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THERMAL INFLUENCE ON PRINTLET QUALITY IN THE SELECTIVE LASER SINTERING OF PHARMACEUTICAL FORMULATIONS

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ABSTRACT

The objective of this research is to determine the influence of temperature on the mechanical and dissolution performance of pharmaceutical printlets (tablets) fabricated via selective laser sintering (SLS) additive manufacturing. When compared to traditional high-volume pharmaceutical manufacturing, additive manufacturing has the potential to effectively cater to personalized and just-in-time medicine. Among additive manufacturing methods, SLS has the advantage of not needing to reconstitute the drug(s) with other liquids or powders, as well as the ability to tailor certain location-specific properties via process parameter control. One of the critical parameters that affect the printlet quality is the temperature during the printing process. To explore the thermal effects, two separate experiment sets were conducted. First, process parameters including chamber temperature were studied based on a partial-factorial design of experiments, and their effects on parameters such as weight, hardness, structural disintegration and dissolution rates studied. Next, a smaller scale study was conducted to correlate surface temperatures with structural integrity. Results showed the beneficial and detrimental effects of operating at chamber and bed temperature ranges, in relation to the polymer percentage and melting point. A certain minimum energy density needed to be imparted onto the powder mixture combinations (resulting in a certain surface temperature) for proper fusion and performance of the printlets. This work served to investigate and show the potential of using SLS to reliably fabricate pharmaceutical formulations.

Keywords: Printlet, Selective laser sintering, Pharmaceutical, Drug, Formulation, Dissolution, Reconstitute, Kollidon

1. INTRODUCTION

1.1 Background

Traditionally, medication tablets (pills) are manufactured via a primarily-mechanical set of processes. The tablets typically consist of the drug (or active ingredients) and excipients (or additives that hold the pill together and ensure that the pill achieves the mechanical properties specified by the US Pharmacopeia). Some of the standards include tablet size, hardness, friability, and other parameters (USP, 2017 [1]). The mechanical processing of pressing the active ingredients and excipients together to form a tablet is a reliable and scalable process that allows for tablets to be mass produced. However, this method does not allow for significant customization of manufacturing tablets, whether in composition, dosage, etc. This lack of customizability is a hindrance if the patient requires a very specific combination and dosage of medication with a short turnaround; this issue is exacerbated in the case of specialized pediatric formulations and dosages which are not typically within the supply chain of most pharmaceutical companies.

Additive manufacturing, or 3D printing, is a class of manufacturing techniques that allows for a wide range of customization when manufacturing various products involving different classes of materials. This customization can extend to the medical field when manufacturing pharmaceutical formulations via 3D Printing; among these, selective laser sintering (SLS) is a method being currently explored that shows potential for manufacturing highly customizable tablets. SLS is a method of additive manufacturing whereby one layer of powder is added to a bed area where a laser is used to heat and sinter the powder into a solid in the laser applied region [2]. Then, a new layer of powder is 'coated' over the existing layer, and the laser sinters the same place as before, adding a second layer on top of the first. This process is repeated until the final product is made. SLS is quite popular in the metal-based additive manufacturing of products that span industry sectors such as aerospace, biomedical, automotive, defense and energy, among others. In such cases however, a high-energy laser (typically 100-1000W) is used for sinter and/or melt metal power and fuse them in a similar manner. The 3D printing of pharmaceutical formulations via SLS follows a similar route, with some key differences. First, the laser used is a diode laser

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with significantly low power (typically, ~2.3W) when compared with commercial metal-based SLS machines. Next, there is an internal heat lamp (typically, an IR lamp) that raises the chamber temperature to very close to (but below) the melting point of the excipient (a polymer, with a melting point typically less than 150 °C), and the laser is used to provide an incremental amount of power to melt the polymer and fuse the printlet into a structure. In the case of metal-based SLS, the high energy laser typically provides all of the heat energy instantly; there are exceptions where a heated bed/chamber of ~200 °C could be utilized, but the melting point of the metal/alloy is typically many times this temperature.

The powder that is used to make the tablets is similar to the powder used to make the tablets in the traditional mechanical processing. The powder requires active ingredients (drugs), binders or polymers that ensure the structural and mechanical properties of the tablet are acceptable, and usually an additive (coloring/sheen) that allows for the effective absorption of laser energy to raise the temperature of the powder mixture. Because the tablets are not bound by the size of a mechanical press, SLS allows for different concentrations and types of drugs in each powder batch, and these batches can be used to make different sizes (dosages) of printlets as well.

