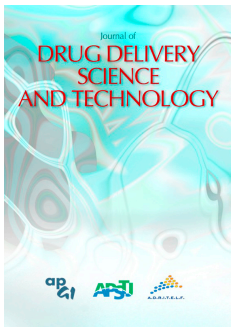

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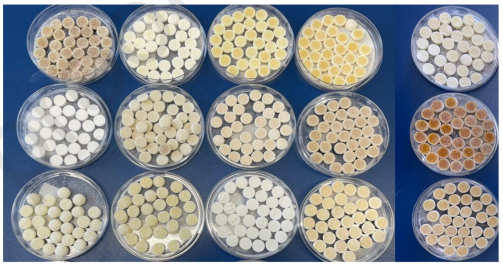
Powder blend

Selective laser sintering



Pharmaceutical dosage forms

Selective Laser Sintering for printing pharmaceutical dosage forms

Atabak Ghanizadeh Tabriz[2], Hannah Kuofie[1], James Scoble[1], Sam Boulton[1], Dennis Douroumis[1,2*]

[1]Faculty of Engineering and Science, University of Greenwich, Medway Campus, Chatham Maritime, Kent ME4 4TB, United Kingdom

[2]Delta Pharmaceutics Ltd., Chatham, ME4 5NG, Kent, United Kingdom

[*] Correspondence: Medway School of Science, University of Greenwich, Medway Campus, Chatham Maritime, Kent ME4 4TB, UK. Tel.: +44 (0) 208 331 8440; Fax: +44 (0) 208 331 9805. *E-mail address*: D.Douroumis@gre.ac.uk

Abstract

Three-dimensional (3D) printing has revolutionised the field of pharmaceutical manufacturing due to the unique capabilities to tailor the dosage forms properties and overcome constrains of conventional technologies. There is a plurality of 3D printing techniques that offer flexibility on the shape, geometry, active(s) dose and dissolution rates for improved patient treatment. Over the last few years selective laser sintering (SLS) has captured research interest for the development of innovative drug products. SLS possess technological features that can transform medicine manufacturing from one-size-fits-all to personalised dosage forms with improved clinical outcomes, patient acceptability, and adherence. Moreover, SLS has the capacity to pave the way for decentralised manufacturing and introduce new supply chain models with reduce complexity. In this review we present the technological features, manufacturing challenges, advantages and limitations of SLS for manufacturing medicines.

Keywords: selective laser sintering, 3D printing, manufacturing, personalised, medicines, decentralised, oral, polymers

1. Introduction

Three-dimensional printing (3DP) has gained increasing popularity over the last 10 years in healthcare due to its enormous capability for resolving several of the limitations associated with conventional drug delivery and therapeutic technologies[1–3]. Binder jetting, fused deposition modelling (FDM), powder bed fusion (PBF), and vat polymerization are just a few of the printing technologies that have been developed and employed in the pharmaceutical and biomedical industries throughout the years. Around 1981, Hideo Kodama developed a method for creating 3D models using photo-hardening polymers and UV radiation [4]. A few years later, Chuck W. Hull created the first 3D printing technology, stereolithography, which was marketed by 3D systems [5]. Initially, these technologies were limited in their application due to poor printing quality and excessive costs. Nevertheless, technological breakthroughs have resulted in the development of cost-effective, high-print-speed, and high-precision 3D printers that have already been employed in a multitude of sectors including biomedical, space, education, automotive, and art over the last two decades.

In recent years, considerable technological advancements (Fig. 1), resulted in the development of Spritam®, an antiepileptic drug, the first commercially available 3D-printed oral medication approved by the FDA (Food and Drug Administration) in 2015. Two years later, FDA produced the "Technical Considerations for Additive Manufactured Medical Devices," a guide for industry and FDA employees while research in 3D printed medicines continues [6].

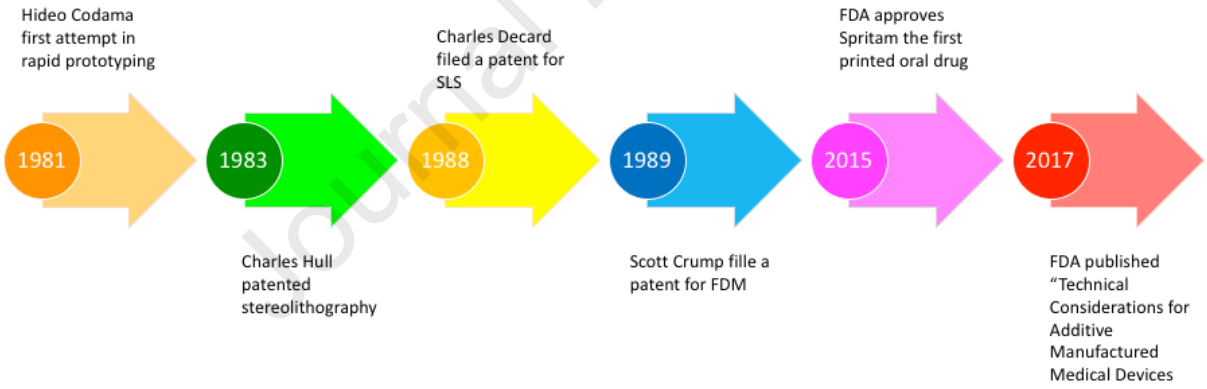


Fig. 1: Historic timeline of 3D-printing (adopted by[3])

3D printing or additive manufacturing refers to the fabrication of three-dimensional (3D) object from a computer-aided design (CAD), in a layer-by-layer manner. The CAD file is converted into a stereolithography file (.stl file) that contains the necessary information for the spatial geometry of the object to be produced using CAD programmes. The .stl file is divided into multiple segments after initiation, one of which is the slice file (SLI segment), which is subsequently transferred to the 3D printer for printing. Most of the 3D printing technologies have the capacity to transform the pharmaceutical sector from one-fit-for-all tablet and capsule mass manufacturing to customised dosage forms that fit the clinical needs of the patients [7].

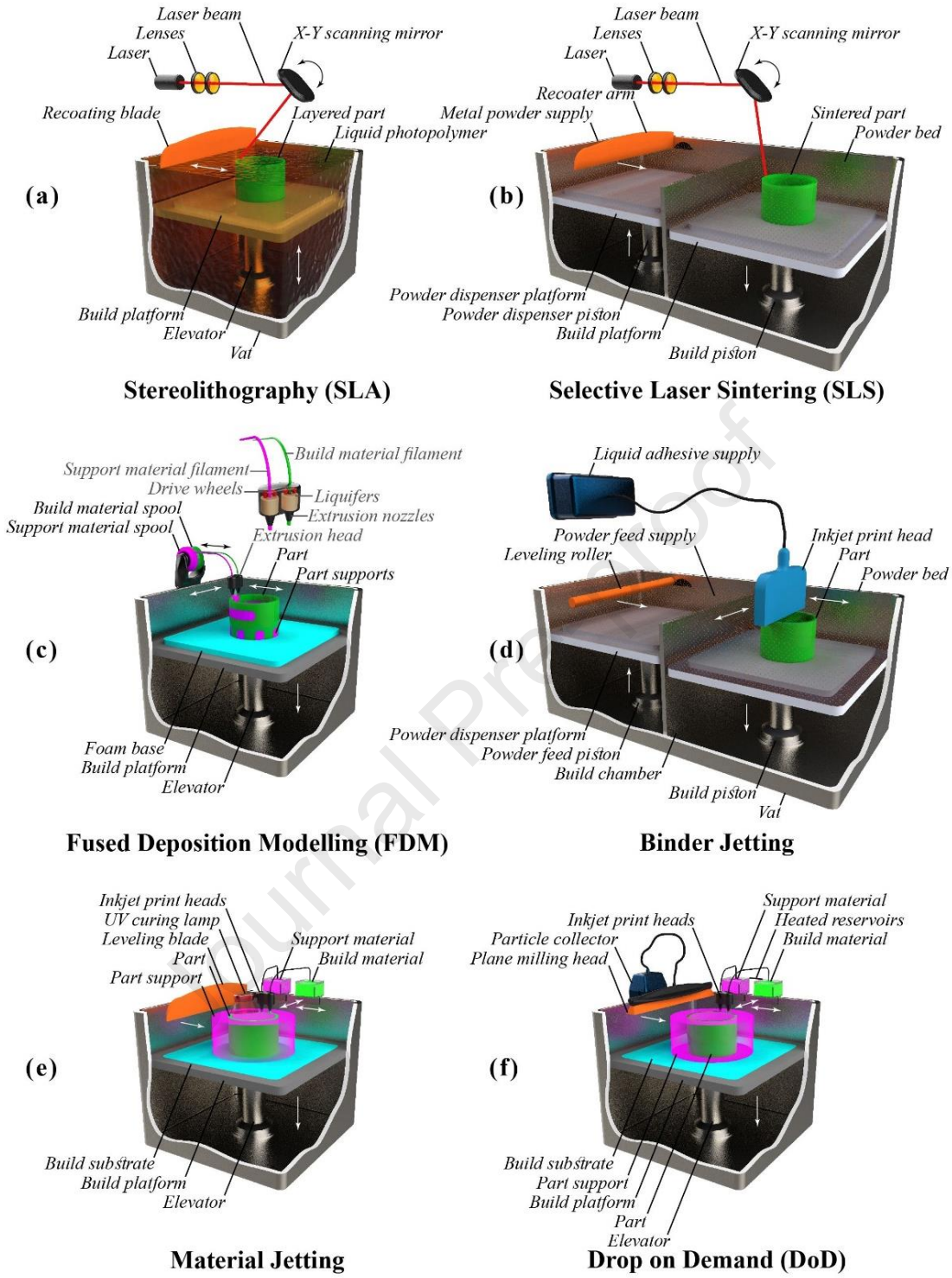


Fig 2 : Typical schematic diagrams of six major 3D printing technologies: (a) stereolithography; (b) Selective laser sintering; (c) Fused deposition modelling; (d) Binder jetting; (e) Drop on demand; (f) Material jetting (courtesy of Peyman Sohrabi)

Since the introduction of 3D printing with stereolithography, various more techniques have been established (Fig. 2), allowing for the processing of a broader range of materials, such as polymers, metals, and ceramics. Nanomaterials, medicines, and biological materials like cells

can all be included into 3D constructions, opening a whole new world of possibilities for medical 3D printing.

