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ORIGINAL ARTICLE

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Building porous biopolymeric microstructures for controlled drug delivery devices using selective laser sintering

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Abstract The capability to build parts with predetermined porous microstructure and dense walls using powdered biomaterials makes selective laser sintering (SLS), one of the more flexible rapid prototyping (RP) processes, a strong candidate for building biodegradable controlled release drug delivery devices (DDD). The objective is to design a varying-porosity circular disc with an outer region being denser and acting as diffusion barrier region while an inner more porous center acts as a drug encapsulation region. This is to achieve a zero-order of release over a desired duration of time in drug administration.

A key study in this paper was to determine the influence of critical SLS process parameters, namely, laser power, laser scan speed and part bed temperature on dense wall formation and control of the porous microstructure of SLS-fabricated parts built with biomaterials. The physical characteristics of the fabricated devices were investigated through microstructure examination using the scanning electron microscope (SEM). Two biodegradable polymers, namely, polycaprolactone (PCL) and poly (-L) lactic acid (PLLA), were investigated. For a PCL varying-porosity disc, the laser power is set at 3 W (inner region) – 4 W (outer region), the scan speed at 5,080 mm/s and the part bed temperature at 40°C. For poly(-L) lactic acid (PLLA), the laser power is set at 12 W, the scan speed at 1,270 mm/s and the part bed temperature at 60°C. With the set of SLS parameters tabulated for specific polymers, a polymeric matrix with specific porosity can be fabricated as a drug delivery device.

Keywords Rapid prototyping · Selective laser sintering · Drug delivery devices · Biodegradable polymers · Porous microstructure

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1 Introduction

Rapid prototyping (RP) technology has presented the product designer with a vast array of tools and technologies unprecedented in the history of manufacturing [1]. Selective laser sintering (SLS) is a RP process for converting computerised three-dimensional solid designs to physical objects by using a layered powder-based laser manufacturing method. Over the last ten years, it has been shown that SLS can process a wide variety of materials with new materials showing improvement in part accuracy and strength aimed at increasing SLSs range of functional applications. Future development of SLS is directed towards biomedical applications such as tissue engineering and controlled release devices.

A drug delivery device (DDD) is a controlled release device that can control or delay the release of drugs in a predesigned manner. The DDD can be implanted into the human body and will deliver drugs to the body system as and when required. The rationale for the usage of controlled release devices is to improve efficacy and prevent under- or over-dosage. The objective is to achieve a reliable device with zero-order release that can yield consistent drug level in the blood over the desired duration of therapy [2].

The primary mechanism of controlled drug release in polymeric DDDs is by diffusion. This is done by controlling the volume and porosity of porous regions for drug loading and the thickness of dense wall formation for the diffusion barrier layer to achieve a zero-order of drug release [3]. The two most influential SLS process parameters on part density are laser power intensity and laser scan speed. Variation of the laser power and scan speed controls the degree of local densification. Therefore, to build dense regions as the barrier layer, the SLS process parameters are set either with higher laser power intensity, or lower laser scan speed [4].

2 Design of test specimen

2.1 Polymeric DDD design

For initial testing to determine the appropriate process parameter settings, an annular circular disc was designed

using CAD software PRO-Engineer Version 2000i (Parametric Technology Corporation, Needham, MA). The designs were exported in a standard industrial format STL (STereoLithography), a de-facto standard recognised by RP systems, to the SLS system, Sinterstation 2500 [5]. The configurations of the samples are 1.524 mm thick (10 layer thickness), with an outer diameter of 24 mm and an inner diameter of 16 mm. The design is such that it is in the form of an annular circular disc with internal porous microstructure and external dense walls. The internal porous microstructure allows drugs to be embedded and the external dense walls slow down the release of drugs. This will enable the control of the rate of diffusion of the embedded drugs. The varying porosity is attained by controlling the two main SLS process parameters, namely, the laser power and the laser scan speed thereby enabling the control of the quantity of drug loaded onto the device.