1.2 Selective Laser Sintering of Pharmaceuticals

When compared to other methods of 3D printing, SLS has a distinct advantage because some other methods of 3D printing involve pre-processing the drug mixture into a filament form such as in fused deposition modeling (FDM), or conducting post-processing de-binding and sintering steps such as in binder jetting. Selective laser melting (SLM) could be considered as variation of SLS, where all of the powder mixture completely melts and fuses to a solid. This is necessary and advantageous where strong (metallic) chemical bonds are required, such as in metal 3D printing [3]. FDM is quite different than both SLM and SLS, where polymer filaments are heated and deposited through a nozzle to form the desired shape or part layer by layer [4]. However, these methods involve completely melting their powder or polymer mix. Completely melting the printlet mixture may change the properties of the drug, either altering or degrading the drug capabilities [5, 6]. Pharmaceutical SLS only heats the powder mixture just enough to where it can fuse together to a solid by barely melting the polymer, while not completely melting the mixture. Thus there is a fine balance required between not sufficiently melting the polymer (leading to structural/mechanical deficiencies) vs. melting the polymer too-much/completely, whereby the drug starts dissolving in the polymer.

Using SLS to manufacture printlets introduces many new parameters that must be controlled in order to make printlets that achieve the desired standards. Some of these parameters include laser speed, laser intensity/power, hatch distance, chamber temperature, powder particle size/distribution and surface area [7]. Each of these parameters are associated with temperature and changes in temperature while printing. Maintaining the desired temperature is important because too low of a temperature may lead to a decrease in the printlet's mechanical strength and too high of a temperature may lead to degradation of the drug's performance. Thus, the objective of this study is to ascertain how various parameters, especially temperature influences the properties and performance of manufactured printlets.

2. MATERIALS AND METHODS

2.1 Materials

2.1.1 Study 1: Temperature, Speed and Lactose Effects

Powder mixture: Diclofenac (Leap Chem, Hangzhou, China) – nonsteroidal anti-inflammatory drug, Kollidon® VA 64 (BASF, Germany [8]) – biodegradable polymer, Candurin® NXT Ruby Red (Merck, Darmstadt, Germany) – coloring/sheen, lactose monohydrate (LMH, SuperTab® 14SD, DFE Pharma, Paramus, NJ) – sugar.

2.1.2 Study 2: Surface Temperature Effects

Phenytoin - anti-epileptic drug, Kollidon® VA 64 (BASF, Germany [8]) – biodegradable polymer, Candurin gold sheen (Merck, Darmstadt, Germany) – coloring/sheen.

2.2 Methodology

2.2.1 Study 1 Experimental Design

Fifteen trials were conducted to discover how weight, hardness, disintegration time, and dissolution would be affected by printing parameters. The trials are shown in Table 1. The independent variables in the experiment were temperature, laser scanning speed, and lactose concentration. The chamber temperature settings were 120, 130, and 140 °C. The laser speeds were 270, 300, and 330 m/s. The lactose concentrations were 8, 10, and 12%. For studying 3 input variables having 3 levels each, a full-factorial design of experiments would result in a large number of trials. Instead, a Box-Behnken design was used to assemble a smaller number of runs that would span the design space effectively. Further, study-1 had to be limited to 3 temperatures to effectively explore the multi-dimensional space. Since ascertaining temperature effects need to be explored further, we have undertaken a follow up study with more than 3 levels for temperature. The fixed parameters in the experiment included the drug concentration, which was fixed at 30%, the Candurin® NXT Ruby Red concentration, which was fixed at 3%, the laser power, which was fixed at 5 mW, and the printlet sizes, which were fixed at 8 mm diameter and 4 mm height. Note that a partially-similar, but different study (different process parameter ranges and printlet sizes) was conducted by the authors previously [7] that corroborate some of the observations derived from this investigation.

Kollidon® VA 64 was chosen to be the polymer for these experiments due to the available particle sizes, particle shape, and melting point. As shown by Figures 1 and 2, Kollidon® VA 64 powder particles have a mostly spherical shape and also have a relatively wide size distribution from 200 - 1000 μm. The scale bar on these images measure 1000 μm (1 mm), and the magnification is 10x. Further, a spherical particle shape along with a wide range of particle sizes (within the given

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range) have been reported to have good flowability and spreadability when handling during SLS printing [9].