Extrusion-based technologies, such as FDM, are by far the most extensively used 3D printing technology. The technology was invented by Scott Crump, Stratasys' co-founder, and patented in 1989[8]. An FDM printer system (Fig. 2c) comprises of a feeder gear system that enables material to be driven through the system, a heated liquefier that is located in the print head and is a system for making the material extrudable, the print head and nozzle, the printer's axels that allow the print head to move following cartesian patterns, and finally the build platform. In this process, layers of molten or softened thermoplastic materials in the form of filament are deposited via the printer's head at specified directions controlled by the computer software for the fabrication of the designed structure. In comparison to other 3D printing technologies, FDM is comparatively inexpensive, and has been successfully implemented in a variety of industries [9–11].

Material Jetting (MJ), also known as Poly-jetting, and Drop on Demand (DoD) are two other type of 3D printing technologies that have been used for the manufacturing of medical devices and pharmaceutical dosage forms (Fig. 2e, f). These technologies deposit similarly to a typical inkjet printer, but the object is formed by stacking numerous layers of material on top of each other. Both MJ and DoD deposit very small polymer droplets, but MJ applies UV irradiation to cure separately each layer after deposition. In contrast, DoD uses wax-like substances that solidify quickly, while a fly cutter passes the build area after the deposition of each layer to minimize wastage. Binder Jetting technologies (Fig. 2d) fuse sequential layers of each cross-section layer using a low viscosity liquid binder. The layer is formed, and the next layer of powdered material is prepared for the deposition of liquid binder in a similar way to PBF processes. The post processing includes the removal of loose powder and infiltration of the layered structure with a liquid such as an epoxy resin, to help build strength and improve appearance.

2. Operational Principles of Selective Laser Sintering

Selective laser sintering (SLS is a common powder fabrication technique which has found several applications within the biomedical and pharmaceutical fields, and it can be used for mass manufacturing. It was developed by Carl Deckard in 1984, at the University of Texas and subsequently patented in 1990 [12]**.** The technology was using a neodymium-doped yttrium aluminum garnet (Nd:YAG) laser (100 W) and acrylonitrile butadiene styrene (ABS) powder as thermoplastic material.

SLS has been widely used for the design and fabrication of physical models through selective solidification of various types of powders[13]. applications of SLS may include, oral and maxillofacial prosthetics[14–18] and implants, tissue engineering, or for making tools for neurological surgery. In addition, it has been used for disease diagnosis planning, patient treatment and rapid prototyping.

SLS is classified as a PBF AM technique, wherein a directed high-powered energy source, such as a laser, sinters or melts a bed of powder resin, metal or polymer to fuse powder particles together resulting in solidification.[19,20]

An SLS 3D printer (Fig. 3)comprises of the printing chamber and powder reservoir (reserve chamber) where both are heated to a temperature just under the melting point or the glass transition of the used material. Afterwards, a high-power X-Y axis laser beam is emitted on to the top surface layer of powder within the pre-heated printing chamber and begins to sinter a pre-determined 2D pattern according to the object design. After each layer is completed, another thin layer of powder is dispersed. This process is achieved by lowering the printing chamber to a pre-set height and raising the reservoir chamber to a set height, this then allows the roller to apply a fresh powder surface on top of the completed layer. This process is repeatedly performed until the final layer is printed. Eventually the powder melts down by the heat generated through the laser scanner system. After printing is complete, the sintered object which is contained in a powder cake within the printing chamber is extracted by shaking and sieving off the excess powder. This step can be done using an external post-processing instrument. Factors that can affect the outcome and quality of an SLS printed object include powder particle size, scan spacing, scan speed, and the power of the laser [21]. Other factors such as refresh rate, layer thickness, part bed temperature, raster angle, and hatch pattern can also have an effect on the mechanical properties of SLS printed objects.[22]

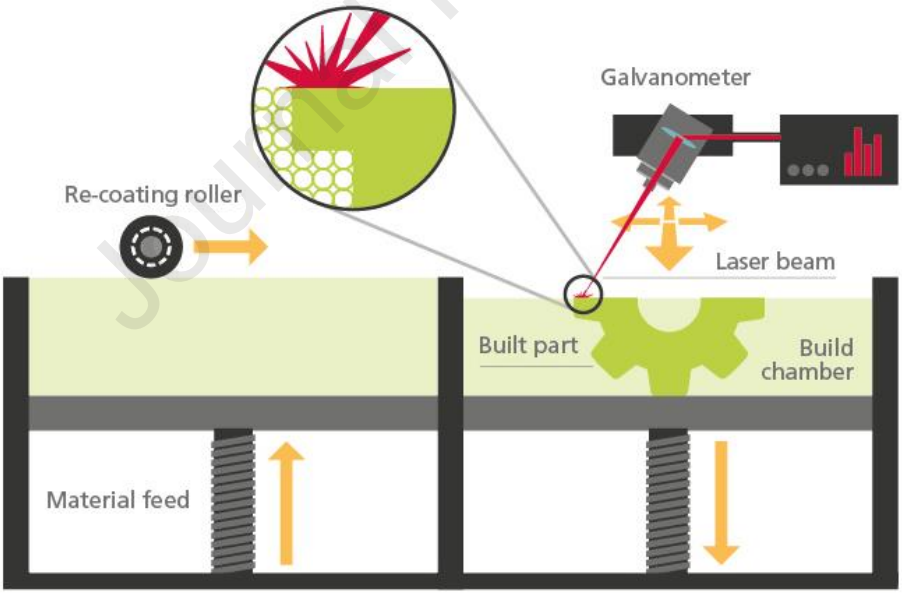


Fig. 3: Diagram of SLS process

The powders used for the SLS technique are freely packed or loosely arranged and they will only range from few microns, but the powder characteristics like morphology, granulometry, density and flowing capacity are considered over their selection. The main property to be considered is the flowing capacity of the powder as it should spread uniformly while the particle size varies from 40-180 micrometers. The powder should also be within good sphericity and there are some agents which are used for increasing the flowing capacity and

reduce cohesiveness of the powder molecules (e.g., SiO_2). An important feature of SLS is that the powder bed in the printing chamber acts as a support structure and hence overhanging layers of a design do not require the addition of supports in comparison to other 3D printing technologies such as in SLA and FDM. Thus, SLS can be effectively used for printing complex geometries and a wide range of designs.

2.1 Manufacturing challenges for SLS

SLS has been broadly used for printing metals, ceramics, and pharmaceutical products. However, for the development of oral solid dosage forms the literature is limited and there are barely any reports in regard to the critical process parameters (CPP), powder critical material attributes (CMAs) and critical quality attributes (CQAs). There are several parameters that can affect the product quality while pausing a significant challenge in process of understanding and the design of a full process control strategy. The SLS parameters can be classified in four categories [23]:

a) laser-related and scanning parameters including laser power, spot size, pulse duration, pulse frequency, scan speed, scan spacing, and scan pattern
b) powder material parameters such as particle shape, size, distribution, morphology, melting temperature, and surface roughness.
c) powder-bed and recoater parameters such as density, layer thickness, and powder bed temperature.
d) build environment parameters including shield gas, thermal conductivity, ambient temperature, oxygen levels, and surface free energy.

The Ishikawa diagram in Fig. 4 illustrates the aforementioned properties that must be considered when using SLS.

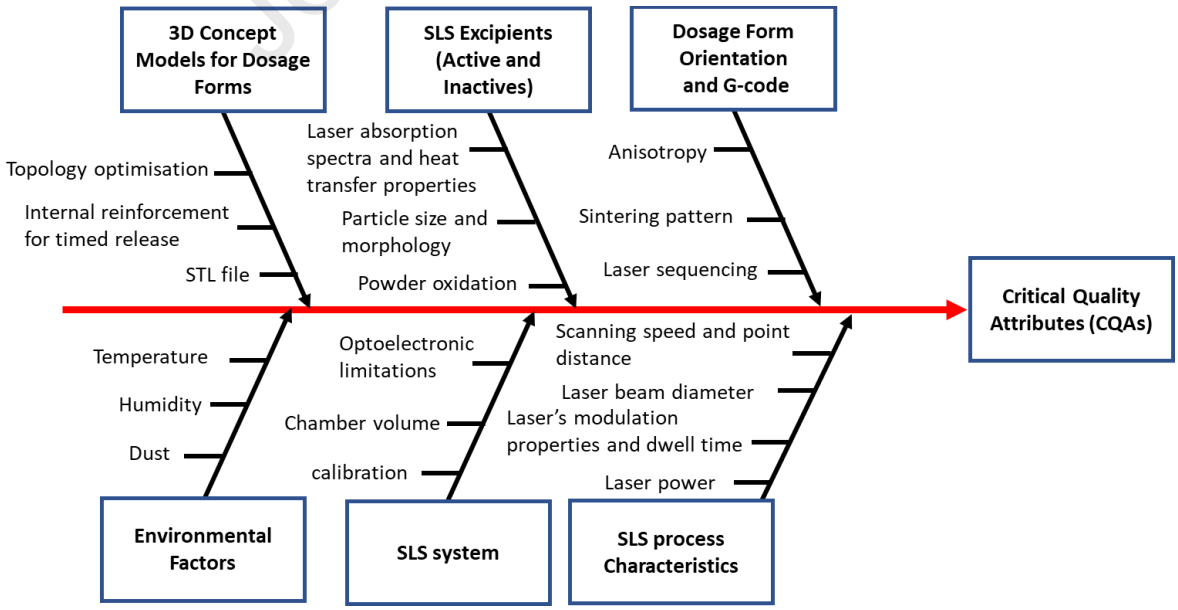


Fig. 4: Ishikawa diagram of critical process parameters (CPP), powder critical material attributes (CMAs) and critical quality attributes (CQAs) of SLS.