Biodegradable materials are used for DDDs as they can degrade inside the human body and any by-products can be removed by the body's waste removal systems without leaving any undesirable substances behind. Moreover, earlier studies have proved that it is capable of producing porous structures ideal for drug infiltration in the DDDs [3].

3 Methodology

3.1 Sintering of biodegradable polymers

The sintering of the two biodegradable polymers, namely, polycaprolactone (PCL) and poly (-L) lactic acid (PLLA), are carried out on the selective laser sintering (SLS) machine (Sinterstation 2500).

3.2 Preparation of powder

PCL is available in raw powder form of particle sizes less than 100 μm [6]. As for PLLA, raw PLLA granules were prepared into powder of particle sizes 125 μm via a centrifugal grinding machine. The PLLA powder was then sieved through a 125 μm test sieve (Cole Palmer Testing Sieve). It is then placed on a vibratory sieve shaker (Octagon 2000) for a cyclic period of sixty minutes to sieve out the powder of particle size 125 μm. The powders are sieved as the required powder particle size for selective laser sintering should not be more than 180 μm [7]. The average particle size for the standard SLS raw material, DuraForm Polyamide, is about 58 μm [8]. These two particle sizes are thus considered to be the upper and lower limits for satisfactory sintering. To obtain good sintering results, the particle size is controlled to be between 58 μm and 180 μm. The powder is then sintered and built on the SLS into disc-shaped samples.

3.3 Differential scanning calorimetry

Differential scanning calorimetry (DSC) is utilised to verify the properties of the polymeric powder milled, such as the glass transition temperature T_g and the melting temperature T_m.

3.4 Methodology of sintering

Building the part on the full powder bed with powder feeding cartridges was not used in this study. This was because there was insufficient powder ground to fill the powder feeding cartridges which need 8–10 kg of powder. Moreover, the cost of filling up the powder cartridge is exorbitantly high. Instead, a method of test sintering utilising a sinter tray container acting as the part bed is used. The sintering tray measuring 63×51 mm was filled and compacted with the sieved powder. The tray was then placed on the part bed in the SLS system. In order to build multiple layers, additional powder was added manually. This was done by halting the roller action for every run and new powder was added manually at the edge of the sintering tray. When the roller passed over the sinter tray, it would level the powder, covering the previous layer.

During the process, particles in each successive layer were fused to its neighbour and to the previous layer by raising their temperature with the laser beam to above the glass transition temperature. As a result, the particles softened and deformed owing to their own weight. The surfaces in contact with other particles began to deform and fuse together at these contact surfaces. This simultaneous process also built up the disc-shaped sample from the bottom up. The process was repeated for a total of ten-layer thickness of 1.524 mm (0.06 in). Disc-shaped specimens of PCL and PLLA were sintered and fabricated on the SLS system. These specimens were built by varying the three critical SLS parameters: part bed temperature, laser power, and scan speed to determine the most suitable sets of SLS parameter settings for PCL and PLLA. The specimens built were then analysed under a scanning electron microscope (SEM). A JSM-5600LV scanning electron microscope was used to view the surface integrity of the specimens. To ensure that the most suitable sets of SLS parameters were obtained, the theoretical porosity of the specimens were also determined by weighing the specimens and calculating the volume of the specimens from their physical dimensions. This is to establish the porosity obtainable from the settings of these parameters which can then be used to control the loading and delivery rate.

4 Results and observation

4.1 Differential scanning calorimetry (DSC) of materials

From the DSC results, it is concluded that the variation in the melting temperatures of the powder sample is not significant because most polymers have no definite melting point as they melt over a range of temperatures. The melting temperature stated in the material specification is usually the closest estimation of the actual values and they are often quoted within a certain range [9]. Moreover, DSC

tests performed on different forms of the same polymer do yield slightly different results. As such, the variation of melting temperature is within the acceptable range as stated in the material specifications.