TABLE 1: DESIGN OF EXPERIMENTS FOR STUDY #1 WITH 3 INPUT PARAMETERS

Run	Chamber Temperature (°C)	Laser Speed (m/s)	Lactose Concentration (%)
1	120	300	8
2	130	330	8
3	130	330	12
4	130	270	8
5	140	330	10
6	130	300	10
7	140	270	10
8	130	300	10
9	130	300	10
10	120	270	10
11	120	300	12
12	140	300	12
13	120	330	10
14	140	300	8
15	130	270	12

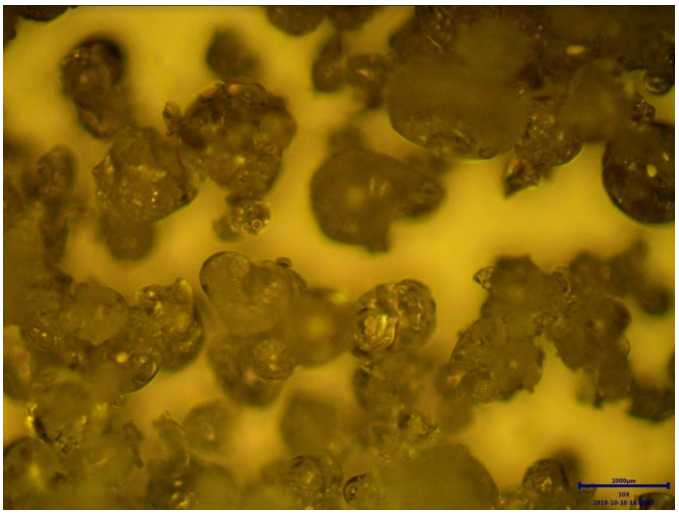

FIGURE 1: KOLLIDON® VA 64 POWDERS

A Sintratec Kit [10] was used for SLS printing procedure. A caliper and scale were used to respectively measure the final printlets' weight and hardness [11]. The test used for determining disintegration time was 701: Disintegration (US Pharmacopeia, 2016 [12]). The test represents how many seconds the printlet takes to completely disintegrate after being placed in water. The test used to determine the drug dissolution percentage over time was 701: Dissolution (US Pharmacopeia, 2011 [13]).

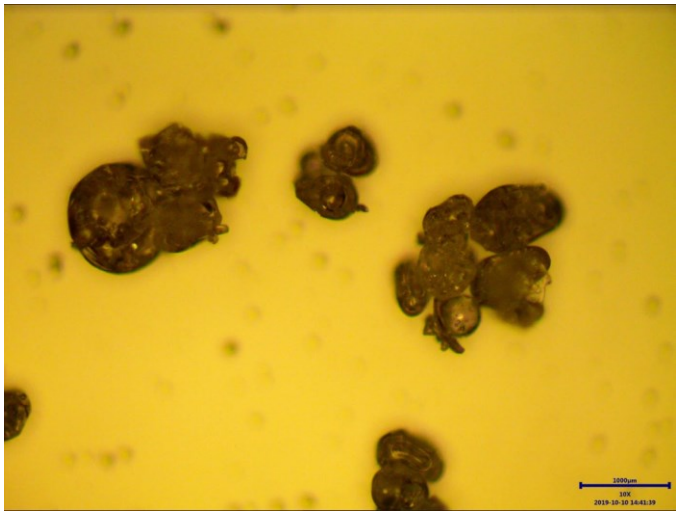

FIGURE 2: KOLLIDON® VA 64 PARTICLES ISOLATED TO SHOW SHAPE

2.2.2 Study 2 Experimental Design

Nine trials were conducted to find the correlation between printlet mass loss in a friability test with the independent variables being the drug to polymer ratio and the chamber temperature. Each trial had a different drug to polymer ratio or chamber temperature. The different polymer ratios were 60, 70, and 80%. Respectively, the different drug ratios were 37, 27, and 17%. The gold sheen amount was fixed at 0.03% of the total powder mixture composition; this amount was determined by preliminary trials, as having too little resulted in the powder mixture not being heated by the laser sufficiently, and having too much sheen resulted in the powder mixture being burned by the laser. The laser speed, laser intensity, and printlet size were also fixed parameters. The speed was fixed at 200 mm/s, the laser power was fixed at 5 mW, and the printlet size was 10 mm diameter and 3 mm height. An outline of the experimental design is tabulated in Table 2.

TABLE 2: DESIGN OF EXPERIMENTS FOR STUDY #2 WITH 2 INPUT PARAMETERS

Tablet Composition		
Polymer: Kollidon VA 64	Drug: Phenytoin	Coloring Agent: Candurin Gold Shein
0.6	0.37	0.03
0.7	0.27	0.03
0.8	0.17	0.03

A FLIR TG165 IR (FLIR Systems, 2020 [14]) camera was positioned to measure the temperature of the surface of the powder bed. Figure 3 illustrates the setup of the printer and a representative illustration of how the IR camera was used to acquire surface temperature during printing. The emissivity of the IR camera was set to 0.95 for the needed temperature range.

