoir platform or hopper, which holds and dispenses fresh powder onto the building platform; (v) a mechanical roller that spreads and flattens fresh powder on the building platform; and (vi) a material vat that recovers unsintered powder material (Figure 1) (Akande et al., 2016; Ma et al., 2018; Tiwari et al., 2015).

Insert Figure 1

Figure 1. Graphical illustration of an SLS 3D printer, highlighting its major components.

The printing process entails raising the building platform to its uppermost position, whereupon a fresh layer of powder is spread and flattened by the roller (Gokuldoss et al., 2017). This is followed by the activation of the laser beam, which scans across the powder and sinters it by following the pattern from the 3D file. The building platform is then lowered, creating enough space for a new powder layer. Then, the reservoir platform ascends, and the roller spreads a new layer of powder. The process repeats until the printing job is finished (Sillani et al., 2019). Upon the completion of the

process, the printer is left to cool. Subsequently, excess unsintered material is brushed off or cleaned using compressed air and the printed object is recovered. In some cases, the final object may require post-processing (e.g. coating, polishing or surface finishing) to improve its mechanical properties (e.g. tensile strength and hardness) or appearance (e.g. dimensions and surface precision).

4. Fine-tuning the process

The processing parameters utilised during printing can significantly influence the final object (Figure 2). To attain optimum characteristics, the parameters have to be optimised to suit the powder properties and the intended application. As such, it is critical to have a clear understanding of the correlation between the processing parameters and their effect on the powder (Pilipović et al., 2018). The main processing parameters relating to the SLS technology can be described as follows:

Insert Figure 2

Figure 2. A graphical illustration of the different processing parameters involved in the SLS 3D printing process.

4.1. Printing Temperature

The powder bed temperature refers to the temperature of the powder in the building platform. This is usually regulated using two parameters; the surface temperature, which refers to the temperature on the superficial layers of the powder in the building platform, and the chamber temperature, which is the temperature inside the printer chamber. Controlling the bed temperature is essential for promoting the sintering

process (Gibson and Shi, 1997). The amount of energy required from the laser for sintering is reduced when the powder bed is pre-heated, limiting internal stresses and thermal deformations. Since thermoplastic polymers can be either amorphous or crystalline, the optimum bed temperature will be highly variable. In the case of amorphous polymers, the bed temperature is usually set to or just above the glass transition temperature (T_g). This is because at this temperature the polymers are highly viscous, enabling their consolidation. In the case of crystalline polymers, consolidation is achieved by setting the bed temperature a few degrees (e.g. 3 - 4°) lower than the melting temperature (T_m). For semi-crystalline materials and polymer mixtures, the optimum bed temperature is usually set close to their T_g, which can be calculated using the simple Fox equation:

$$\frac{1}{T_g} = \frac{W_1}{T_g'} + \frac{W_2}{T_g''} \quad \text{(Eq. 1)}$$

W_1 and W_2 refer to the weight fractions of each polymer and, T_g' and T_g'' refer to the T_g of each individual polymer, respectively (Gibson and Shi, 1997).

4.2. Laser beam

Absorptance refers to the efficiency of a material in absorbing energy and is defined as the ratio of absorbed radiant energy to the incident radiant power (Tolochko et al., 2000). The absorptance (A) is usually calculated by measuring the reflectance (R) of a material, wherein the latter is defined as the ratio of reflected radiation to the incident radiation. The relationship between both values is derived using the following equation:

$$A = 1 - R \quad \text{(Eq. 2)}$$

Typically, the absorptance will depend upon several factors, including the laser wavelength (λ), the type of material used, the morphology of the powder particles, the nature of the ambient gas within the controlled atmosphere and the bed temperature. Each laser has a defined wavelength; typically, in the case of metals, the lower the wavelength, the higher is their absorption (Bergström, 2008; Schuőcker, 1998). In the case of polymers, their absorption increases as the wavelength is increased (Kruth et al., 2003b; Tolochko et al., 2000). Moreover, the general trend that most materials follow is that the denser the material is, the smaller is its absorption depth and vice versa. An exception to this is transparent materials, wherein light can pass through the material, resulting in limited light absorption. In the case of loose powders, due to the presence of pores between powder particles, the incident radiation is distributed between the surface of the powder particles on the top layer and the powder particles on the layers underneath it. As such, the energy is absorbed deeper as compared to dense material.

The earliest models of SLS printers employed Nd:YAG lasers (λ = 1.064 μm). These are crystal lasers that are pumped into excitation using an external source (e.g. flash lamp or diodes) (Figure 3). However, Nd:YAG lasers have a short lifespan, requiring constant replacement. As such the majority of industrial SLS printers are designed to operate with either single or multiple carbon dioxide (CO_2) lasers (λ = 10.6 μm), with power ranges between 50 to 200 W. These are gas lasers that encompass a CO_2 mixture that is excited using an electrical current (Figure 3). Some of the newer industrial SLS platforms employ carbon monoxide (CO) lasers, which have an ultra-fine spot size (e.g. diameter of the laser beam) that is half that of a CO_2 laser,