4.2 Characterisation of PCL at different SLS parameter settings

As mentioned in Sect. 3.4, test sintering was carried out on PCL to determine the preferred processing parameters on the SLS system. Several specimens with different settings of parameters in terms of part bed temperature, laser power, and scan speed on the SLS system were fabricated. To determine the preferred values for each parameter, the parameters were varied one at a time while the other two kept constant.

4.2.1 Part bed temperature

The first test sintering was done to establish a suitable part bed temperature. The test was done by building a one layer DDD disc and varying the part bed temperature between 30°C (room temperature) and 50°C (near to the melting point of PCL) in steps of 5°C while keeping the laser power and scan speed constant. The laser power and scan speed was set at 2 W for the inner disc and 3 W for the outer disc, using a scan speed of 3,810 mm/s (150 in/s) for both discs.

Figure 1 shows the views taken from SEM micrographs of the inner porous region and outer dense wall for the discs built at the temperatures of 30, 40 and 50°C at 100 times magnification.

From the SEM micrographs shown in Fig. 1, it could be observed that at low part bed temperature (30°C), the particles experienced little or no necking. The sintering

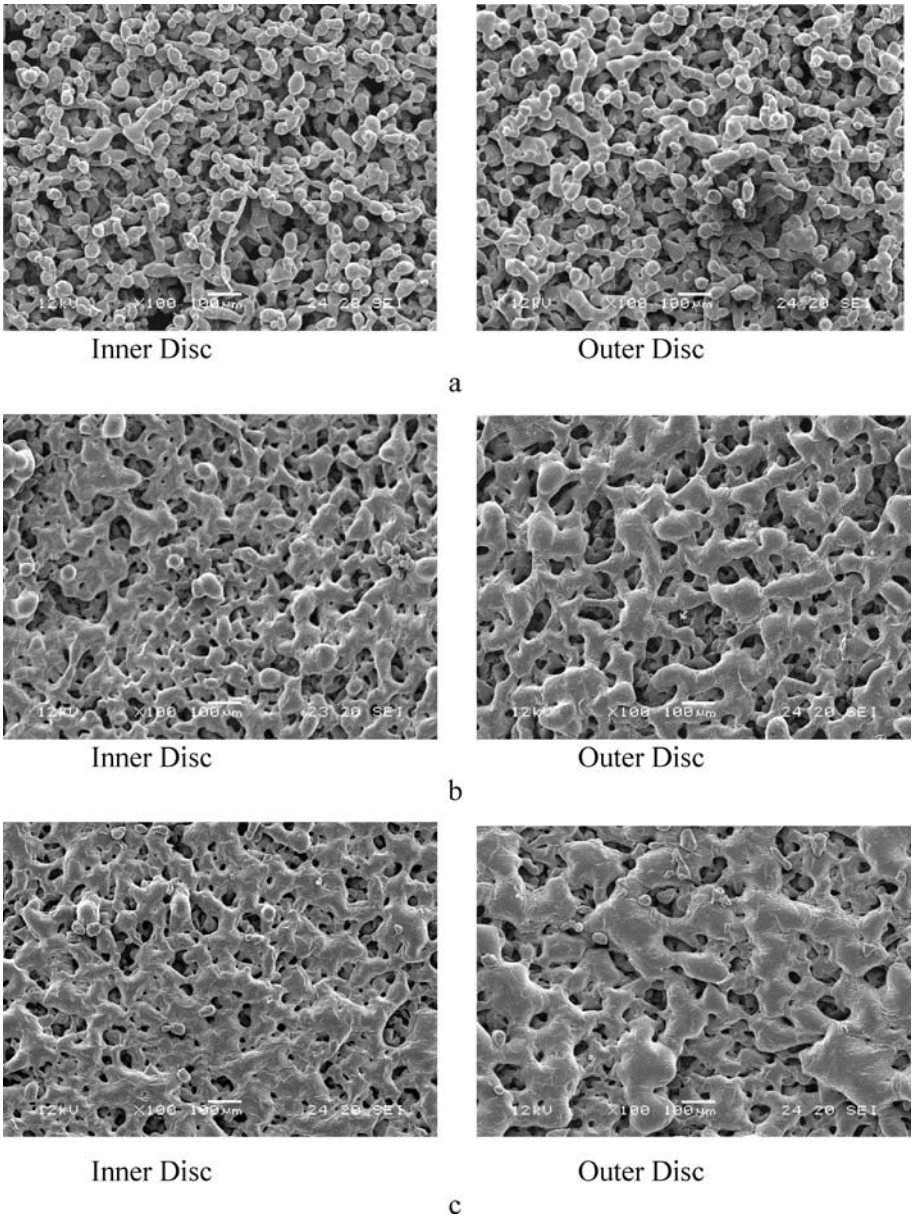

Fig. 1 Micrographs from SEM of the inner and outer region for one layer disc at 100× magnification within the temperature range **a** 30°C, **b** 40°C, and **c** 50°C

showed highly porous and fragile structure. At 35°C, the particles experienced more necking and start of melting can be observed and it was less porous than when sintered at 30°C. When the temperature went above 40°C, the PCL had more melting and the specimen had more regular pore size. At 50°C, the particles had melted almost completely and spread out, forming a dense but strong structure with virtually no porosity observed.

Generally, as the temperature increase, the specimen became less porous and denser. The specimen also showed good necking with more regular pore size and had stronger structure. Based on these experiments, 40°C part bed temperature was chosen for building the DDD for better control of the porosity.

4.2.2 Laser power