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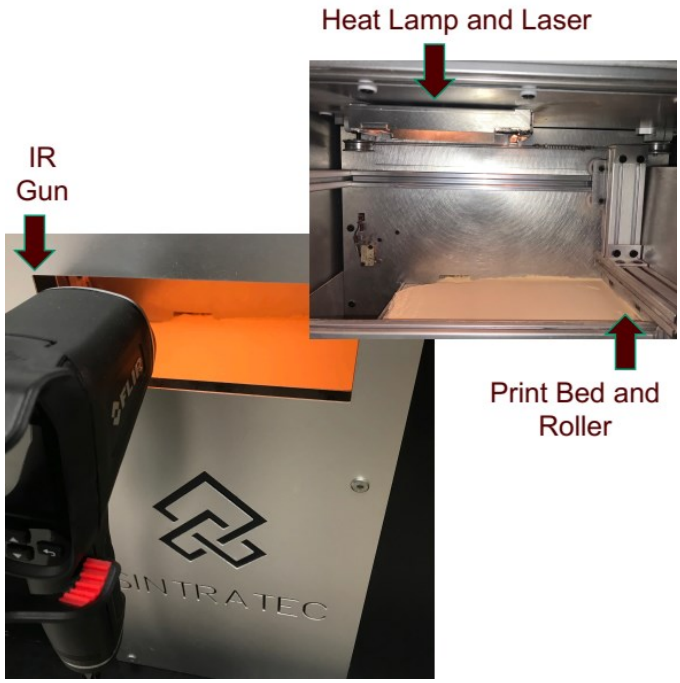

FIGURE 3: PRINTER & IR CAMERA (REPRESENTATIVE) SETUP

3. RESULTS AND DISCUSSION

3.1 Study 1: Temperature, Speed and Lactose Effects

Each parameter was analyzed individually in JMP statistical software and Microsoft Excel to ascertain what affects and at what level, it had on the printlets. The weight, hardness, disintegration time and percent dissolution amount were each analyzed for different combinations of temperatures, laser speeds and lactose concentrations. Figures 4-7 capture the chamber temperature effects on the four output variables (dissolution percentage, hardness, disintegration time and printlet weight). The graphs are plotted against laser speeds and lactose concentration, with each data point denoting the lactose concentration (*e.g.*, "L8" means 8% lactose). The trend lines drawn (all 2nd order) seemed to be centralized between lactose percentages suggesting that the intermediate lactose % (10%) would fall on the line itself. Figures 8 and 9 show respectively the weight and disintegration time relationships vs. chamber temperature for all the printlets (*i.e.*, the data points contain information for laser speed and lactose percentage as well); a 'weak' quadratic fit can be used to capture the general trend.

The chamber temperature, when separated into different laser speeds, represented by the Excel figures appeared to consistently have a second-degree polynomial trend with the data in the sense that the change in three of the parameters was greater from 130 – 140 °C than from 120 – 130 °C. The trend is positive for weight and disintegration time, and it is negative for dissolution amount. The variability in the hardness readings was too high, so no trend was fitted to the combined hardness data across all data points. The closer the polymer was to its melting point (SDS No. 30239644, 2012), the more material fused together. This led to a higher weight and hardness. Because there was more material packed closer together with a higher temperature [15], the time to disintegrate the printlet was longer, as there was more material to disintegrate [16]. The dissolution negative trend also aligns with the previous trends because if the printlet made at 140 °C is packed more tightly with material than the other two temperatures, it will have less porosity and, so less material will be lost in the dissolution test.

The laser speed results align with the chamber temperature trends. A higher laser speed translates to the powder having less time exposed to the laser. Less time exposed to the laser means the powder receives less heat from the laser [15]. The trends in the weight, disintegration time, and dissolution amount align with the claim that less time exposed to the laser leads to less heat transferred to the powder. The overall weight of the printlets lower from 120 – 130 °C, but the overall weight rises from 130 – 140 °C. This increase in weight could be because the laser only needed to raise the powder temperature by 5 °C in the 140 °C chamber temperature trials to achieve fusion between layers, as the melting point of Kollidon VA64 is 145 °C. However, for the rest of the dependent variables, laser speed results matched with temperature. A higher laser speed, which means less overall heat reaching the powder, resulted in lower hardness, lower disintegration time, and higher dissolution rate.