2.2 Laser selection and scanning speed

The interaction of the laser and the powder is crucial to the SLS process, and the laser used depends on the materials. Materials only absorb light energy from certain wavelengths based on their optical characteristics due to light-matter interactions. The CO_2 laser (10.6 m) due to its good optical absorptivity is far more ideal for pharmaceutical polymers, whereas the Nd:YAG, Yb:YAG, or Nd:YVO4 (1.06) lasers used in industrial selective laser melting (SLM) equipment are preferable for metals and carbide ceramics[24–26]. Furthermore, CO_2 is less costly while the pulsing system allows the powder to better absorb the laser. It is known that the selection of the laser beam has an impact on the end product properties such as mechanical strength, surface texture and physical density (porosity). The laser density is defined by the following equation:

$$E = \frac{\rho}{\nu h}, \left(\frac{J}{mm^2}\right) \quad (1)$$

Where E is the energy density, ρ is the laser power, ν is the scan speed, and h is the hatch distance.

An important process parameter, usually controlled, is the speed over which the laser is scanned. Laser scan speeds typically vary from 10-100 mm/s. Single-scan, repeated scan, or cross-scan scan patterns are available, with or without contouring. The scan pattern should be selected depending on the material qualities, as it might influence the end product's surface roughness and mechanical properties. For example, repetitive scan patterns have shown to reduce balling while contouring produces the same quality for all scan lines. The scan pattern directly affects the heat transfer and thermal gradient and hence the environment. The laser maximum power, the laser mode (continuous or pulsed), the region to which the beam energy is focused (spot size), and the length of time the energy is supplied to a certain area of the powder bed are all factors that influence the total power that is delivered by the laser.

There is a limited number of studies that investigate the effect of processing parameters on the quality of the printed products. Polyamide 11 (PA11) (e.g., Duraform EX natural), polyamide 12 (PA12), and some thermoplastic elastomers are widely utilised materials. The effect of the energy density on the mechanical properties was investigated by Caulfield et al., using polyamide (DuraFrom^{TM}) as model powders [27]. They introduced Eq.1 for the determination of suitable mechanical properties for the printed structures. Ryse et al., further studied the impact of laser power and bed temperature using a semi-crystalline elastomeric polyester [28]. By varying the laser power and bed temperature (laser speed remained the same) it was revealed that printed structures presented better mechanical properties and higher density. Limited studies have shown that slow scanning speeds result in higher energy input due to the long interactions of the particles and the laser while shorter hatch space supports greater energy transfer [29,30].

Bai et al., (2016) investigated the impact of processing on the mechanical properties of polyethylene using SLA [30]. It was noticed that the geometry changed when the laser power gradually increased from low (5W) to high (7-11 W). The printed structures swelled at the bottom and transformed from square shape to trapezoid and eventually to semicircular

structures as shown in Fig. 5. At low laser energy there was less swelling and dimensional accuracy was improved but highly porous and weak designs were printed.

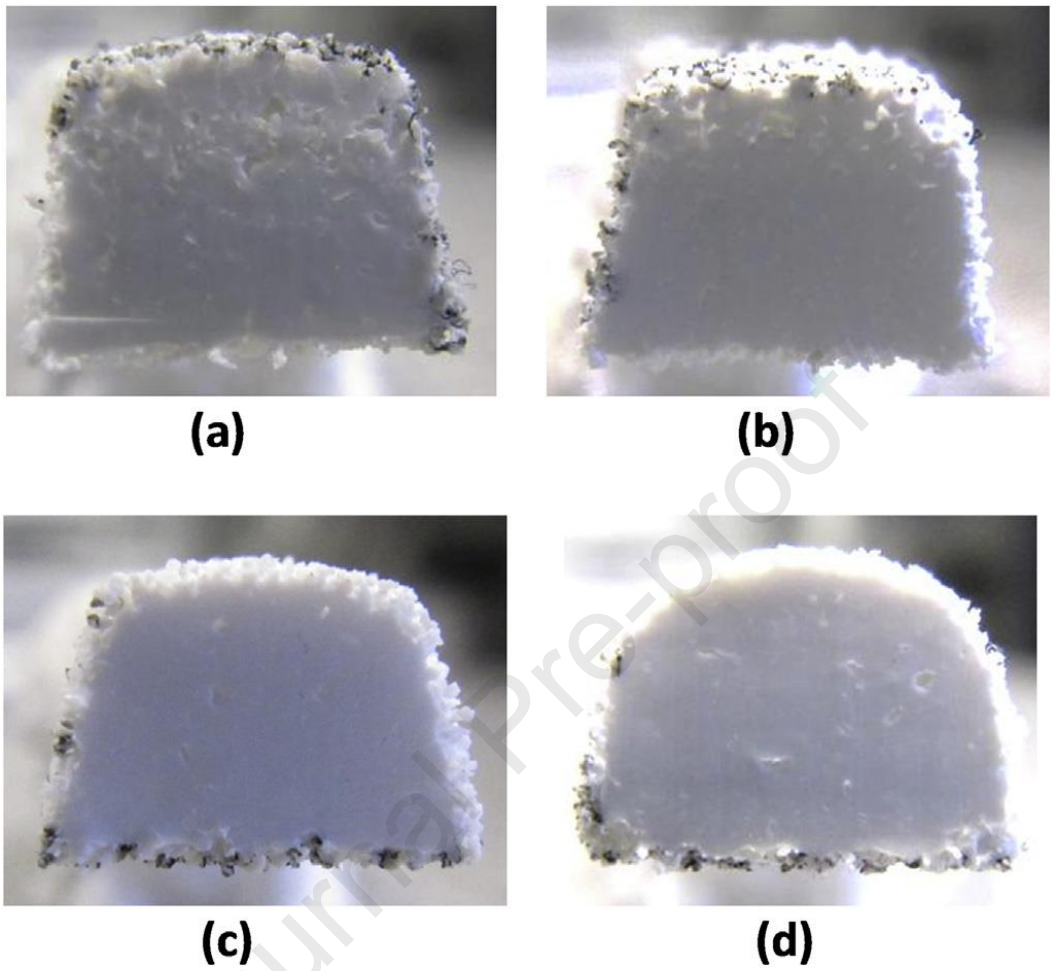


Fig. 5: Cross sections of laser sintered PE parts at, (a) 5 W, (b) 7 W, (c) 9 W, (d) 11 W.

2.3 Powder material parameters

Powders have a significant impact on SLS as the laser melting effectiveness is influenced by powder size. Large particles tend to diminish the powder bed's pack density and melting consumes more energy. To the contrary, smaller particles, are prone to clumping, making powder layering harder [30–32]. Powders with a particle size range from 45-90 μm are ideal for SLS printing as for smaller particles spreading is difficult because of static forces [33]. However, this restriction doesn't always apply for pharmaceuticals dosage forms as powders with particle sizes varying from 150 – 350μm could provide highly porous structures which affect the disintegration and dissolution times. The powder flow ability is a key component in determining particle size distribution on the powder bed. Coarser particles capture laser energy more efficiently than finer particles because they have a larger surface area. To ensure consistent laser energy absorption, sufficient powder flow is essential to generate a smooth powder surface and a consistent height of powder layers. As flowability is affected by particle morphology, and size distribution and hence flow improves for powders with increasing sphericity and narrow size distribution (Fig. 6). Furthermore, the packing efficiency,

mechanical characteristics, and surface roughness are all affected by flowability. Powders with multimodal particle distribution can be used in SLS printing as smaller particle filling the voids in larger particles and increase powder density while the flowability is satisfactory. The addition of inorganic materials improves powder flow and can significantly impact on the table physicochemical properties. The selection of laser parameters and end product qualities are also influenced by the powder composition, density, melting point (or glass transition), optical properties, heat capacity and thermal conductivity properties. All these properties impact the light absorption which in turn affects the packing of the powder bed and the layer uniformity after the recoating deposition.

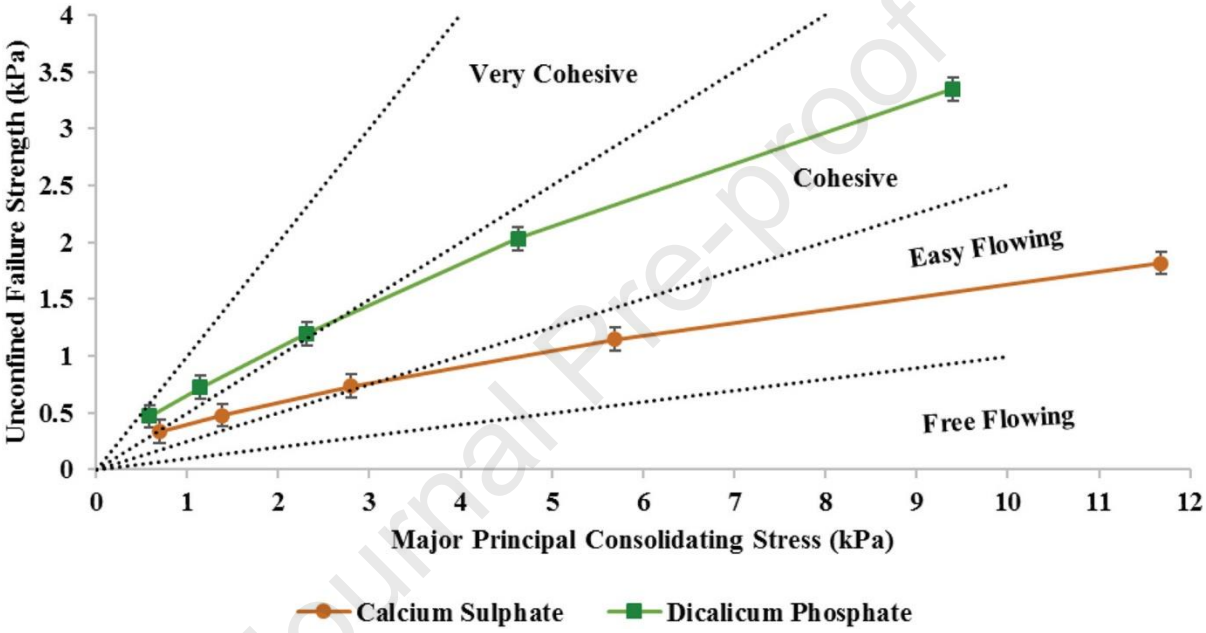


Fig. 6: Flow function of various powders used for SLA printing.[34]

2.4 Powder bed and recoater parameters

The powder bed properties are similar to, but distinct from, those of the bulk powder of which are made off. The density of the powder bed, which is influenced by powder shape, particle size, distribution, and spreading process, has a significant impact on the quality of the printed structure. Powder bed densities for most pharma grade polymers are normally between 50 and 60%, however polymers such as EUDRAGIT EPO or Klucel ELF/EF grades can be as low as 25-35%. For high powder packing densities, the heat conductivity of the bed and the mechanical characteristics of the printed forms are greater.