In order to determine the suitable laser power, a sintering test was done by varying the laser power from 1 W to 7 W in steps of 1 W with constant scan speed (3,810 mm/s or 150 in/s) and part bed temperature (40°C).

SEM micrographs of the specimens, similar to those shown in Fig. 1, were take and observed. At 1 W laser power, it was observed that the PCL powder was not fully sintered. There was little necking of particles as only some of the PCL particles had been sintered. The structure of the DDD was also found to be thin and very fragile that it could be torn easily on handling.

At 2 W laser power, it was observed that the PCL particles were better sintered as there was more necking of the particles observed. The DDD was porous and has stronger structure than that made using 1 W laser power.

As the laser power was increased, it was observed that the porosity of the DDD reduces. The particles were also observed to have progressively more necking and the structure was stronger and harder. It was noted that at 7 W laser power the sintering test started to experience curling around the edge of the circular disc, which made it impossible for DDD building.

To ascertain that the laser power chosen was suitable, the porosity measurement based on mathematical calculation was done. The formula to determine the porosity is given by Ma and Choi [10], where porosity, $\varepsilon = 1 - \frac{\rho_{\text{sinteredPCL}}}{\rho_{\text{PCLpowder}}}$ [10], where $\rho_{\text{sinteredPCL}}$ is the density of the PCL DDD and $\rho_{\text{PCLpowder}}$ is the density of the PCL powder. The density of the PCL DDD was obtained mathematically by dividing its measured mass by the volume calculated from the physical measurements of the PCL DDD. The volume was calculated from the formula of a cylinder. The density of the PCL powder was obtained from measurements using a Ultrapycnometer. The density of PCL powder was measured and found to be 1.1962 g/cm^3.

Table 1 shows different porosity values of the single layer DDD at different laser power. It was observed that the higher the laser power, the less porous the specimen. This is consistent with what was observed from the SEM micrographs. It also indicates that the porosities for laser power between 3 W and 4 W are higher at more than 50%.