permitting higher printing precision and the fabrication of finer objects. Benchtop systems on the other hand, utilise diode (λ is variable) or fibre (λ = 1.064 μm) lasers, both of which can supply a comparable laser power to that of CO_2 lasers but are much cheaper (Formlabs, 2020b). Fibre lasers function using a seed laser that induces the generation of a beam, which is amplified in glass fibres energised by pump diodes. Compared with CO_2 lasers with analogous powers, fibre lasers have a thinner laser spot size, enabling the delivery of a greater laser power density and reducing the time needed for sintering the powder (Shellabear and Nyrhilä, 2004; Yasa et al., 2012). Diode lasers utilise semiconductors connected to fibres or mirrors to induce laser irradiation (Figure 3). The type of semiconductor material that is selected dictates the wavelength of the emitted laser beam. Thus, diode lasers can span from the infrared to the ultraviolet (UV) regions of the spectrum. Due to their higher efficiency and lower energy density, diode lasers have shown higher consistency in melting and heating zones when compared to Nd:YAG, fibre and CO_2 lasers (Bergmann et al., 2013; Zavala-Arredondo et al., 2017).

Insert Figure 3

Figure 3. Graphical illustration of the differences between carbon dioxide (CO_2), neodymium-doped yttrium aluminum garnet (Nd:YAG), diode and fibre lasers. HR: High reflection; LR: Low reflection; FBG: Fibre Bragg Grating.

Owing to their optical characteristics, materials can only absorb energy of specific wavelengths. Thus, each laser type is suitable for a different range of materials. For thermoplastic polymers, superior absorption is achieved at a higher wavelength. As

such, CO_2 lasers are considered more efficient because a higher absorptance can be achieved with a lower energy (Table 1). In some cases, materials cannot be sufficiently sintered on their own. These materials require addition of a temporary binder to improve the sintering process. Upon the completion of the sintering process, the additional binder can be removed in a furnace (Kruth et al., 2003b).

Table 1. Absorptance (A) of thermoplastic polymers from two different laser beams: (a) neodymium-doped yttrium aluminum garnet (Nd:YAG) (λ = 1.06 μm), and (b) carbon dioxide (CO_2) (λ = 10.6 μm). The data presented here are from those presented in the original sources **(Kruth et al., 2003b; Tolochko et al., 2000)**.

Thermoplastic polymer	Nd:YAG absorptance	CO_2 absorptance
Polytetrafluoroethylenes	0.05	0.73
Polymethylacrylates	0.06	0.75
Epoxypolyethers	0.09	0.94

The wavelength of the laser beam is one of the few parameters that cannot be adjusted. Instead, to maximise the absorptance of a polymer, the energy transmittance from the laser beam is adjusted by modulating its power and scanning speed. The laser power (P) refers to the power at the powder bed surface. To ensure optimum sintering, the laser power should be fine-tuned to yield an appropriate bed surface temperature. This also plays a role in the overall printing time. A summary of the different benchtop SLS printers and their characteristics is shown in **Table 2**.

Table 2. Summary of some of the benchtop SLS 3D printers, alongside their unique characteristics.

3D Printer	Laser type	Laser wavelength (µm)	Laser power (W)	Layer thickness (µm)	Build volume (L x W x H in mm)	Reference
Formlabs Fuse 1	Fibre	1.066	10	100	165 x 165 x 320	(Formlabs, 2020a)
Natural Robotics VIT SLS	CO_2	10.6	40	100-150	250 x 250 x 300	(Natural Robotics, 2020)
Sharebot Snowwhite	CO_2	10.6	14	100	100 x 100 x 100	(Sharebot, 2020)
Red Rock 3D	Diode	0.450	2.5	100	180 x 180 x 180	(Red Rock 3D, 2020)
Sinterit Lisa Pro	Diode	0.808	5	75-175	150 x 200 x 260	(Sinterit, 2020)
Sintratec Kit	Diode	0.445	2.3	50-150	110 x 110 x 110	(Sintratec, 2020)

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4.3. Laser scanning speed

The laser scanning speed (V_s; also known as beam speed) refers to the rate at which the laser beam travels when drawing the 3D pattern. The laser scanning speed can highly affect the laser energy density on the surface of the powder, where the relationship between both parameters can be explained using the equation (Kumar, 2020):

$$E_v = \frac{P}{S_d \times V_s} \quad \text{(Eq. 3)}$$

Where E_v refers to the laser energy density, P is the laser power and S_d is the laser spot size.

Generally, lowering the laser scanning speed induces in a high laser energy density and increases the contact time between the powder bed and the laser beam (Fred et al., 2014). This allows higher energy transmission to the powder bed, resulting in a higher degree of sintering and producing denser objects. The downside to this is that it results in longer printing times. A greater laser scanning speed results in a low energy density and less energy being transmitted to the powder and thus leads to less sintering and so more porous objects.