3. 3D Printed Oral Dosages

SLS is a rapid prototyping 3D printing technology using single powders or blends as materials. The properties of the obtained structure depend heavily on the printer parameters such as laser intensity, scan speed, bed temperature and spot diameter of the laser beam including the powder

properties as previously discussed. SLS has gained interest for the development of oral solid dosage forms especially after the commercialisation of Spritam® by using the ZipDose technology [2].

One of the first studies was conducted by Leong et al.[35] who investigated the potential to print structures with predetermined porosity for sustained drug release using polylactic acid and polycaprolactone blends . The laser power, scan speed and the bed temperature were found to play critical role in the printing process. SEM analysis showed that higher porosities were obtained at temperatures of 40 °C while at 30 °C no necking was observed. Further increments in the bed temperature reduced the porosity of the specimens. The density of the printed tablets at low laser intensity (2W) presented the highest porosity (67.3%) with the best sintering. In contrast, while at high laser power (7W) the porosity was reduced, and curling appeared at the edge of the printed structure. High scan speeds showed uniform sintering and high porosity but relative fragile structures. By using average scan speed (5080 mm/s) strong tablets with 50% porosity were printed.

Salmoria et al., investigated the effect of laser energy density and particle size distribution using blends of polycaprolactone/progesterone powders on the morphology of the printed structures [36]. SEM analysis showed high degree of sintering was observed when the laser intensity was increased while particle size was reduced. High laser intensities promoted progesterone recrystallization on the surface due to the drug melting. The Tg of PCL was affected by the plasticization effect induced by progesterone where shifts at lower temperature were accompanied by reduced PCL crystallinity. Furthermore, low laser intensity resulted in faster tablet erosion over time and faster progesterone release as a consequence of the increased surface contact area. In addition, smaller particle size of the powder blends led to faster dissolution rates following a zero-order drug release kinetics. Hence, progesterone release rates could be tuned by altering the laser intensity and the particle size of the blends. Fatigue test analysis showed that tablets printed at lower laser intensity with large particle size presented low strength [37].

Fina et al. (2017) investigated the SLS printing of pharmaceutical dosage forms using thermoplastic polymers such as Kollicoat IR and Eudragit L100-55 which are suitable for immediate and pH dependent drug release. Paracetamol – polymer blends at 5, 20 and 35% loadings were processed at various intensities to identify potential drug degradation with increased intensities. As the printer was supplied with a blue diode laser (445 nm) the printing was not possible without the addition of Candurin® gold sheen to facilitate the sintering process. As shown in Fig. 7, the polymer demonstrated different porosity properties (open and closed) with Kollicoat IR having the same values irrespectively of the drug loading and Eudragit with almost no pores at all due to the high sintering degree with increased paracetamol amounts. However, all printed tablets showed low friability but high crushing strength (>284 N) as a result of the complete sintering. Furthermore, only at very low drug loadings (5%) paracetamol dissolution rates were fast and all printed formulations showed sustained release varying from 2-12h. Nevertheless, the proof-of-concept study demonstrated the use of

pharmaceutical polymers for the printing of drug formulations using SLS while avoiding drug degradation.

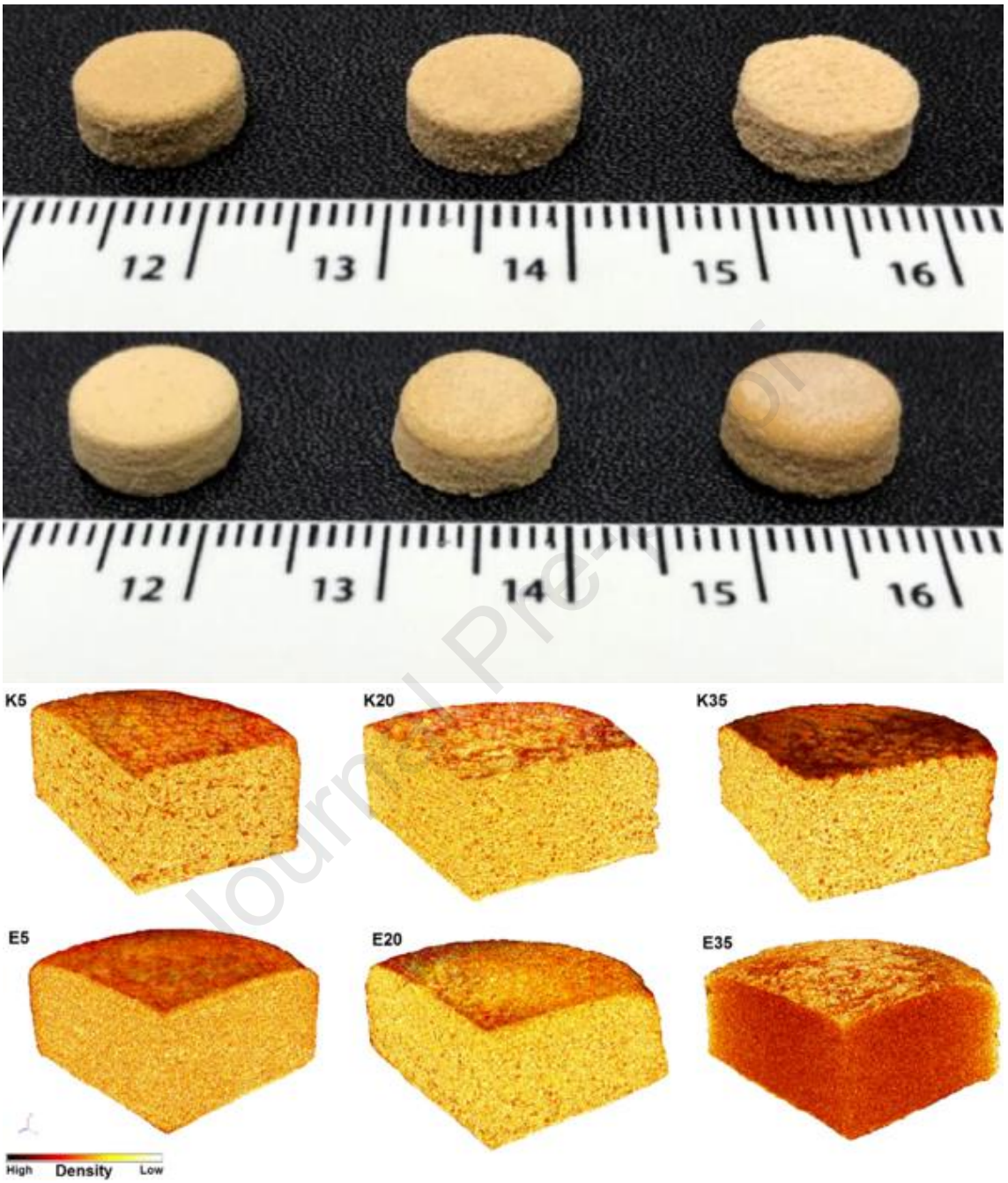


Fig. 7: Kollicoat and Eudragit L100-55 printlets [38].

The same group investigated the feasibility of SLS for the printing of ODT formulations in the form of printlets. For the purposes of the study hydroxypropyl methylcellulose (HPMC) or vinylpyrrolidone-vinyl acetate (Kollidon VA64) were co-processed with paracetamol (5%, PCM) to produce loaded formulations. As shown in Fig. 6, the printlets were optimised by adjusting the applied laser intensity and varying the scanning speed (100, 200 and 300 mm/s). High scanning speeds resulted in low tablet strength (14 N) with high porosity and vice versa as a result of lower sintering extent. Interestingly printlets comprising of Kollidon VA64

featured fast disintegrating times (<4 s) when sintered at very high scanning speeds. However, the fast disintegration times were the result of the extremely low tensile strength of the printed tablets. The drug dissolution studies showed slow rates for HPMC varying from 75-100% after 2h even for tablets with low tensile strength. Different results were observed for Kollidon with rapid dissolution rates of 100% in 5 min for tablets with high porosity but low tensile strength. It is obvious that dissolution rates were affected by the polymer nature, laser scanning speeds and the low drug loadings of paracetamol. Hence the low printlet strength, the high friability and the low drug loading may render the process non-viable for the design of ODTs.