Table 1 Porosity values of PCL discs at varying laser power

Laser power (W)	DDD density $\rho_{\text{sinteredPCL}}$ (g/cm^3)	PCL powder density $\rho_{\text{PCLpowder}}$ (g/cm^3)	Porosity ε (%)
1	0.391	1.19615	67.3
2	0.498	1.19615	58.4
3	0.586	1.19615	52.7
4	0.551	1.19615	53.9
5	0.755	1.19615	36.9
6	0.899	1.19615	24.8
7	0.958	1.19615	19.9

Therefore, from the SEM micrographs, analysis and calculation above, the laser power of 3 W was chosen for the inner region and 4 W for the outer region since these values gave good porosity with strong and rigid structure to build the first PCL DDD. The outer region was built using higher laser power in order to protect the drug encapsulated later on so that it would not easily diffuse due to its denser microstructure.

4.2.3 Scan speed

After determining the suitable values for laser power, the next step was to establish the appropriate values for the scan speed to build the DDD with desired porosity. This was done by varying the scan speeds and keeping the laser power (3 W and 4 W respectively for the inner and outer discs) and part bed temperature (40°C) constant. SEM micrographs of the test sintering of the DDD at different scan speeds with 100× magnification were taken and observed.

From these SEM micrographs it was observed that at scan speed of 1,270 mm/s (50 in/s), the particles of PCL were fully sintered as indicated by the full necking of the particles. The structure was found to be strong, rigid and dense. It was also found that at this speed, the circular PCL DDD experienced curling around its edges.

At a higher scan speed or 2,540 mm/s (100 in/s), the PCL structure showed better stability, no curling was observed and it was more porous with slightly regular pore size. The

Table 2 Porosity values of PCL discs at varying scan speed

Scan Speed (mm/s)	DDD Density $\rho_{\text{sinteredPCL}}$ (g/cm^3)	PCL powder density $\rho_{\text{PCLpowder}}$ (g/cm^3)	Porosity ε (%)
1,270	0.537	1.19615	55.1
2,540	0.740	1.19615	38.1
3,810	0.784	1.19615	34.1
5,080	0.595	1.19615	50.2
6,350	0.493	1.19615	58.8
7,620	0.333	1.19615	72.1

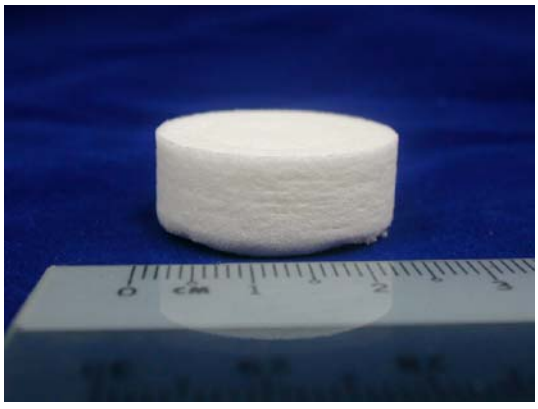

Fig. 2 Polymeric cylindrical DDD built with laser power 3 W (inner region)–4 W (outer region), scan speed 5,080 mm/s (200 in/s) and part bed temperature 40°C

structure was still strong and rigid, but not as hard as those built using 1,270 mm/s (50 in/s) scan speed.

As the scan speed increased, it was observed that the DDD disc tended to be more porous, but at the same time the structure became more fragile. At 7,620 mm/s (300 in/s), the structure became very fragile and could be easily broken. It could be seen from the resulting SEM micrographs that the PCL particles were not uniformly sintered at this scan speed.

Using the equation in Sect. 4.2.2, the porosities of the DDD samples with different scan speed were calculated and summarized in Table 2. From Table 2, it can be observed that the higher the scan speed, the more porous the DDD disc, which confirmed the observations made on the SEM micrographs. Table 2 also shows that a scan speed of 5,080 mm/s (200 in/s) results in the DDD structure having relatively high porosity.

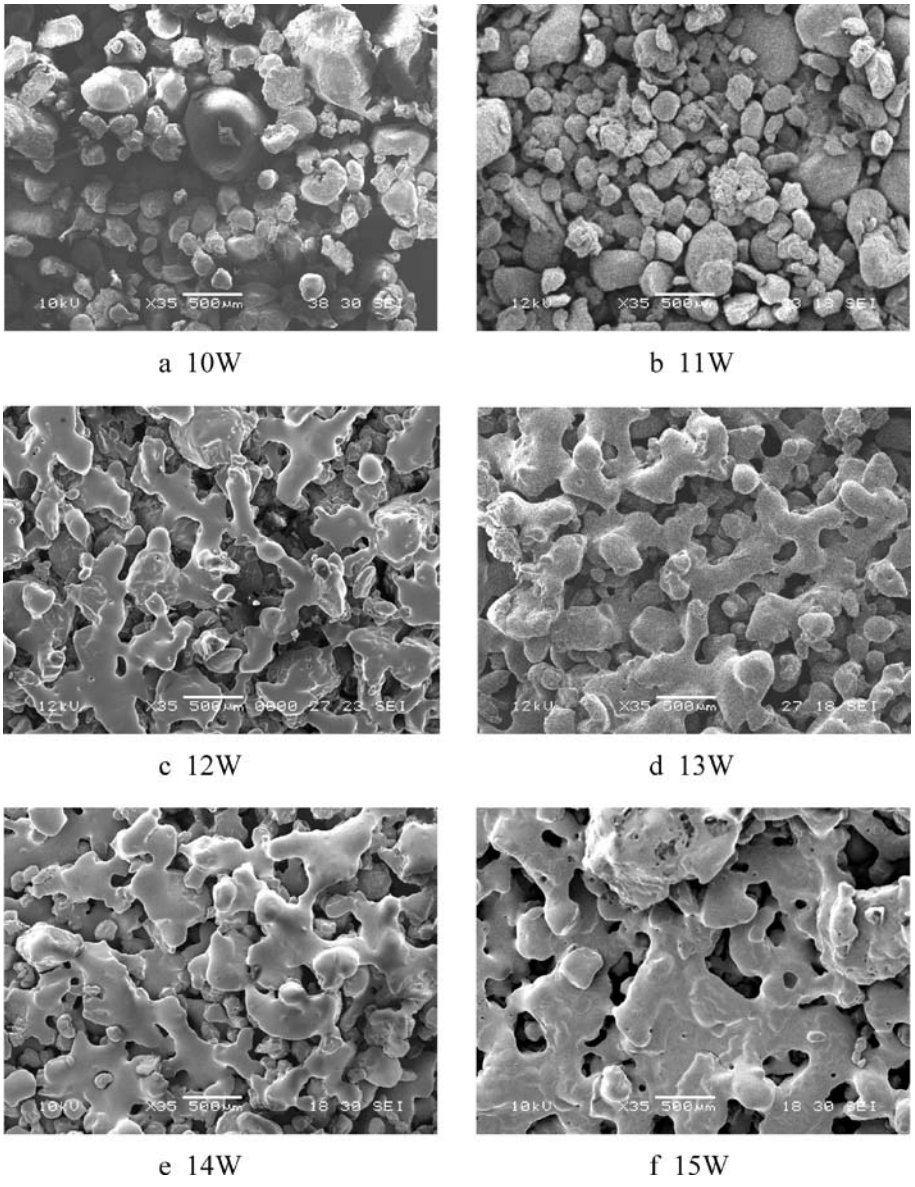

Fig. 3 SEM micrographs of PLLA sintered at part bed temperature of 60°C, 1,270 mm/s and at different laser power of **a** 10 W, **b** 11 W, **c** 12 W, **d** 13 W, **e** 14 W, and **f** 15 W

Therefore the scan speed at 5,080 mm/s (200 in/s) is chosen to produce structure with high porosity and strength. The scan speed of 5,080 mm/s will result in a higher porosity structure that is essential for building the DDD used for drug loading.