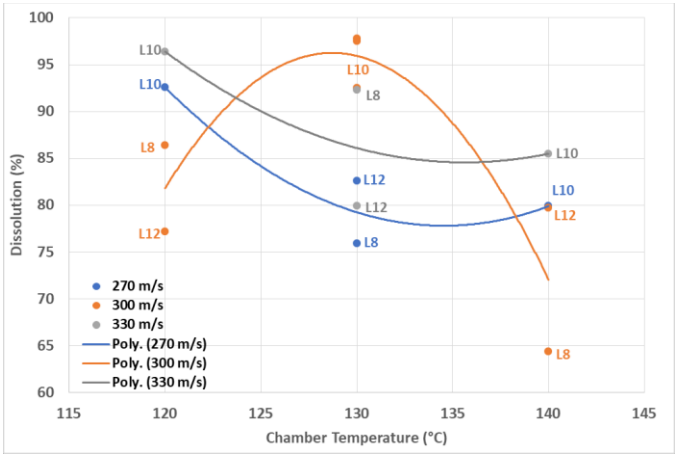

FIGURE 4: PARAMETER EFFECTS ON DISSOLUTION %

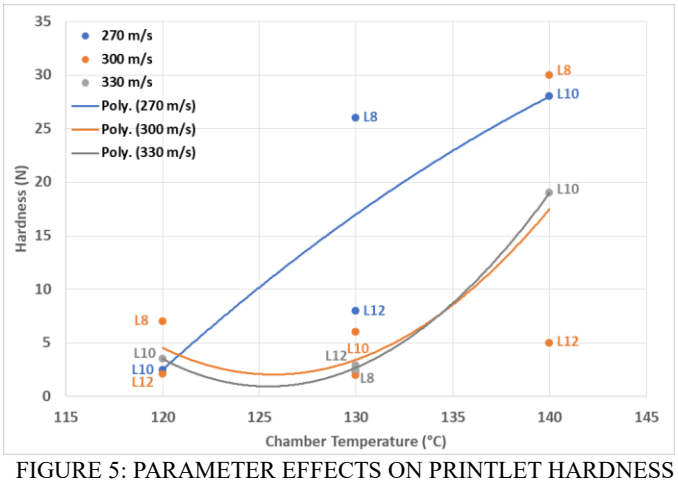

FIGURE 5: PARAMETER EFFECTS ON PRINTLET HARDNESS

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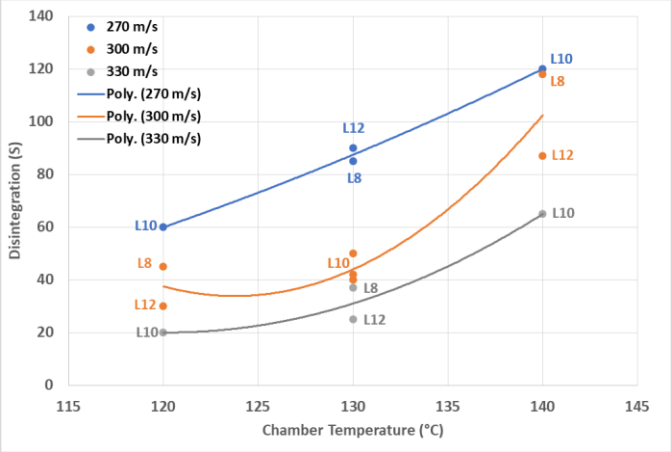