A similar study was conducted by investigating the effect of various polymers such as polyethylene oxide (PEO), Eudragit (L100-55 and RL) and ethyl cellulose (EC) in paracetamol formulations for the printing of cylindrical gyroid lattices with customised dissolution profiles [39]. The use of gyroid lattices was an interesting approach aiming to the modification of the microstructures with random or periodic designs each featuring open or closed cells [40,41] For such structures small unit cell sizes present high densities as a result of the short scanning lengths while Young's modulus increases with the decrease of the unit cell size. For successful SLS printing, it is critical to identify the optimal bed temperatures due to the different Tg of the thermoplastic polymers. By identifying the right balance between the laser speed and the bed temperature, it is the possible to print the complex gyroid lattices.

The tensile strength of the printed structures varied according to the polymer characteristic with PEO and Eudragit RL presenting the lowest tensile strength (not detected) while the other polymers showed higher strength (280 N). The low tensile strength is attributed to the low intensity sintering process that was applied and led to greater gyroid porosity. When a more energetic sintering was applied the observed molten areas increased on the surface of the structures. The tuning of the sintering, the polymer nature and the selection of the polymers impacted on the porosity and tensile strength of the gyroid lattices and subsequently on the obtained dissolution rates. Despite the low paracetamol loading, the study was a good paradigm of how to develop personalised dosage forms with customised dissolution profiles (Fig. 8).

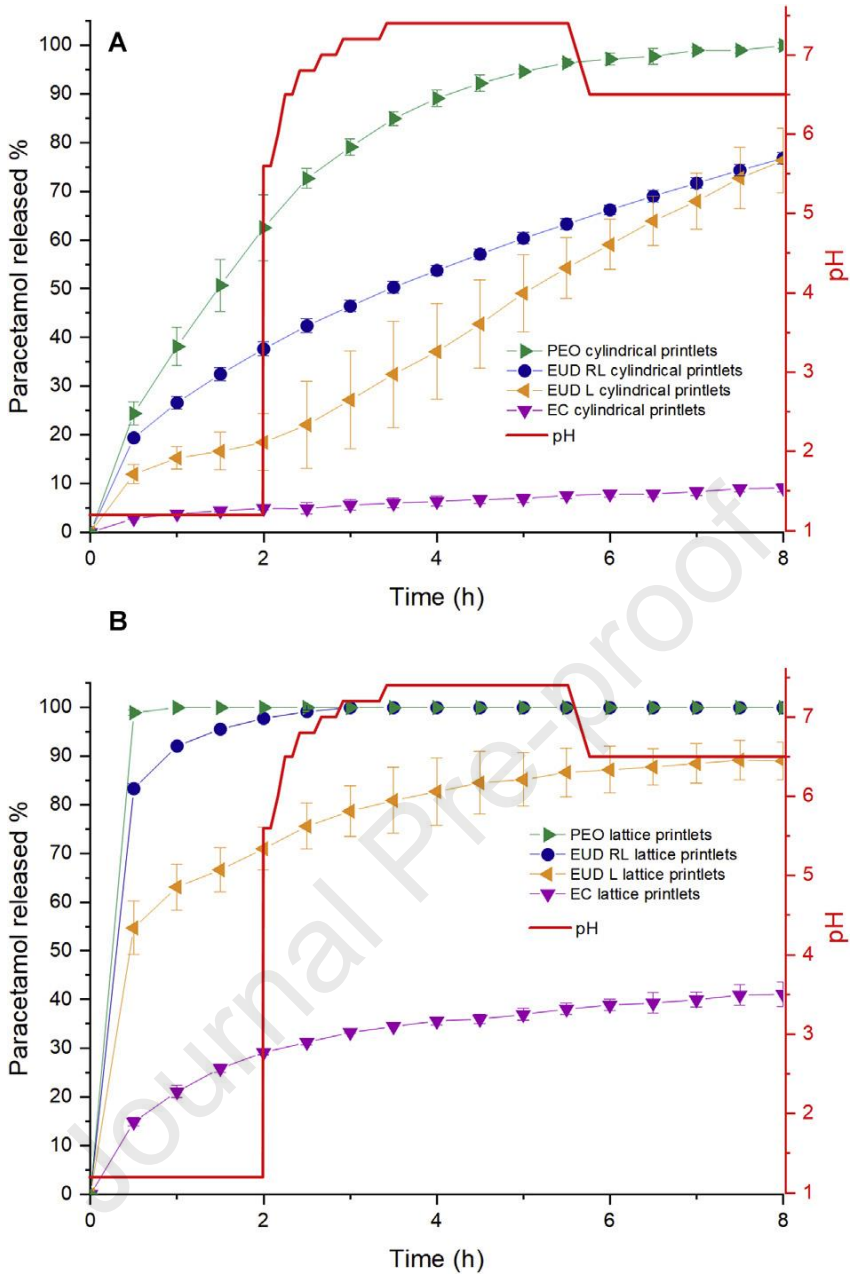


Fig. 8: Paracetamol dissolution profiles of A) the cylindrical and B) gyroid lattice constructs. The red line illustrates the pH values in acidic media (2 h), followed by higher pH values (alkaline media).

A further application of SLS was introduced by Awad et al., (2019) for the fabrication of multi-drug miniprintelets in a 2-step process [42]. By using powder blend combinations of polymers with paracetamol and ibuprofen (IBU). The aim was to alter the configuration of PCM/Kollicoat and IBU/EC and vice versa in order to customise the drug dissolution rates and achieve dual release profiles (Fig 9).

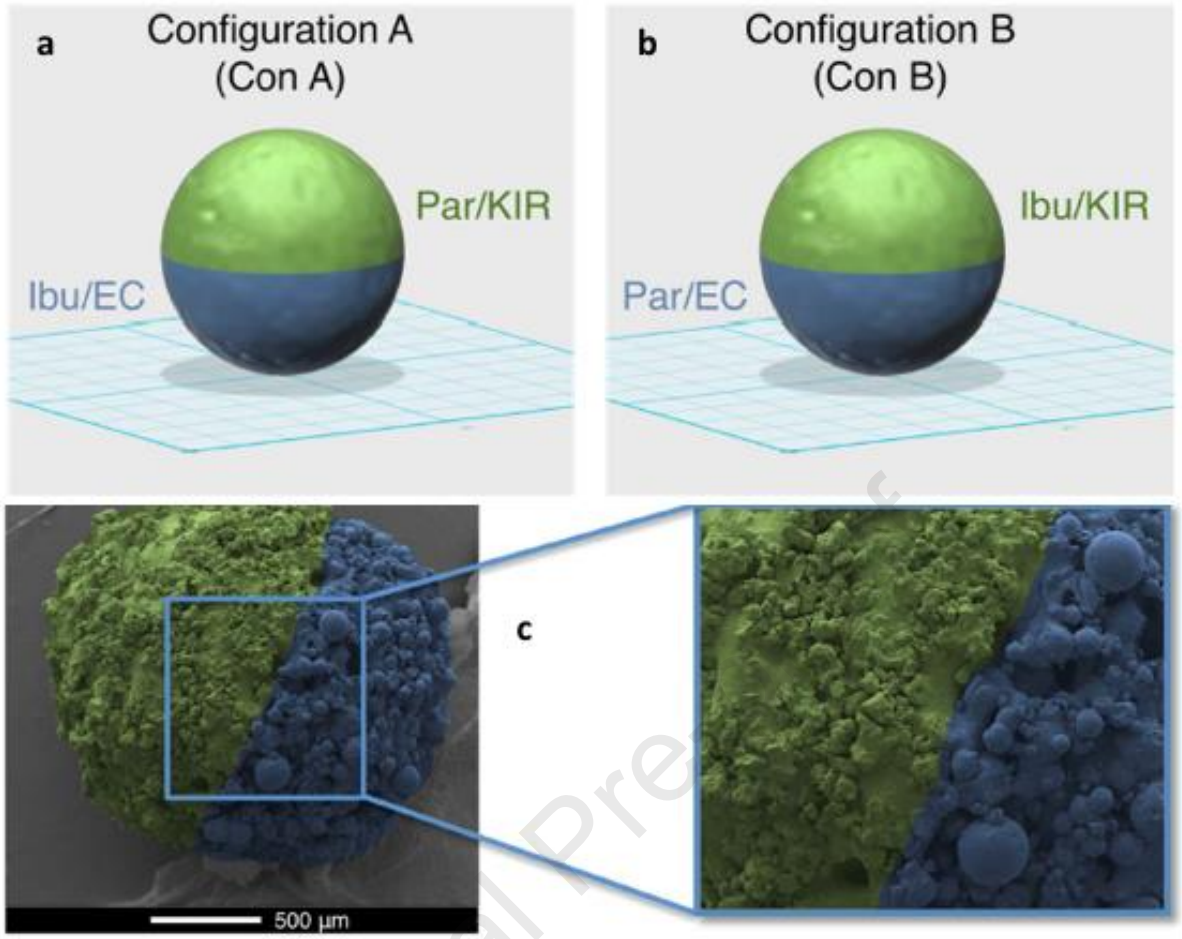


Fig. 9: Printed minipellets using SLS. Schematic representation of the compositions of (a) configuration A and (b) configuration B of the dual miniprintlets. (c) Scanning electron microscopy (SEM) images of the 2 mm dual minipellets.

The sintering process varied depending on the polymer properties with Kollicoat undergoing low intensity sintering due to their round shape. The irregular shapes of EC (large and flaky) resulted in an intense sintering. The drug dissolution could be controlled through the selection of the processed blends so Kollicoat advanced fast rates while for EC sustained release was observed for both drugs. Furthermore, by varying the pellet size (1-2mm) it was possible to partially obtain different release rates for IBU and PCM for up to 24 h when sintered with EC. In this work dual drug release was feasible with fast dissolution of the first drug followed by sustained release of the second from the printed minipellets.