4.2.4 Summary

From these observations, the fabrication of a controlled DDD with over 50% porosity can be carried out with laser power 3 W and 4 W for inner and outer regions, respectively, scan speed of 5,080 mm/s (200 in/s) and part bed temperature of 40°C. This is sufficient for the PCL DDD to hold a drug for delivery since the successful polymer matrix built by Mainchent et al. using an oil-in-water (o/w) emulsification-solvent evaporation method to dissolve a drug called nifedipine inside a PCL polymer matrix only had a porosity of 40% [11].

The DDD designed and built using the SLS parameters determined had an inner region with diameter of 16 mm, an outer region with diameter of 24 mm (the dense wall) and thickness of 10.0584 mm (66 layer thickness), as shown in Fig. 2. The SLS process parameters are set at a laser power of 3 W (inner region), 4 W (outer region), scan speed of 5,080 mm/s (200 in/s) and part bed temperature of 40 °C.

The DDD was fabricated successfully with sintering and bonding between each layer. The structural integrity of the fabricated DDD appears strong and has a dense periphery. It has sufficient porosity that enables the infiltration of drugs into the inner core forming a DDD matrix.

4.3 Characterisation of PLLA with different SLS parameter settings

In the case of PLLA, the same set of parameters was monitored with the part bed temperature set to 60°C, closer to its glass transition temperature T_g. The selection of scan speed of 1,270 mm/s (50 in/s) was based on the work conducted by Ku [12] on the Universal M25 Laser Engraving System.

Figure 3 shows the SEM micrographs of sintered PLLA at 60°C and 1,270 mm/s (50 in/s) at varying laser power set at 10 W–15 W at 1 W intervals. It was noted that attempts to sinter PLLA at laser power of 11 W and lower did not result in any plausible sintering of the specimens. As such, the laser power was increased to 12 W. With laser power setting at 12 W and above, fusion and necking between the PLLA particles were observed. As seen in Fig. 3, successful sintering was observed on all specimens, indicating the viable processing range for PLLA on SLS to be between 12 and 15 W to obtain a porous structure. For the sintering at high laser powers of 14 W (see Fig. 3e) and 15 W (see Fig. 3f), it is observed that the structures are rather dense with very little porous regions. Therefore, the optimal laser power should be 12 W with an adequate amount of porous regions and necking of particles.

As such, to have successful sintering with necking of particles and porous structures using PLLA as the build material, the preferred SLS parameters are at a laser power of 12 W, scan speed of 1,270 mm/s (50 in/s) and part bed temperature of 60°C.

5 Conclusion

Controlled release devices can improve patient compliance and drug efficacy, while simultaneously minimizing the risk of toxic side effects. The main objective of this research is to explore the feasibility of using biodegradable polymers as the matrix to build drug delivery devices (DDD) using selective laser sintering (SLS). The biopolymers studied include PCL and PLLA. The relationship of the various SLS parameters such as laser power, scan speed, and part bed temperature with the porosity of the DDD matrix are studied. Methods of fabricating a DDD matrix with varying porosity and density to optimise drug loading and diffusion rate were investigated. The relationship of the SLS parameters and the microfeatures of the DDD matrix such as dense wall layers and internal pores were also investigated.

Characterisation was done on PLLA and PCL disc samples fabricated by SLS. Samples were analysed under the SEM for the preferred parameters with good sintering effects. For PLLA, the preferred parameters are at a laser power of 12 W, scan speed of 1,270 mm/s (50 in/s) and part bed temperature of 60°C. For the PCL varying-porosity disc, the preferred parameters are laser power set at 3 W for the inner region, 4 W for the outer region, a scan speed of 5,080 mm/s (200 in/s) and part bed temperature of 40°C. Porosity of more than 50% was attained and this indicates that feasible quantity of drug can be loaded into these devices.

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