FIGURE 6: PARAMETER EFFECTS ON DISINTEGRATION

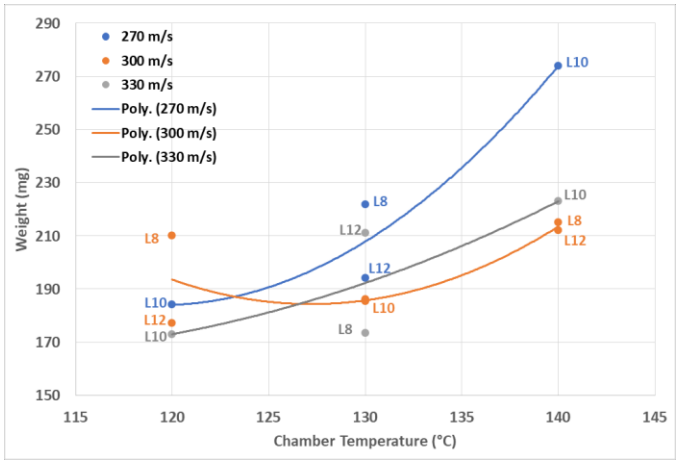

FIGURE 7: PARAMETER EFFECTS ON PRINTLET WEIGHT

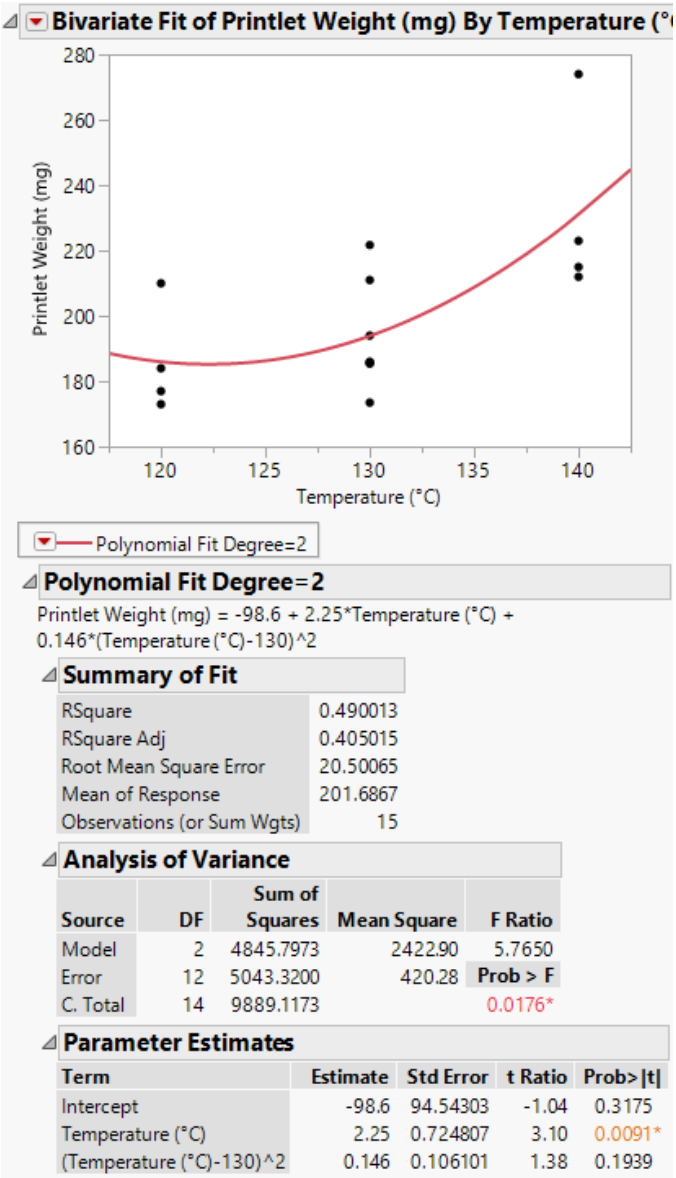

FIGURE 8: ALL PARAMETER EFFECTS ON PRINTLET WEIGHT

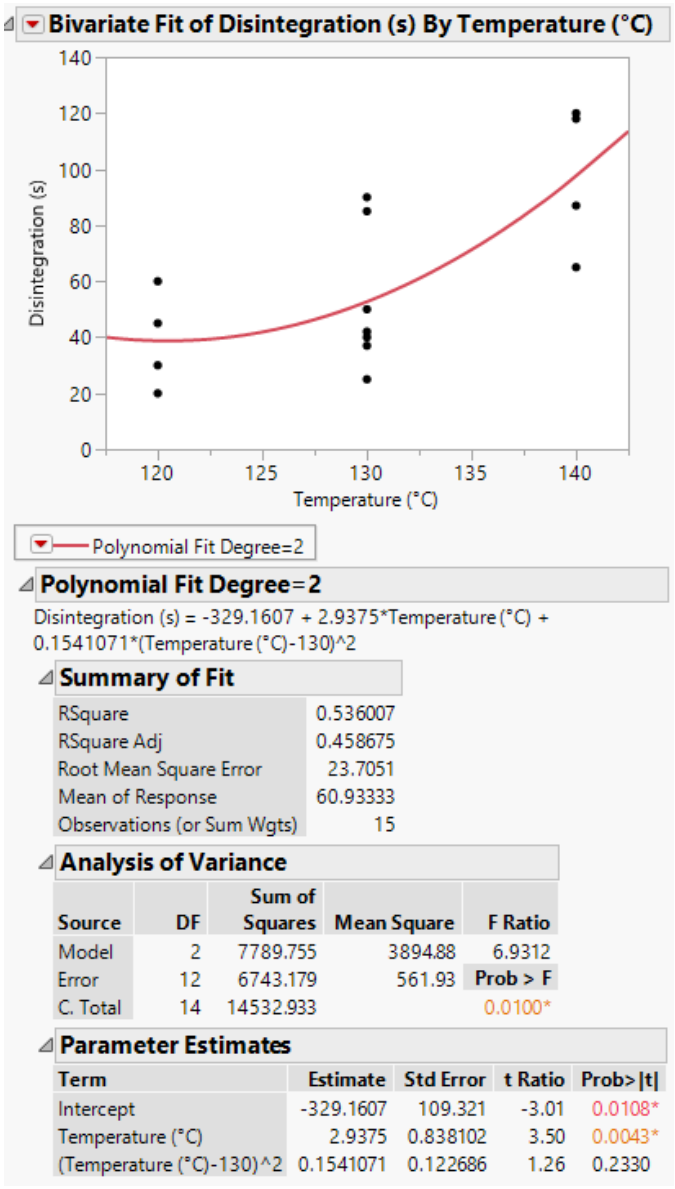

FIGURE 9: ALL PARAMETER EFFECTS ON DISINTEGRATION

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The data points in the figures have a lot of variability, but the lactose concentration can explain some of the variability in this model. The trendlines created for the weight for when laser speeds were 270 m/s and 330 m/s show that printlets with lactose percentages of 8 and 12 deviate a similar amount from the polynomial relationship used for the model. The variability due to lactose percentage also appears in a similar fashion when analyzing the disintegration time and the dissolution amount. A notable phenomenon is that the relationship with the variability in the trends for laser speed 270 m/s and 330 m/s due to lactose are opposite. This inverse relationship can be attributed to lactose having a different melting point than the Kollidon. The melting point of lactose is 201 °C (National Library of Medicine, 2020 [17]) , over 50 °C higher than the Kollidon. Therefore, on lower laser speeds and higher chamber temperatures, one would assume that more lactose would melt during the print. However, the relationship is opposite of this logic. Printlets with less lactose weigh more on slower laser speeds, and printlets with more lactose weight more on faster laser speeds. Because the final printlet material percentages was not taken, it is unknown how much of the finished printlets were lactose. A potential explanation for this phenomenon is that the lactose melting rate is steady, and the polymer fusion has higher variability based on temperature. However, without additional weight percentage analysis, this claim is just an assumption. The results for each run, shown by Table 3, illustrate similar trends as plots - where weight increases, so does hardness and disintegration time, and consequently dissolution amount decreases.

TABLE 3: RESULTS FROM EXPERIMENTAL DESIGN 1

Run	Printlet Weight (mg)	Hardness (N)	Disintegration Time (s)	Dissolution (% dissolved in 15 minutes)
1	210	7	45	86.4
2	173.5	2.5	37	92.3
3	211	2.9	25	79.9
4	221.7	26	85	75.9
5	223	19	65	85.5
6	185.4	6	42	97.5
7	274	28	120	79.9
8	185.7	2.3	40	92.5
9	186	2	50	97.8
10	184	2.5	60	92.6
11	177	2.1	30	77.2
12	212	5	87	79.7
13	173	3.5	20	96.4