A more detailed study was presented by Ali et al., (2019) who investigated the effect of the formulation and process variables on the quality of the printed dosage forms by applying a Quality by Design (QbD) approach [43]. The implementation of an experimental design (DoE) assisted in the investigation of critical processing and material parameters where the laser scanning speed (mm/s), surface temperature (oC) and the concentration of lactose monohydrate (LMH) were selected as the dependent variables. The DoE helped to identify the effect of the process variable on the critical quality attributes (CQA) known a dependent variable. As such, the selected CQA were the weight, disintegration time and drug dissolution rate at 15 min. The main drug carriers were Kollidon VA64 and LMH but only the latter was found to be a key material attribute. The chamber temperature had a positive effect on the tablet weight

(increased) while laser scanning speed and LMH (8-12%) showed a negative impact. Higher sintering was observed for high chamber temperatures, while low sintering resulted in, at high scanning speeds or with increased LMH amounts.

In a follow up study, the same group applied QbD approach for the development of clindamycin palmitate hydrochloride using SLS [44]. Here the concentration of lactose, microcrystalline cellulose (MCC) and the laser scanning speed were selected as critical processing parameters and tablet weight, tensile strength, disintegration times and dissolution rates as CQAs respectively. The integration of the Box-Bencken design showed significant effect of the laser scanning speed for all of the dependent variables. For the CMAs the analysis revealed that MCC affected significantly the tablet tensile strength, disintegration time and dissolution while lactose on the tensile strength and dissolution rates. The composition of the print formulation affected the powder flowability and thus printability with successful printing at >5% of lactose or MCC concentrations. As previously mentioned, the decrease in laser scanning speeds led to increased tablet weight due to higher sintering that is caused by the energy absorption and subsequent melting/softening. The authors observed that lactose decreased the tablet mechanical properties as it was partially melted or non-melted in the printed formulations. Despite the relatively high lactose amounts in the formulation sintering led to the formation of tablets with low tensile strength but high disintegration times. As expected, higher chamber temperatures resulted in stronger tablets with high tensile strength due to intense sintering while fast laser scanning produced weaker tablets and had a negative effect. Similarly, stronger tablets produced in formulations with increase Kollidon amounts. Fast disintegration times were aligned with tablets of low tensile strength which became longer with increasing tablet hardness. The laser speed and the chamber temperature had a significant impact on both the disintegration time and dissolution rates of Na-diclofenac. High dissolution rates obtained for low tablet weight, tensile strength or disintegration times and contrariwise.

Gueche et al. (2021) studied the sinterability of CO_2 laser for the formation of solid oral dosage form (SODF) via SLS [45]. For the study, Kollidon® VA64, paracetamol, and Duraform® polyamide 12 (PA12) were used as polymeric carrier, model drug, and reference powder respectively. The work focused on the printing of different PCM grades with one of large and plat-like particles while the PCM-fine grades comprised of thin and needle-like particles. Previous studies have demonstrated that by increasing the laser wavelength, absorbance also increases for a wide range of polymers [24]. FTIR analysis showed that KVA64 absorb at wavelength 1of 10.2-11 μm which was in the range of polyamide λ= 10.6 μm) and thus the addition of absorbance enhancer was not required [46]. The blending of powders with different shapes affects the powder flowability and hence the selection of PCM grades and the PCM/polymer ratios were found to be critical for the compactness of the blends. In this study PCM loadings varied from 10-30% which are more representative compared to previous studies [47] and can reveal a more realistic prospect on the SLS suitability for personalized medications.

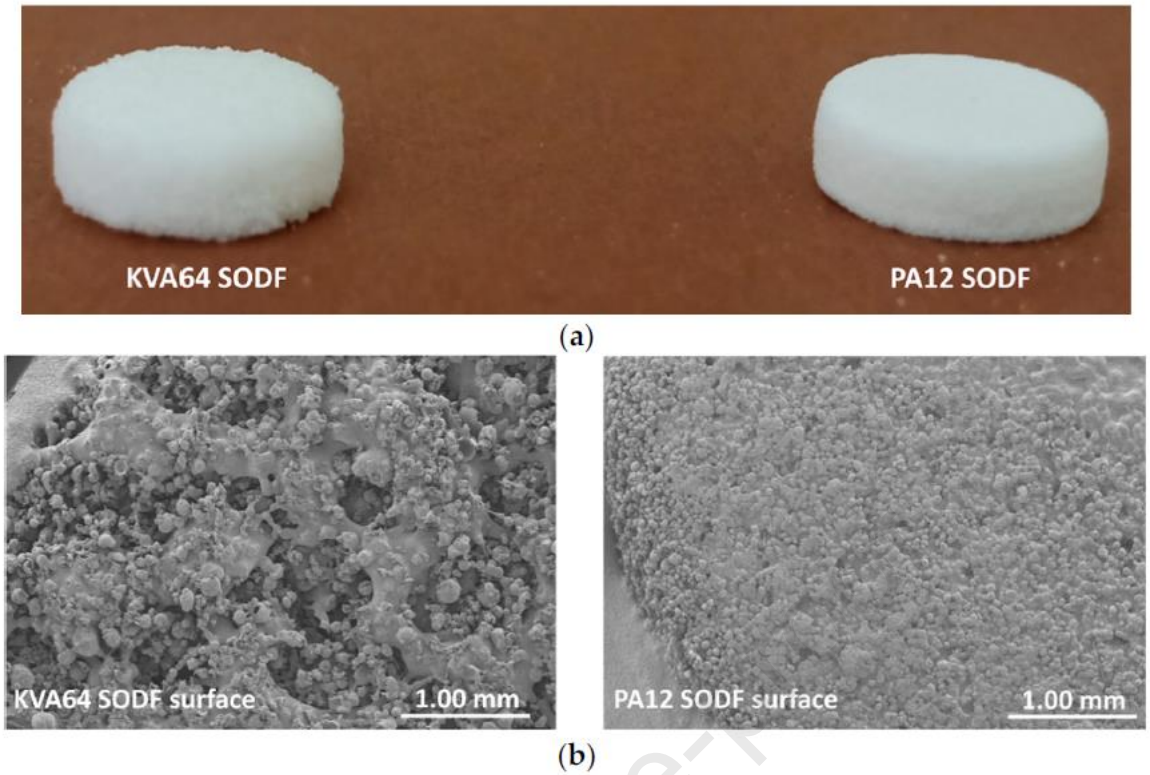


Fig. 10: (a) Printed KVA64 and PA12 SODFs at optimal parameters and (b) SEM images of printed tablet surface (magnification × 30).

The printed SODFs showed that a high proportion of PCM was in amorphous state without been degraded even within SODFs printed at high laser intensities. The morphology of the printed tablets was affected by the proportion of coarse particles which form rough surfaces with irregular shapes when their content increases. As shown in Fig. 10, the coarse particles of VA64 produced tablets with higher porosity compared to the control PA12 which presented denser structures. Furthermore, the paracetamol loading affects the tablet porosity as non-sintered amounts prevent the formation of a continuous melting phase and hence increased porosity was observed. Overall, the implementation of CO_2 laser resulted in SODFs with excellent tensile strength while PCM rapid dissolution which reached 100% within 20 min that meets pharmacopeia specifications. The study was an outstanding paradigm for the design and printing of actual drug loaded tablets using CO_2 SLS technology.

Kulinowski et al. (2022) investigated a polymer-augmented complex formulation, for the development of floating drug delivery systems (FDDS), and the use of water-insoluble nylon as an inert excipient for high metronidazole (Met) loading using SLS technology [48]. Despite the fact that carbon-stained polyamide (PA12) is not a typical pharmaceutical grade polymer thare are reports stating its biocompatibility[49]. The use of PA12 aided Met loadings of 82-92% with suitable hardness (40N) for 800 mg tablets. As shown in Fig. 11 the printed tablets presented a grey colour due to nylon with a rough surface.

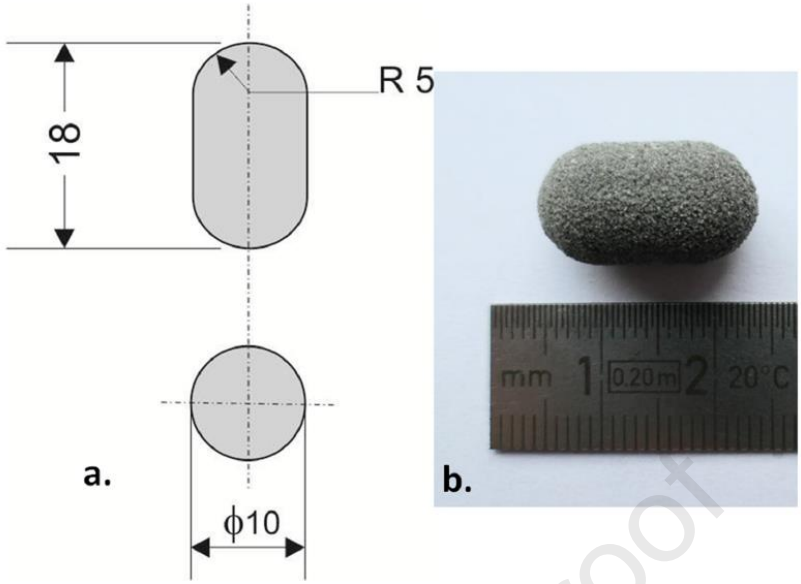


Fig. 11: The example of printlet: (a) technical drawing (dimensions in mm), (b) printed Formulation A (Met/PA12/NaCl, 80/20/0/100).

Analysis of the phase transitions of nylon and Met during sintering showed the transformation of PA12 from the γ′ γ form [50–53], and the presence of crystalline Met with melting endothermic peaks at 179.79°C and 159.63°C respectively. The drug release studies showed variable Met dissolution rates depending on the apparatus employed for the studies (USP4 or USP3) and the addition of NaCl (2% v/v) in the printed tablets. The study demonstrated another implementation of SLS technology to produce oral dosage forms with good tablet properties and customizable dissolution rates.