4.4. Scan spacing

Scan spacing, which is also known as hatch distance or line offset, refers to the distance between two consecutive scanning vectors. The optimum scan spacing should be set with respect to the laser beam diameter and energy density. If the scan space is too large, the layers might undergo incomplete sintering, wherein the layers

would not be connected, leaving unsintered parts in between and yielding objects with low mechanical strength. Like the slice thickness, the scan spacing is proportionate to the printing time. As such, increasing the scan spacing reduces the time needed for printing each layer. Decreasing the scan spacing lengthens the fabrication process, but it is best for creating thin and intricate structures. However, this decrease should not exceed the recommended limit, because if the scan spacing is too short, it might induce thermal deformations.

4.5. Particle Size and Shape

Particle morphology plays a major role in in the sintering process (Williams et al., 2005). To achieve optimum sintering, a balance between optimum size and shape of the powder particles should be achieved. If the particles are too big, they would require more energy for proper sintering. More importantly, bigger particles will leave larger empty spaces between each other, resulting in poor mechanical properties, which cannot always be overcome with higher laser energy. On the other hand, the flow properties of very small particles are often hindered by high electrostatic forces, resulting in their agglomeration (Schulze, 2008). More importantly, the particle size distribution should be narrow to ensure even absorption of energy. Similarly, irregularity in particles shape could also result in uneven sintering and obstruct flowability. Ideally, the powder particles should be spherical in shape, with sizes ranging between 58 to 180 µm (Leong et al., 2006). This imparts good flow properties and permits homogenous energy transmittance amongst the powder bed.

4.6. Layer thickness

Layer thickness (h), which is also known as the slice thickness, refers to the height of each individual layer. This is controlled by adjusting the depth by which the building platform is lowered before the start of each layer. The slice thickness will usually depend on the 3D printer and typically ranges between 0.07 to 0.5 mm (Kruth et al., 2003b). Like other 3D printing technologies, the thinner the layers are, the higher the printing resolution is. On the other hand, the thicker the layers are, the rougher the surface is and the lower is the printing resolution. Nonetheless, to ensure accuracy, the layer thickness should not fall below the average particle size of the powder (Gibson and Shi, 1997). It should be noted though that the printing resolution is directly proportional to the printing time; the higher the printing resolution, the longer is the printing time.

Due to the complex nature of SLS 3D printing, there are other parameters that also contribute to the final outcome of the process. This includes the flow of inert gas (e.g. argon or nitrogen) inside the printing chamber, which prevents oxidation by removing condensates produced during printing. Another important factor is the dwell time, which refers to the cooldown time required at the start and end of each layer. Typically, the longer the dwell time, the better the overall geometrical features of the object (Arregui et al., 2018). The building orientation (e.g. horizontal, vertical or diagonal) controls the physical properties and mechanical performance of the final object (Kundera and Kozior, 2016, 2018). Similarly, the building position (physical location on the build plate) could also influence the mechanical properties of the end-products, because objects built in the middle regions tend to undergo higher intensity sintering due their ability to retain heat for longer periods of time. Another dominating factor is post-treatment (e.g. coating, annealing or surface finishing), which could significantly

affect the tensile strength, surface hardness, dimensional accuracy and precision (Dizon et al., 2018; Gibson and Shi, 1997; Nelson and Vail, 1991).

5. Diversity of feedstock

Thermoplastic polymers are the most commonly used materials in SLS 3D printing. To fabricate parts with high resolution and dimensional accuracy, amorphous polymers, such as polycarbonates (PC), are mainly used (Kruth et al., 2003b). However, 3D objects made with PC lack strength and robustness. Instead, semi-crystalline polymers, such as nylons (also known as polyamides, PA), are utilised. Due to the ability of PA to be fully consolidated into highly dense objects, it is employed to create highly functional prototypes (Salmoria et al., 2012b; Salmoria et al., 2011). Other frequently used thermoplastic polymers include, poly-L-lactide (PLLA) (Duan et al., 2010; Lee et al., 2008), polylactic acid (PLA) (Bai et al., 2017; Zhang et al., 2019), poly(ether-ether-ketone) (PEEK) (Tan et al., 2003; Tan et al., 2005b), polycaprolactone (PCL) (Leong et al., 2007; Williams et al., 2005), high density polyethylene (HDPE) (Salmoria et al., 2007b; Salmoria et al., 2013a), polymethylmethacrylate (PMMA) (Leite et al., 2010; Salmoria et al., 2007a), polyurethane (PU) (Sun et al., 2020) and polyvinyl alcohol (PVA) (Chua et al., 2004).

6. Industrial applications

Typically, the use of 3D printing within industrial production helps streamline a more sustainable and efficient manufacturing process. By combining flexibility in materials and freedom in design, SLS can be exploited in a myriad of fields. As an example, SLS has been widely applied for the manufacturing of electronics, substituting traditional micro-patterning methods (Theodorakos et al., 2015). Within the automotive

and aviation industries, SLS has been utilised to create lightweight parts whilst cutting down energy consumption during production (Hettesheimer et al., 2018). The military has investigated the potential of utilising SLS to generate explosives in a harmless manner (Jiba et al., 2019). In the medical field, SLS has been utilised to fabricate implants specifically tailored to the patient (Williams and Revington, 2010) and for surgical tooling (George et al., 2017). SLS has shown noticeable application in tissue engineering for repairing or regenerating tissues (Chua et al., 2004; Eosoly et al., 2010; Partee et al., 2006; Tan et al., 2003; Tan et al., 2005a). Similarly, SLS has been explored in dentistry to create prosthetics (Di Giacomo et al., 2016) and dental appliances (Revilla-León and Özcan, 2017).

7. Pharmaceutical applications

The United States (U.S.) Food and Drug Administration (FDA) approval of the first 3D-printed tablet (Spritam®) marked an important milestone in the history of 3D printing, setting a benchmark for manufacture of pharmaceuticals (Aprecia Pharmaceuticals, 2018). Since then, 3D printing has continued to evolve rapidly, with cutting-edge research showing the many novel prospects the technology can offer. This has led researchers to investigate and explore more 3D printing technologies to evaluate their suitability for pharmaceutical applications. Compared with some of the other 3D printing technologies, SLS has had a slow-moving journey within pharmaceutical research. This is primarily due to initial fears of drug and excipients degradation caused by the laser beam (Alhnan et al., 2016) and absence of pharmaceutically approved materials that are commercialised for SLS use.

7.1. Adapting the technology

The powder blend in SLS mainly consists of a thermoplastic polymer. However, one important aspect to consider is that these polymers need to be biocompatible and biodegradable (i.e. generally recognised as safe, GRAS) and accredited by the FDA. As such, commercial SLS materials are not suited for pharmaceutical use. The selection of the polymer will depend primarily on the intended application (e.g. dosage form and site of action) and required drug release characteristics (e.g. orally disintegrating, immediate or sustained profile). Regardless of the final application, the selected polymer also needs to meet the printing requirements, such as having appropriate flow properties with suitable particle shape and size (≤ 180 µm). A range of polymers have been successfully employed within pharmaceutical research. These include PCL (Salmoria et al., 2017a; Salmoria et al., 2012a; Salmoria et al., 2017c; Salmoria et al., 2016; Salmoria et al., 2013b; Salmoria et al., 2013c), HDPE (Salmoria et al., 2017b; Salmoria et al., 2018), Kollicoat IR (e.g. polyvinylalcohol and polyethylene glycol co-polymer) (Awad et al., 2019), Eudragit (e.g. methacrylic acid and ethyl acrylate co-polymer) (Fina et al., 2017), hydroxypropyl methylcellulose (HPMC) (Fina et al., 2018c), Kollidon VA64 (e.g. vinylpyrrolidone-vinyl acetate co-polymer) (Allahham et al., 2020; Barakh Ali et al., 2019), polyethylene oxide (PEO) (Fina et al., 2018b), cellulose acetate (Salmoria et al., 2009) and ethyl cellulose (EC) (Awad et al., 2019; Fina et al., 2018b).

The most important constituent in a pharmaceutical dosage form is the drug agent. The choice of the drug substance will predominantly depend upon the treatment purpose. One of the factors that limits the choice of drugs suitable for SLS printing is sensitivity to light and heat. Sensitivity can be reduced by pairing the drug substance with a polymer that has high laser absorption. Another approach involves

microencapsulation of the drug substance within a polymer matrix (Duan et al., 2011; Zhou et al., 2008). As the sintering process occurs at the surface, the integrity of the drug is maintained throughout the printing procedure. Alternatively, the drug can be incorporated into the dosage form after the printing process has finished. For instance, the drug substance can be selectively bound onto the surface of the printed dosage form by integrating a suitable substrate into the printed matrix (Duan and Wang, 2010).

Depending on the selected polymer and the laser type of the SLS printer, some powder blends may require the addition of an absorptance enhancer. The type of absorptance enhancer will depend on the wavelength of the laser. Pre-processing the polymer powder could improve the particle morphology. For instance, grinding and milling could reduce the particle size, spray drying could improve particle morphology (Maa et al., 1997; Vehring, 2008), whilst sieving could aid in controlling the size distribution (Awad et al., 2019). Likewise, the inclusion of flow enhancers (e.g. magnesium stearate, talc and colloidal silica) could improve the flow characteristics of the powder (Vasilenko et al., 2011).

7.2. Historical perspectives

The use of SLS in pharmaceutics dates back to 2001 (Low et al., 2001). The technology was first exploited to create porous drug delivery systems by fine tuning the laser power and scanning speed. Cubes (8 x 8 x 8 mm) were fabricated using nylon and infiltrated with a methylene blue dye, and the 3D printing platform was based on a CO_2 laser. The porosity was found to be directly proportional to the scanning speed but was inversely proportional to the laser power. Although the printed devices were highly porous, they had two highly dense sides resulting from the inter-layer

dwelling time. As such, the drug diffusion from these sides was retarded compared with the rest of structure. Subsequent studies aimed at understanding further the effect of the processing parameters (Cheah et al., 2002). It was found that minimal scanning length of 2 mm was needed to yield the desired porosity. Moreover, it was demonstrated that the printing orientation could be utilised to reposition the dense walls and thus, enabling higher control over porosity and drug release.

This was followed by the first attempt to utilise biodegradable polymers for SLS 3D printing in 2006 (Leong et al., 2006). Two different polymers, PCL and PLLA, were employed. To obtain optimum porosity whilst maintaining strong mechanical properties, it was necessary to balance the laser power and scanning speed. It was determined that the ideal porosity could be achieved by lowering the laser power and accelerating the scanning speed. Subsequently, the first attempt to incorporate a drug within the polymer mixture prior to sintering was made in 2007 (Leong et al., 2007). A uniform drug distribution was obtained, wherein the dissolution pattern unfolded with a burst release followed by a sustained drug release. To reduce the initial drug burst release, additional exterior barrier rings created by the dwell of the laser were included into the structures. As the number of circular barriers increased, the burst release was reduced. It is worth mentioning that none of the aforementioned studies investigated the effect of the laser beam on the drug stability. As such, doubts regarding the suitability of this technology for pharmaceutical production still existed.

In 2017, the first SLS printed oral dosage forms were fabricated (Fina et al., 2017). For the first time, a diode laser (λ = 0.445 μm; P = 2.3 W) was used for SLS printing within pharmaceutical research. Two pharmaceutical grade polymers, Eudragit L100-

55, having prolonged release properties, and Kollicoat IR, with immediate release characteristics, respectively, were successfully utilised to create paracetamol 3D printed tablets, termed Printlets™. With drug degradation from the diode laser being a major concern, degradation studies showed that no drug degradation has occurred. It was evident, however, that no sintering can be achieved using the polymer and drug mixture on their own. This is because the diode laser absorbs in the visible light region and with most pharmaceutical powders being white, no absorption will occur. This instigated the addition of a pharmaceutical grade colourant (e.g. Candurin® Gold Sheen) to enable the absorptance from the diode laser.

7.3. New opportunities

SLS brings along a set of advantageous features, making its applications within the pharmaceutical field distinct. An example is the ability of SLS in creating free-form 3D objects without the need for additional support materials, opening up opportunities for the fabrication of a wide array of dosage forms. SLS also enables the creation of objects with high degrees of porosity (e.g. which refers to the percentage of void spaces out of the total volume of the object) and pore connectivity (e.g. which refers to the overall volume of pores within an object) (Leong et al., 2003). Unlike other printing technologies (e.g. fused deposition modelling (FDM) and stereolithography (SLA)), SLS does not require the pre-processing of its starting material, nor does it necessitate the inclusion of additional excipients that could pose potential toxicity. The absence of solvents within the process enhances safety and provides better stability to drug substances that are liable to hydrolysis.

Previous studies have shown that SLS is more cost effective for the production of personalised parts when compared to other 3D printing technologies (e.g. FDM and SLA) and conventional production processes (e.g. injection moulding) (Awad et al., 2018; Hopkinson and Dicknes, 2003). Moreover, printed objects can be stacked on top of one another, increasing the capacity of the build platform and enhancing productivity, making it highly amenable for scale up and mass production. Additionally, SLS offers the option of recycling and reprocessing feed material, reducing waste and supporting green pharmaceuticals.

7.4. Novel designs

SLS is an adaptable technology suitable for printing a variety of dosage forms with unique properties. A summary of the cutting-edge pharmaceutical creations fabricated using SLS 3D printing is shown in **Table 3**. SLS offers a wide selection of materials with different inherent properties. By selecting a suitable polymer and fine-tuning the processing parameters, an array of drug release modes could be achieved.

Table 3. Summary of the cutting-edge pharmaceutical creations fabricated using SLS 3D printing.

Pharmaceutical application	Active pharmaceutical ingredient(s)	Polymer(s)	Other Excipients	References
Orally disintegrating Printlets	Ondansetron	Kollidon VA64	β-Cyclodextrin, Candurin® Gold Sheen, Mannitol	(Allahham et al., 2020)
	Paracetamol	Kollidon VA64	Candurin® Gold Sheen	(Fina et al., 2018c)
	Diclofenac sodium	Kollidon VA64	Candurin® NXT Ruby Red, Lactose monohydrate	(Barakh Ali et al., 2019)
Immediate-release Printlets	Paracetamol	Kollicoat IR	Candurin® Gold Sheen	(Fina et al., 2017)
	Paracetamol	HPMC	Candurin® Gold Sheen	(Fina et al., 2018c)
Controlled-release Printlets	-	PCL, PLLA	-	(Leong et al., 2006)

	Paracetamol	Eudragit L100-55	Candurin® Gold Sheen	(Fina et al., 2017)
Multi-reservoir drug delivery system	Progesterone	PCL	-	(Salmoria et al., 2017a)
	Progesterone	PCL	-	(Salmoria et al., 2012c)
Tissue and bone regeneration implants	5-fluorouracil	PE	-	(Salmoria et al., 2017b)
	Ibuprofen	PCL	-	(Salmoria et al., 2016)
	5-fluorouracil	PCL	-	(Salmoria et al., 2017c)
Gyroid lattices and bi-layered Printlets	Paracetamol	PEO, Eudragit L100-55, Eudragit RL and EC	Candurin® Gold Sheen	(Fina et al., 2018b)
Miniprintlets	Paracetamol, ibuprofen	Kollicoat IR, EC	Candurin® Gold Sheen	(Awad et al., 2019)

Intrauterine devices	Progesterone, 5-fluorouracil	HDPE		(Salmoria et al., 2018)
Printlets for the visually-impaired	Paracetamol	Kollidon VA64	Candurin® Gold Sheen	(Awad et al., 2020)

IR: instant release, HPMC: hydroxypropyl methylcellulose, PCL: Polycaprolactone, PLLA: Poly (-L) Lactic Acid, PE: polyethylene, HDPE: high density polyethylene, PEO: polyethylene oxide, EC: ethylcellulose.

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7.4.1 Orally-disintegrating Printlets

SLS is capable of forming 3D objects solely by loosely binding powder particles on the surface, resulting in very porous and fast-dissolving Printlets. Due to the absence of compression forces, the Printlets are highly porous. As such, once dispersed in water, the water molecules quickly penetrate into the Printlets, leading to their rapid disintegration. This effect is intensified by increasing the laser scanning speed used for sintering. This decreases the contact time between the laser beam and powder bed surface and yields Printlets with acceptable mechanical properties and rapid disintegration times. On this basis, Printlets incorporating Kollidon VA64, a vinylpyrrolidone-vinyl acetate copolymer, were fabricated (Figure 4A and B). The disintegration times of the Printlets made of identical compositions varied from >600 s, when printed at a laser scanning speed of 100 mm/s, all the way to 15 and 4 s, when printed at a laser scanning speeds of 200 and 300 mm/s, respectively (Allahham et al., 2020; Fina et al., 2018c). As a result, the Printlets fabricated at 100 mm/s required 1 h for the complete drug dissolution, whereas those printed at 200 and 300 mm/s achieved a complete drug release within 5 min (Figure 4C).

Insert Figure 4

Figure 4. Images of the (A) ondansetron and (B) paracetamol orally disintegrating Printlets fabricated using Kollidon VA64. (C) *In vitro* drug dissolution profiles from the paracetamol Printlets fabricated at different laser scanning speeds. Scale shown in cm. Reprinted with permissions from (Allahham et al., 2020; Fina et al., 2018c).

In another study, 30% diclofenac sodium was incorporated into the formulation, reducing the disintegration rate and changing the mechanical properties of the Printlets (Barakh Ali et al., 2019). This required the addition of lactose monohydrate to help modulate the mechanical characteristics and disintegration time of the Printlets. The partial least squares (PLS) concentration images of the Printlets displayed a uniformity in colour, indicating that the drug is uniformly distributed within Printlets (Figure 5).

Insert Figure 5

Figure 5. Partial least squares (PLS) concentration images of different Printlets, showing the distribution of the drug within the Printlets. Red and blue pixel in the PLS concentration image refer to the low and high drug concentration, respectively. Reprinted with permission from (Barakh Ali et al., 2019).

7.4.2 Immediate-release Printlets

By selecting a polymer with immediate-release properties, it is possible to produce Printlets with instant release characteristics. An example is Kollicoat IR, which exhibits a pH-independent profile (Fina et al., 2017). The Printlets can be fabricated to include various drug loading percentages, ranging between 5% to 35%, all of which are prepared under the same printing conditions (e.g. temperature and laser scanning speed) (Figure 6A). Depending on the amount of drug, the Printlets tend to have different energy absorption, and thus different release behaviours. The higher the drug loading, the higher was the absorption and the slower the release characteristics. As a result, Printlets with 5% drug loading attained a complete drug release within 2 h,

whereas those with 35% drug loading required 8 h (Figure 6B). It should be noted though, this effect might change depending on the drug substance and the composition of printing mixture. Similarly, immediate release Printlets were fabricated using HPMC at varying laser scanning speeds, including 100, 200 and 300 mm/s (Figure 6C) (Fina et al., 2018c). The Printlets disintegrated within >600 s and achieved a complete drug release within 4 h, 3 h and 2 h, respectively (Figure 6D).

Insert Figure 6

Figure 6. (A) Images and (B) *in vitro* drug of the Kollicoat IR Printlets. (C) Images and (D) *in vitro* drug of the HPMC Printlets. Scale shown in cm. Reprinted with permissions from (Fina et al., 2017; Fina et al., 2018c)

7.4.3 Controlled-release Printlets

SLS has the potential to create structures with predetermined porous microstructures and dense walls. In doing so, it is possible to design controlled-release systems with zero-order kinetics. More specifically, it is possible to create cylindrical Printlets with dense outer regions, which act as diffusion barriers, and porous cores enabling high drug loading. In one study, both PCL and PLLA were shown to have suitable characteristics with densities and porosities which were a function of laser power, scanning speed and powder bed temperature (Figure 7A) (Leong et al., 2006). In another approach, Eudragit L100-55, which is a pH-dependent polymer, was incorporated to impart prolonged-release properties (Fina et al., 2017). The Printlets were formulated to include different drug loadings, including 5%, 20% and 35% w/w (Figure 7B). In the first 2 h, the Printlets displayed limited drug release (< 20%) in an

acidic medium (Figure 7C). Once under intestinal conditions, the Printlets exhibited an increase in the drug release, with complete drug release within 12 h. Interestingly, the drug release was independent of the drug loading.

Insert Figure 7

Figure 7. Images of the (A) PCL and PLLA and (B) Eudragit L100-55 cylindrical Printlets. (C) *In vitro* drug dissolution profiles from the Eudragit L100-55 Printlets with varying drug loadings. Scale shown in cm. Reprinted with permissions from (Fina et al., 2017; Leong et al., 2006).

7.4.4 Multi-reservoir systems

Due to the high resolution of the laser beam, SLS can be utilised for the fabrication of complex and precise objects, such as multi-reservoir systems, enabling controlled drug delivery (Salmoria et al., 2013b). The systems are designed to contain a PCL shell and a vacant core, and the device can be fabricated to contain the drug in both reservoirs or solely within the core. By varying the content of the reservoirs, different progesterone release patterns, extending up to 290 days, were achieved (Salmoria et al., 2012c).

7.4.5 Implants for tissue and bone regeneration

PCL implants incorporating ibuprofen have been exploited for tissue and bone regeneration (Salmoria et al., 2016). It was shown that the addition of ibuprofen increased the intensity of sintering. This resulted in an increase in the flexural modulus, wherein approximately 75% of the drug was released within 26 h. Likewise, 5-

fluorouracil implantable systems composed of either a PE (Salmoria et al., 2017b) or PCL (Salmoria et al., 2017c) matrix were fabricated for cancer therapy. Both systems showed an initial drug release burst followed by sustained delivery, wherein the PE implants had longer-lasting effect. By combining these concepts within a single device, dual drug therapy systems could be created.

7.4.6 Complex and multi-layered systems

Loose powder particles within the printing platform act as raft structures capable of maintaining the integrity of structures during the printing process. This permits the fabrication of intricate drug-loaded dosage forms, which are otherwise complex or impossible to produce using conventional methods. For instance, it is possible to produce gyroid lattice Printlets, enabling higher control over drug release (Fina et al., 2018b). Due to their mesh-like structure, these lattices have shown faster drug release when compared with their corresponding cylindrical Printlets (Figure 8A and C). By engineering different arrangements of both configurations and creating bi-layer Printlets, it is possible to tune the drug release to achieve the intended release kinetics (Figure 8B and D).

Insert Figure 8

Figure 8. 3D designs of the (A) gyroid lattice and (B) bi-layer Printlets and images of the (C) gyroid lattice and (D) bi-layer Printlets. Scale shown in cm. Reprinted with permission from (Fina et al., 2018b).

In the same vein, SLS 3D printing can be exploited to prepare paracetamol miniprintlets (e.g. 3D printed pellets) for personalised therapy (Figure 9A) (Awad et al., 2019). Typically, controlled-release multiparticulate systems are produced using extrusion-spheronisation and coating, which are multi-step processes requiring dedicated equipment, making them laborious to produce and expensive **(Ghebre-Sellassie and Knoch, 2007)**. On the contrary, SLS 3D printing is a single process, and the strong coherence between the drug and polymer particles induces a sustained effect which moderates the initial burst release (Figure 9C). Via the manipulation of the matrix content, dual miniprintlets incorporating two spatially separated drugs, paracetamol and ibuprofen, were also fabricated (Figure 9B). Despite their small and intricate structures, the dual miniprintlets could be programmed to have varying release profiles for each drug substance, providing a novel platform for multi-drug therapy. Compared with monolithic dosage forms, the risks of dose-dumping and peak plasma fluctuations are curtailed with this multiparticulate system, because each miniprintlet behaves as a discrete drug depot. As such, these miniaturised dosage forms could be programmed to maximise treatment by providing the benefits of convenient dosing and longer lasting therapy.

Insert Figure 9

Figure 9. Images of a (A) single miniprintlet and (B) dual miniprintlet. (C) *In vitro* drug dissolution profiles from the paracetamol single miniprintlets with varying diameters. Reprinted with permission from (Awad et al., 2019).

7.4.7 Intrauterine devices

Due to the ability of SLS to overcome geometry limitations imposed by conventional manufacturing techniques, this has paved the way for SLS to be an attractive approach for the fabrication of intrauterine devices containing two distinct drugs, progesterone and 5-fluorouracil, having synergistic activities in the treatment of endometrial and ovarian cancers (Figure 10A) (Salmoria et al., 2018). The devices were made of HDPE, due to its biocompatibility, inertness and mechanical flexibility. The devices were fabricated using two different laser powers, 3 W and 5 W. 5-fluorouracil showed an initial burst release within the first hour, attributed to its high water solubility (Figure 10B). This was followed by its sustained release over a period of more than 35 days. The drug release from the devices fabricated using a laser power of 3 W was higher than that of those fabricated at a laser power of 5 W, which was believed to be due to the higher porosity of the former, expediting the drug diffusion. Progesterone on the other hand, displayed zero-order kinetics throughout the dissolution studies.

Insert Figure 10

Figure 10. (A) Image of the intrauterine device fabricated using SLS and (B) *in vitro* drug dissolution release profiles of 5-fluorouracil and progesterone from intrauterine devices fabricated using 3W and 5W laser powers. Reprinted with permission from (Salmoria et al., 2018).

7.4.8 Printlets for the visually-impaired

Whilst a clear trend towards tailored doses remains the predominant focus of most 3D printing technologies, a range of other opportunities remain underexplored. As an example, the distinctive laser features of SLS 3D printing can provide a novel and

691 sophisticated approach for making dosage forms suited for specific patient groups,
692 such as those with visual impairment. In particular, orally disintegrating Printlets have
693 been designed with Braille (Figure 11A) and Moon patterns on their surfaces, enabling
694 patients to identify medications when taken out of their original packaging (Awad et
695 al., 2020). With all the Printlets disintegrating within ~5 s, they avoid the need for water
696 and thus facilitate self-administration of medications (Figure 11B).
697
698 Additionally, Printlets with novel shapes, including a sun, a moon, a heart, a caplet
699 shape, a pentagon and a square, were fabricated (Figure 11C). These shapes offer
700 additional medication information to the patients, such as medication indication and/or
701 dosing regimen. For instance, a caplet shape could represent paracetamol simply
702 because several commercialised paracetamol products are sold in this form. Similarly,
703 a heart shape could represent cardiovascular medications because of its resemblance
704 of the organ of treatment. Sun and moon shapes could be indicative of morning and
705 evening dosing, respectively. Furthermore, the number of edges in the pentagon and
706 square shapes could be utilised to correspond to the time of medicine intake. A caplet
707 containing three Braille letters can be designed, further extending the possibilities with
708 this technology and showing that three-letter abbreviations could be printed onto
709 bigger-sized formulations (Figure 11D). As an example, PAR could be used as an
710 abbreviation for paracetamol. Overall, this reduces medication errors and improves
711 medication adherence in patients with visual impairment.
712
713 Insert Figure 11
714

Figure 11. (A) 3D designs of cylindrical Printlets containing the 26 Braille alphabets. Images of cylindrical Printlets containing the 26 (B) Braille alphabets, (C) Printlets with different shapes having Braille or Moon patterns and (D) Printlet with three Braille letters, including (from left to right): P, A, and R. Reprinted with permission from (Awad et al., 2020).

7.5. Undesirable pitfalls

One of the main disadvantages of SLS lies in its effect on laser-sensitive substances, in particular natural polymers and drugs (Vail et al., 1996; Walker and Santoro, 2017). As such, posing restrictions on the suitability of materials and drugs. Furthermore, in terms of technical aspects, to ensure consistent layer height and suitable flow of powders, the printing requires large quantities of powder, which might not be feasible in all cases (Telenko and Seepersad, 2010). This is particularly important in the case of expensive drugs or those with limited quantities. In addition, whilst any unsintered powders can be recycled, they can only be reused for a limited number of prints due to concerns relating to chemical stability and physical changes (Dotchev and Yusoff, 2009). As such, with the need for large quantities of powder, part of the material might go to waste if the process is not optimised. Similarly, as the process sometimes might require post-treatment (e.g. the sieving and brushing of printed dosage forms), it may need an extra time-consuming step and impart additional costs (Thomas and Gilbert, 2014).

7.6. Regulatory aspects

Currently, commercial SLS printers do not comply with Good Manufacturing Practice (GMP) specifications and thus it is not possible to make dosage forms within a clinical

setting. This brings about technical and logistical challenges, making it burdensome to ensure batch-to-batch uniformity and end-product consistency, requiring in-process quality control (QC) measures.

Several advancements have been made to bring this technology a step closer to the clinic. For instance, the use of process analytical technologies (PAT), such as near infrared spectroscopy (NIR) and Raman confocal microscopy, as QC measures have been assessed on SLS Printlets. A rapid 'point-and-shoot' method has been successfully validated for use as non-destructive approach for dose verification (Trenfield et al., 2018b). The method was based on Raman confocal microscopy and was applicable for dosage forms having different geometries. It has also shown favourable results in the presence of multiple drug agents (Trenfield et al., 2020). In this approach a portable near infrared (NIR) spectrometer was employed and validated calibration models were developed using partial least squares (PLS) regression. Another technique could involve the use of NIR hyperspectral imaging for the quantification of drugs within the Printlets and assessing their spatial distribution (Vakili et al., 2015). Collectively, these findings further facilitate and support the integration of SLS 3D printing within practice, providing suitable solutions to some of the existing QC challenges.

8.0. Conclusion

Since its introduction, 3D printing has been forecast to pave the way for a new pharmaceutical revolution. Of all the 3D printing techniques, SLS is the most capable of being scaled up for mass production and with its starting materials holding the closest resemblance to current pharmaceutical production technologies, it is potentially highly amenable for adoption as a novel and versatile manufacturing tool for pharmaceutical fabrication. Due to the high resolution of its laser beam, SLS enables the engineering of intricate and delicate dosage forms that could be tailored to meet the needs of certain patient groups. Unlike other technologies, complex dosage forms can be attained without the need for additional support material or processes. Whilst technical and QC restraints have been the principal hinderance for the adoption of such innovative technologies, preliminary results appear promising.

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