14	215	30	118	64.4
15	194	8	90	82.6

At lower laser speeds, printlet weight is higher than at higher laser speeds. The samples that are exposed to the laser at a lower speed interact with the laser for a longer time than the higher speed, causing more fusion. The same trend can be seen with increased chamber temperature. The closer the polymer was to its melting point, the higher amount of fusion was done in the print. The relationship of increased weight can also be seen with increased disintegration time. The higher temperature and increased laser exposure time resulted in printlets that took longer to disintegrate. Also, the dissolution percentage showed an inverse relationship with weight and disintegration time. The printlets with higher weight and higher disintegration time were the printlets that experienced higher fusion than printlets that received less laser exposure time and lower chamber temperature. The printlets with more fusion dissolved less than the printlets with less structural integrity.

3.2 Study 2: Surface Temperature Effects

During the printing process, the IR camera recorded the surface temperature of a specific point (indicated by the small bright yellow circular areas next to the square pointers) where the laser would pass for each layer, eventually forming the printlet. For the data presented in Figure 10, the chamber temperature was set to 100 °C. The valleys indicate the starting temperature, as the valleys represent the temperature when a new layer of powder was placed. The peaks are when the laser passed through, and IR camera measured the increased temperatures; the repeatability behavior of the surface temperatures is to be noted as per the repeating event sequence. The spot temperature measurements during a sequence of events, *viz.*, the moment before the laser turns on a new powder layer, during the laser heating of the spot, and immediately after covering this layer with a new powder layer are shown in Figure 11. Figure 12 shows a completed printlet from the study that is as-printed and structurally sound. All of the printlets were evaluated for mass loss via friability tests, where effects of drug-to-polymer ratios and chamber temperatures were evaluated. Figure 13 shows the effect the two parameters had on mass loss. The bonding between particles, its adhesion strength and porosity is affected by many parameters, such as the chamber temperature, drug to polymer ratio, laser speed, particle size for the drug and the polymer, among others.

As one can see, as a whole, increasing the chamber temperature closer to Kollidon VA 64's melting point of 145 °C (SDS No. 30239644), generally yielded less mass loss regardless of the drug to polymer ratio, the 70% Kollidon VA 64 specimen being the exception for the 100 °C and 110 °C trials. A possible explanation for this exception is that the drug, polymer and sheen combination behaved differently at 110 °C such that the material property combinations at this temperature had an effect. For instance, if the mixture combination yielded a high composite thermal conductivity at a condition, then higher amounts of particle fusion may have occurred, resulting in potentially different hardness and inter-particle adhesion. However, higher hardness could result in brittleness [11], and consequently higher mass loss in friability tests. Further

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investigation is needed to confirm this claim. Overall, where the chamber temperature was higher, the laser was required to do less work (input of heat energy) to bring the powder mixture up to Kollidon's melting point [8].

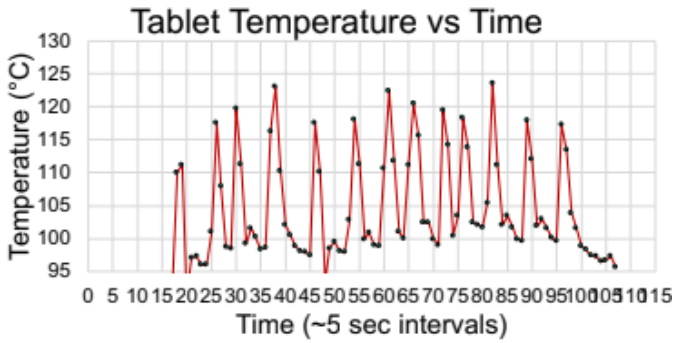

FIGURE 10: SURFACE TEMPERATURE OF POWDER PRINT BED OVER TIME

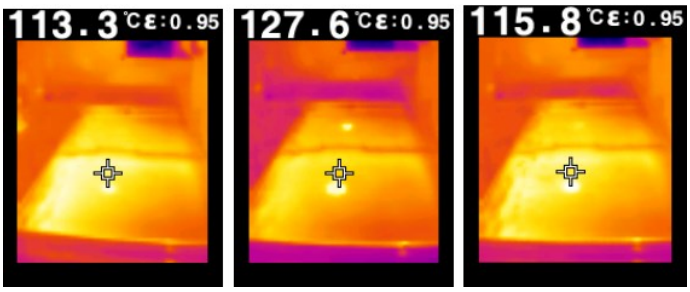

FIGURE 11: SURFACE THERMAL CAPTURES DURING A PRINT SEQUENCE OF BEFORE, DURING, AND AFTER LASER SINTERING OF A POWDER LAYER

FIGURE 12: COMPLETED PRINTLET OD 10 MM DIAMETER, 3 MM HEIGHT

Therefore, the higher the chamber temperature, the longer the Kollidon stayed in a molten state, allowing for better fusion between layers [15]. Being an exploratory phase, these tests were conducted once under each condition, and a study that evaluates variability is under way. Further, this future study will examine how the drug performed after printing from a pharmacokinetic standpoint as well.

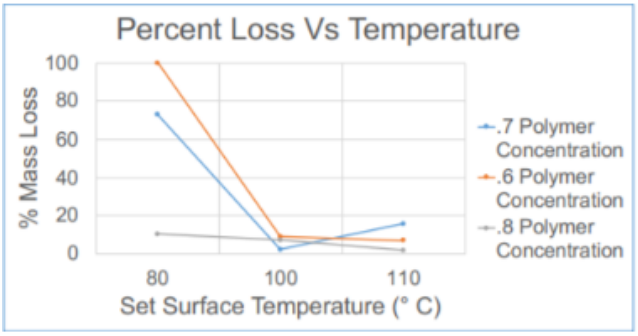

FIGURE 13: PRINTLET MASS LOSS VS. SURFACE TEMPERATURE

4. CONCLUSIONS AND FUTURE WORK

Additive manufacturing, specifically Selective Laser Sintering, is a process that was explored to be able to quickly customize medication, while still maintaining required tablet strength and other requirements. The printer chamber temperature and laser speed each contribute to the overall temperature of the printlet mixture, and this overall temperature significantly influences tablet weight, strength and hardness, disintegration time, and dissolution amount. The data from JMP and Excel shows that changes in temperature are significant factors that must be considered if the desired weight, hardness/strength, disintegration time, and dissolution rate is to be attained. Additionally, the lactose concentration appeared to be a significant factor, influencing how the temperature changes affected the results. Through the thermal monitoring of the surface via an IR camera, the maximum surface temperature rise for each layer was reliably captured. Further, the observed surface temperature was found to have a strong correlation with mechanical stability (friability), especially for temperatures above the melting point.

Future work from this research includes investigating how much of the final printlet is lactose, as compared to the known values in the powders before printing. This investigation could explain the variability in the differing lactose amounts on experiment 1. Also, further research could go into investigating why the 70% Kollidon VA64 specimen had a different mass loss trend than the other two specimens.

ACKNOWLEDGEMENTS

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