Madžarević et al. (2021) evaluated the effect of energy density (ED) and formulation components on the printability of Irbesartan (IRB) tablets by applying a decision tree model (Fig. x) as data mining tool [54]. The decision tree modelling is an interesting approach and entails the use of input data such as energy density, particle size distribution, and the content of the drug carries. The optimal combination of processing parameters can be optimized by splitting the data between a training (70%) and test set (30%). By using more complex formulations comprising of HPMC (good printability), mannitol (good flowability, disintegrant), Kollidon VA64 and Crospovidone (super disintegrant) the printing process was optimized by varying he chamber temperature, surface temperature, and laser speed.

The crospovidone content and the ED were the critical attributes for the printability of the designed formulations. The tablets were printable if crospovidone was >3.5% but for lower concentrations the ED should be ≥0.615 J/mm3 in order to obtain printable tabelts. As shown in the decision tree (Fig. 12) if none of the above condition is met then the HPMC content should be taken into account. A drawback of the approach was that for most of the printed tablet the hardness was not detectable while for the rest varied from 12.5-56.0 N which are still considered weak. Interestingly the addition of supedisintegrant had no impact on the disintegration times which were very high (90-1510 s).

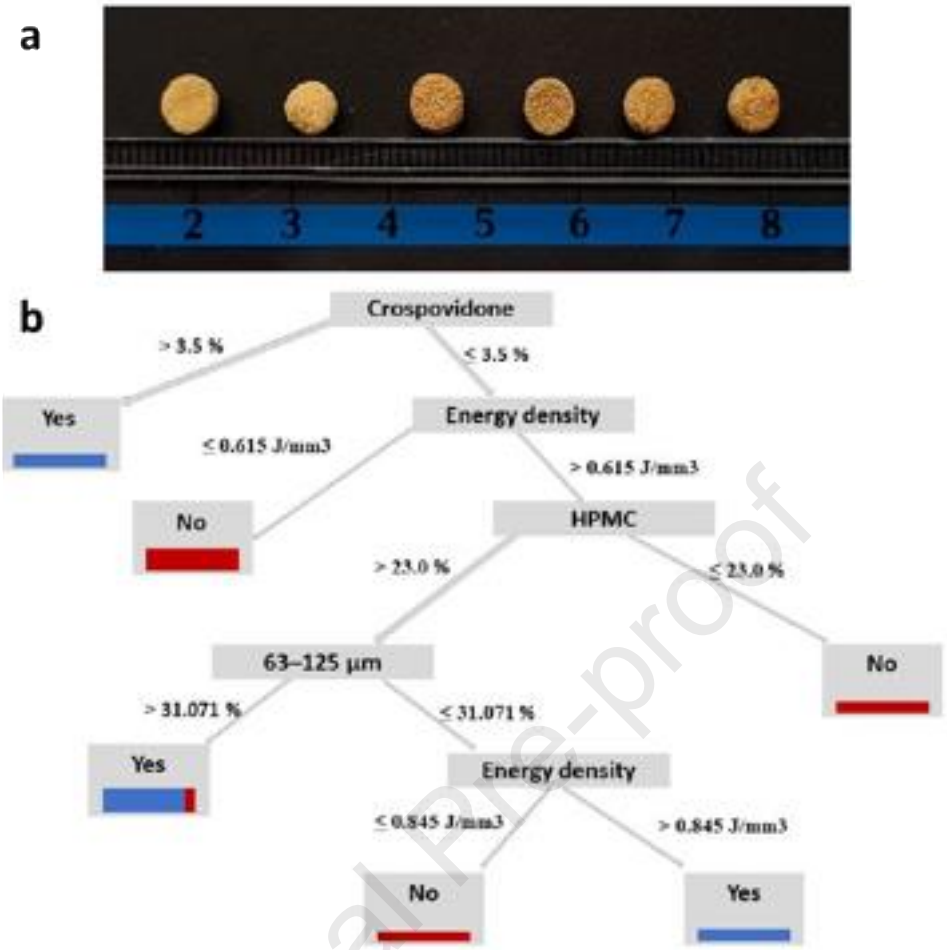


Fig. 12: a) Images of selected SLS-printed tablets printed at different laser scanning speeds. From left to right: 100.00 mm/s, 120.00 mm/s, 140.00 mm/s, 160.00 mm/s, 180.00 mm/s, and 220.00 mm/s. b) Decision tree for SLS printability of powder mixtures with irbesartan

The authors observed that the melting point of crospovidone was close the printing temperature which resulted in good sintering but affected the disintegration times and subsequently the release profiles. To our opinion crospovidone should have been combined with KollidonVA64 which presents excellent printability but most importantly much lower glass transition temperature and thus less ED is required. This is in good agreement with the experimental findings where lower ED resulted in faster disintegration times. Furthermore, the use of superdisintegrants requires a good knowledge of the material properties. For example, the Polyplasdone XL10 grade has a particle size distribution of 30-50 µm which is much smaller to that of HPMC which inhibited the disintegration process. To the contrary XL grades (100-130µm) would result in faster disintegration times due to the large particle size. Two more critical observation are that: a) Polyplasdone grades present excellent performance at concentrations >5%, and b) they present wicking behaviour which is not suitable for sintered tablets. For SLS printed tablets the use of superdisintegrants with swelling properties (e.g., croscarmellose sodium, sodium starch glycolate) would be a better option for rapid disintegration.

The SLS applicability for oral solid dosages was further investigated by Yang et al., (2021) using a range of APIs for immediate and sustained release respectively combined with various polymers [55]. Some of the drugs were coloured and thus it was possible to prepare tablets through direct printing while the rest required the addition of photo absorber (tartrazine lake). The amount of photo absorber is considered critical when using lasers at 450 nm and it should be investigated to achieve printing accuracy. An interesting observation was that the sintered thickness for each layer should be larger than the layer thickness to ensure print integrity between the tablet layers.

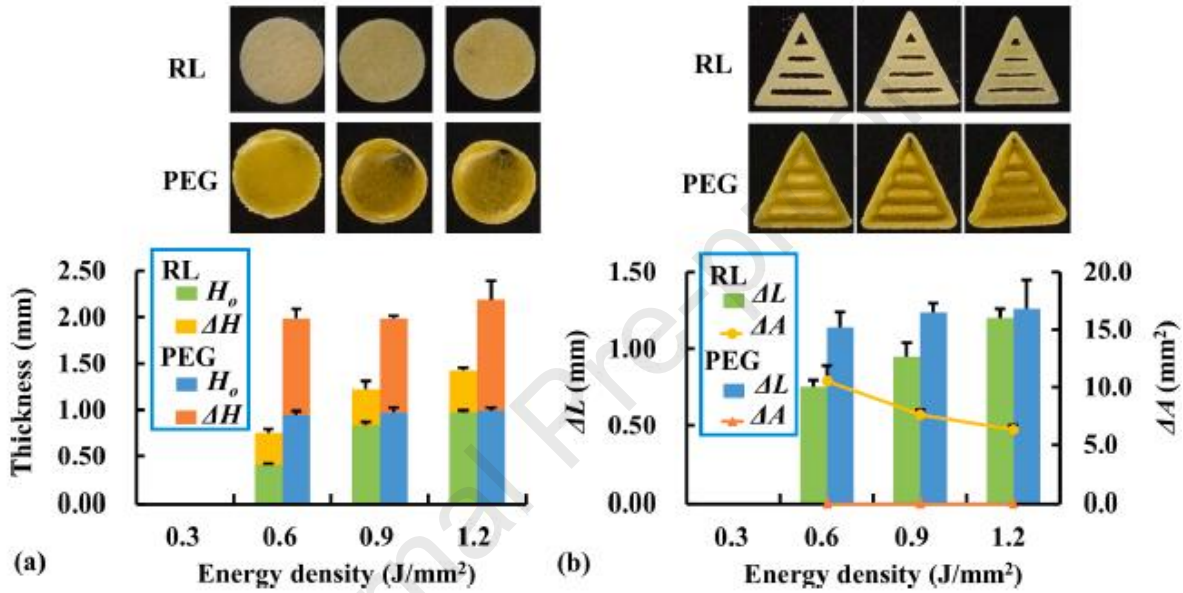


Fig. 13: Effect of laser energy density on the printability of Eudragit RL and PEG: a) circle and b) triangle samples (n = 3).

For some of the pharmaceutical grade polymers (EPO, PEG-4000) widening and warpage deformation was observed at the edges of the tablet while carboxymethyl starch sodium presented poor printability due to the high Tg. As expected, the laser energy intensity affected the printability and low laser intensities (Fig. 13) resulted in poor tablet properties which further improved by increasing the applied energy (>0.6 J/mm^2). The addition of release modifiers (e.g., PEG, PVA) in the powder blends facilitated faster dissolution rates especially for water insoluble APIs such as ibuprofen. The blending of sustained release polymers such as HPMC and Eudragit RL was further investigated. The amount of HPMC was critical in the printing of the designed formulations due to its poor sinterability but also due to the significant drug release reduction. To the contrary RL presented superior printing features and sustained drug release was achieved for 12 h by adjusting the HPMC:RL ratios at 1:3.

In recent study Tikhomirov et al., (2023) process large placebo and drug loaded batches of naproxen blended with copovidone (N-vinyl-2-pyrrolidone and vinyl acetate, PVP/VA) or polyvinyl alcohol (PVA) by adding activated carbon (AC) as radiation absorbent for improving the sintering process [56]. The AC varied from 05.-1.0% while by tuning the laser print ratio it was possible to turn naproxen into amorphous state during printing. X-ray and

DSC analysis demonstrated that due to the applied heat naproxen was dissolved in the polymer matrix which resulted in the absence of any drug melting endotherms or diffraction peaks.The tablet weight was also controlled by altering the aforementioned parameters.

4. Advantages of SLS

Conventional methods used for the manufacturing of oral dosage form incorporate direct compression, spray drying, freeze drying, granulation or extrusion processes. However, some of these technologies present disadvantages with respect to the manufacturing costs, level of complexity and also limitations in the required drug loadings. While not necessarily ridding of the conventional methods of manufacturing oral dosage forms, the use of SLS and its versatility in developing oral dispersion tablets has proven to be a significant advance that appears to be a promising asset to the pharmaceutical industry. As shown in this chapter several pharmaceutical grade polymers have been introduced for printing oral dosages which flexible drug release properties. However, further studies using SLS for developing drug dosage forms with various APIs should be further conducted, including the evaluation of other excipients suited for SLS. Some of the SLS advantages are discussed below:

4.1 Printing features

A great advantage of SLS is that there is no requirement for support structures. The non-sintered powder acts as the support materials to the printed tablet. As a result, the post processing is less complicated and does not damage the printed designs. In many cases the unstinted powder could be reused which is important for expensive APIs. Several studies have shown that there is no need for powder pre-processing (e.g., extrusion) and thus SLS can be considered as one-step printing process. Based on such features the production cost can be significantly reduced in comparison to other printing technologies (e.g., FDM, SLA) rendering SLS a cost-effective technology.

4.2 Control of surface properties

One of the main advantages of SLS is the fabrication of various models by fusing powder particles together through sintering without the use of a solvent or the need for pre-processing of the powder blends. The sintering or melting of powders provides control over important morphological and mechanical surface features such as porosity. For many applications the control of porosity is advantageous as it allows the manipulation and alteration of the surface and its dimensions. The controls the pore interconnection affects the tensile strength, friability and most importantly the drug dissolution rates of drug formulations. The change of laser scanning speeds and the features of pharmaceutical excipients alter the structure of the produced tablets resulting either in smooth or rough surface and dense content. High laser densities and slow scan speeds should be used to avoid carbonization and burning of the tablet surface.

4.3 Printing of complex geometries

SLS is suitable for pharmaceutical applications due to its fast fabrication times and highly accurate dimensional control. When the powder blends (e.g. drug/polymer) are of narrow particle sizes below 100μm SLS allows the fabrication of highly precise geometrically accurate

custom-made designs with complex and properties. As shown above, mini-printelts, gyroid lattices, bilayer tablets, reservoir-type designs, or triangle and star shape designs have been successfully printed with excellent accuracy.

4.4 Using a wide range of materials

SLS can utilize a large variety of different materials for the fabrication of pharmaceutical dosage forms (Table 1). Thermoplastic polymers are the most frequently used materials including other excipients such as lipids and disaccharides (e.g., lactose) that can act as drug carriers or fillers and provide control over the tablet properties. For example, lactose has been shown to improve disintegration times, hardness and dissolution. Similar, effects have been reported when using polymer grades such as Kollidon VA64 or Povidone XL which can promote fast disintegration times or act as superdisintigrants at low concentrations (3-5%). Hence, SLS has shown a great potential for the production of fast disintegrating tablets with relatively good mechanical properties.

As previously discussed, the selection of the polymeric excipients is crucial for the design and customisation of the drug dissolution rates. Several non-ionic or pH dependent hydrophilic polymers have been processed for the development of immediate release dosage forms by controlling the printing settings. Similarly, hydrophobic and high molecular weight polymers have been reported to provide sustained release rates of various APIs. However, hydrophilic polymers can act as sustained release matrices by increasing the sintering process and decrease the tablet porosity.

Table 1: Pharmaceutical grade polymers suitable for SLS applications

Polymers	Chemical name	Dissolution properties	Tg (°C)
Kollidon VA64	Vinylpyrrolidone-vinyl acetate copolymer	Immediate release	106.0
Kollicoat IR	Polyethylene glycol-polyvinyl alcohol graft copolymer	Immediate release	69.7
Plasdone S630	Copolymer of N-vinyl-2-pyrrolidone and vinyl acetate	Immediate release	109.0
Eudragit EPO	Cationic N,N-dimethylaminoethyl methacrylate copolymer	Immediate release up to pH 5.0	46.0
Eudragit RLPO	ethyl acrylate, methyl methacrylate copolymer	Sustained release (highly permeable)	70.0
Eudragit L100-55	Anionic methacrylic acid - methyl methacrylate copolymer	Dissolution above pH 6.0	150.0

Eudragit S100	Anionic metacrylic acid and methyl metacrylate coplymer	Dissolution above pH 7.0	150.0
ETHOCEL™ N7	Ethylcellulose (non-ionic)	Sustained release	106.0
Soluplus®	Polyvinyl caprolactampolyvinyl acetate-polyethylene glycol graft co-polymer	Immediate release	70.0
AQOAT AS-HMP/LMP/MMP	Hydroxypropyl methylcellulose acetate succinate	Dissolution above pH 5.5, 6.0, 6.5	120.0
HPMC (15LV, 4M, 100LV)	Hydroxypropyl Methylcellulose	Immediate/Controlled release	120.0

4.5 Drug loading and dose combinations

An important feature of SLS is the capacity to co-process drug-polymer blends at various drug loadings. As the printability of the formulation solely depends on the polymer carrier a wide range of drug loadings varying from 5-40% have been achieved when using SLS. In addition, the precise drug amount per tablet can be easily adjusted by altering the tablet dimensions and print settings without necessarily need to change the powder blend formulation. Unpublished work in our group showed that accurate drug doses of 3.125, 6.25 and 12.5 mg by using carvedilol as model substance. The tablets could be easily printed and present similar dissolution profiles without altering the drug-polymer blend composition.

Furthermore, SLS has been employed to provide dual drug release by combining two or more APIs at the required drug amounts. The dissolution rates can be adjusted using different formulations for each API. Newly designed CO_2 printers can process different powder feedstock as they are supplied with two reservoirs.

4.6 SLS disadvantages

Despite the major advantages of SLS there are a few minor drawbacks related to its use for pharmaceutical applications. The lead times for printing oral solid dosages are longer compare to other 3D printing techniques such as FDM or SLA. This is because printing requires pre-heating of the powder bed and significant cooling times once the printing is completed. As previously mentioned, the obtained tables present a grainy surface finish while the internal porosity of the tablets requires further processing toe remove un-sintered powder. There is a difficulty to print large flat surfaces and a luck of accuracy when it comes to small holes as they are susceptive to warping and over-sintering.

5. Expert opinion and regulatory considerations

Our expert opinion is that SLS can be introduced for the manufacturing of personalised dosage forms fabricated at the point of patient care[26]. SLS is a technology suitable for small to medium

batch production with small footprint and thus can be used at the point of care such as hospitals or even pharmacies. It is advantageous in comparison to other printing technologies as in one print cycle it is possible to manufacture individualised tablets which vary in size, shape and dose which are suitable for each patient. Hence it reduces medication risks by printing the exact dose strength required to meet patient therapeutic profile. In addition, is ideal for moving from the existing manufacturer-centric to patient-centric business model and decentralised supply chains [56]. The new models will help pharmaceutical industry to fit medicine supply to real demand, decrease stock and maintain investments low. Currently there are studies for fast disintegrating tablets but the customization of palatable dosage forms by using SLS has not been proved. However, we anticipate that this will be exploited in the near future, especially for paediatric and geriatric patients. Januskaite et al (2020) demonstrate that 3D printing is appealing technology among paediatric populations for the fabrication of tablets where SLS was ranked as second preferred approach [57]. Furthermore, SLS could be used for printing polypills for geriatric patients to address issues such as polypharmacy or swallowing difficulties.

A major advantage of SLS is that can be used for mass manufacturing of pharmaceutical dosage forms due to the advances of the technology. SLS printers vary from benchtop to industrial size machines which are less costly to traditional manufacturing pharmaceutical technologies. Such devices feature large build volumes (up to 510 x 510 x 500 mm), fast scan speeds (5-8 L/h), multiple lasers for high productivity and full process control with diagnostic capabilities. The printing of very complex geometries, with internal channels, lattice structures combined with less material waste and reuse of the active formulation renders SLS one of the most suitable technologies for pharmaceutical dosage forms. The capacity to process a wide range of pharmaceutical polymers allows the development of immediate, sustained and controlled release dosage forms.

FDA has published a guidance on technical consideration for the manufacturing of medical devices using 3D printing [58] Many of those considerations apply to SLS and should be taken into account when used for the development of oral solid dosage forms. For example, the overall printer tolerance should be evaluated to ensure that the dosage forms with desired dimension can be fabricated with selected technology. An important feature is the design slicing is critical as layer thickness can influence the sintering process and the bonding of the layers. A major advantage of SLS is that printers are self-contained with well-controlled build volume and hence easy to control environmental conditions in the build volume. Nevertheless, all SLS parameters such as laser power and focal point, build/environment temperature, scan speed, build path or waiting times should be well documented and the printer qualified for use. Furthermore, the technology requires process validation where the variability of process parameters is well verified to ensure the quality of the end product.

Another important feature of SLS technology is the possibility to reuse the printing material. However, as the unsintered powder is exposed to various conditions such as heat, oxygen, humidity and radiation it was possible that the physicochemical properties are altered. In this occasion the reused materials should be carefully characterised and documented.

6. Conclusions

SLS is a straightforward, affordable, and adaptable 3D printing technique that can be utilised for decentralised commercial production at the point of care or the creation of personalised

dosage forms. In contrast to existing technologies, the technology can readily be built to print a variety of medicines without requiring complicated multi-step procedures. Due to the SLS's flexibility, it is possible to precisely customise the active dose, as well as the design, form, and printing of many medications in a single dose (polypills).

SLS's potential hasn't been fully realised and is yet to be fully utilised. So far, the work carried out on SLS printed pharmaceutical dosage forms are limited to the design of simple formulations and only a few involve the incorporation of other functional excipients. Moreover, there are no clinical trials to validate the SLS capabilities by offering proof of the therapeutic effectiveness of 3D printed dosage forms. Yet, we believe that continued research will yield important breakthroughs regarding the application of SLS in the manufacture of novel pharmaceutical medicinal products.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: