Improving the Strength of Binder Jetted Pharmaceutical Tablets Through Tailored Polymeric Binders and Powders

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(ABSTRACT)

Additive Manufacturing (AM) provides a unique opportunity for fabrication of personalized medicine, where each oral dosage could be tailored to satisfy specific needs of each individual patient. Binder jetting, an easily scalable AM technique that is capable of processing the powdered raw material used by tablet manufacturers, is an attractive means for producing individualized pharmaceutical tablets. However, due to the low density of the printed specimens and incompatible binder-powder combination, tablets fabricated by this AM technology suffer from poor strength. The research is introducing an additional composition in the binder jetting powder bed (e.g., powdered sugar) could significantly enhance the compressive strength of the as-fabricated tablets, as compared with those tablets fabricated without the additional powder binding agent. However, no previous research demonstrated comprehensive approaches to enhance the poor performance of the 3D printed tablets. Therefore, the goal of this work is to identify processing techniques for improving the strength of binder jetted tablets, including the use of (i) novel jettable polymeric binders (e.g., 4-arm star polyvinylpyrrolidone (PVP), DI water, and different

weight percentage of sorbitol binder) and (ii) introducing an additional powder binding agent into the powder bed (e.g.., different wt% of powdered sugar).

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(GENERAL AUDIENCE ABSTRACT)

Three-dimensional printing is well-known as 3D printing. 3D printing pills are printed from the 3D printer. As of today, we now stand on the brink of a fourth industrial revolution. By the remarkable technological advancements of the twenty-first century, manufacturing is now becoming digitized. Instead of using a large batch process as traditional, customized printlets with a tailored dose, shape, size, and release characteristics could be produced on-demand. The goal of developing pharmaceutical printing is to reduce the cost of labor, shorten the time of manufacturing, and tailor the pills for patients. And have the potential to cause a paradigm shift in medicine design, manufacture, and use. This paper aims to discuss the current and future potential applications of 3D printing in healthcare and, ultimately, the power of 3D printing in pharmaceuticals.

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1. INTRODUCTION

1.1 AM Work of Personalized Medicine

Precision medication, an emerging medical field, is concerned with adjusting precaution and treatment strategies based upon the unique physiology, biochemistry, lifestyles, and genetics of individual patients [1]. Precision medication aims to provide patients with tailored treatments to match their pathophysiology. Since different patient groups (i.e., newborns, children, adolescents, adults, and the elderly) need different drug dosage schemes, precision medication or personalized drug treatment has garnered notable research interest as it can increase the compliance of patients and help solve challenges in the efficacy and success of medical treatments [2]. However, to realize the promised benefits of personalized medicine, new fabrication approaches are needed that enable producing tablets with tailored (multiple) compositions and concentrations.

As such, achieving the goal of personalized medicine requires a paradigm shift in the current fabrication processes employed to make oral drug forms. In this area of pharmaceuticals applications, Additive Manufacturing (AM) processes, also known as 3D printing, have the ability to selectively deposit/fuse (multiple) materials, which can be leveraged to fabricate customized medicine to satisfy each patient's specific requirements based upon precision medication principles. AM, is a process of joining materials layer by layer to make 3D objects from digital model data [1].

Compared to traditional/subtractive manufacturing, AM technologies have competitive advantages such as on-demand fabrication of customized complex products, reducing time between product iterations, and significant reduction of the waste of production. As it can

directly produce multiple, different products without the need for separate tooling, Additive Manufacturing processes can enable scientists to quickly evaluate different designs and dosages to accelerate their path through clinical trial studies and thus accelerate the drug development and process. The operation of AM systems does not require complicated and intricate training for medical staff, which reduces the overall production cost and working space required for equipment installation and part production, and could therefore enable on-site production of tablets with tailored dosage [6]. In addition to tailoring dosage, the shape and appearance of the pills can be tailored to the individual. For example, the drug dispensing identification number, date, the name of the patient, and additional necessary information can be printed onto/into the pill via AM [7]. AM enables the precise control of the spatial distribution of multiple excipients that feature different diffusion rates to control overall drug release kinetics [5]. These advantages would create opportunities for improving the safety, efficacy, and accessibility of medicines [7].

1.2 Prior Art in Additive Manufacturing of Pharmaceuticals

Modern AM techniques are classified in seven categories: Vat Photopolymerization, Binder Jetting, Directed Energy Deposition, Material Extrusion, Material Jetting, Powder Bed Fusion, and Sheet Lamination. Due to its production flexibility and ability to make multiple, unique parts in a single production batch, many of these modalities have been explored as a means for producing personalized pharmaceutical tablets in prior research. However, there are limitations in tailoring AM processes/materials for pharmaceutical applications, which limits its widespread adoption. Synthesizing these previous studies, the overarching key challenges in pharmaceutical AM include:

(i) printing large and challenging structures,

(ii) reducing printing defects, and

(iii) enhancing the mechanical properties of the printed pills.

In the following subsections, a summary of prior efforts in the area of the pharmaceutical AM is provided and organized by AM modality.

1.2.1 Material Extrusion

The most common method of AM is fused filament fabrication (FFF), which is also known as fused deposition modeling (FDM) [1]. In the FFF method, a continuous filament of a thermoplastic polymer is selectively extruded to deposit layers of a material. The filament is heated at the nozzle to reach the semi-liquid state, and then selectively extruded. For pharmaceutical FFF, a thermoplastic filament, with embedded active drug compositions, is used. The thermoplastic polymer filament presents a critical property for this method, which allows the filaments to fuse together during printing and solidify at room temperature after printing. The advantages of the FFF for pill fabrication include (i) lower costs relative to other AM processes, (ii) ability to print tablets with various geometry and structures, and (iii) capability to create porous structures with tailorable mechanical strength [8]. These characteristics make this process an appropriate technique for manufacturing personalized tablets.

The pharmaceutical AM concept of extruding a polymer containing an active drug was first introduced by Khaled at al. in 2014 [9]. The authors printed two-layer tablets with active guaifenesin, an expectorant used to reduce congestion in the chest. The tablets contained an immediate release compartment consisting of HPMC 2910 as binder agent, and

microcrystalline cellulose and sodium starch glycolate as disintegration. The other portion of the pill included a supported discharge area composed of HPMC 2208 and poly (acrylic corrosive) as a hydrophilic grid. These materials were prepared independently and combined by two viscous pastes, which were then used as feedstock materials for the printing process. FFF has also been utilized to fabricate hollow capsular devices for drug incorporation. Melocchi et al. made hydroxypropyl cellulose fibers and showed the plausibility of the FFF for the reason by contrasting the item acquired with cases fabricated by infusion forming [10].

Despite the advantages this process can offer for pharmaceutical applications, there are serious challenges including limited choices of thermoplastic materials available for the FFF, and the degradation of incorporated drugs caused by the exposure of active ingredients to high temperatures during printing. Furthermore, using the FFF method for pharmaceutical printing of complex geometry would require support structures that need to be removed by some post-processing treatments. These disadvantages often limit the use of the material extrusion method for tablet printing.

1.2.2 Material Jetting Additive Manufacturing

Material jetting AM is a non-contact approach that enables processing of 1-100pl droplets of liquid into two-dimensional and three-dimensional structures [11, 12]. This method is also referred to as a 'mask-less' or 'tool-less' approach since either the movement of an inkjet nozzle or the movement of a substrate enables accurate and reproducible formation of the desired structure [13]. Drops ejected from a micrometer-scale nozzle are commonly generated by either (a) heating of a liquid material to a temperature higher than its boiling

temperature (i.e., thermal jetting) or (b) application of a voltage to a piezoelectric transducer (i.e., piezoelectric jetting), which forces the material extruded out of the nozzle [12] . Advantages of inkjet printing include low processing costs, rapid fabrication rates, minimal waste, scalability, and the ability to process material with minimal contamination [11, 13, 14].

Material jetting AM has also been examined for the pharmaceutical printing in the prior literature. In 2013, Hsu et al. produced drug-polymer films on chitosan and hydroxypropyl methylcellulose substrates through material jetting of solid dispersions containing the polymer polyvinylpyrrolidone and the pharmacologic agent naproxen [15]. Microneedles are small-scale lancet-shaped structures that may be utilized for transdermal delivery of pharmacologic agents and vaccines as well as for transdermal biosensing [16-20]. Many inherent advantages over the drug delivery technologies such as controlled release systems, chewable compressive strength, and multiphase release dosage forms.

1.2.3 Vat Photopolymerization

Vat Photopolymerization (VP), also known as stereolithography (SLA), is the first AM technology applied in medicine for fabrication of a surgical model utilized for alloplastic implant surgery in 1994 [1,3,21]. The manufacturing of 3D objects by VP is based on the spatial control of ultraviolet (UV) light curing of liquid resins through photopolymerization reaction. The pattern of the sliced part is illuminated on the surface of the resin using a computer-controlled laser beam or a digital light projector with a computer driven platform. As a result, the resin in the illuminated areas solidifies to a defined depth, allowing it to adhere to the support platform. After photopolymerization of the first layer, the platform is

moved away from the surface and is recoated with a liquid resin for the next curing process. The whole process repeats until the part geometry is fabricated.

Hydrogels are the common material used in drug delivery applications of vat photopolymerization [17]. Although VP can produce a wide variety of shapes, the resin cost for this process is often expensive, and the cytotoxic nature of most photoinitiators and resins severely limits the further application of the technique.

1.2.4 Binder Jetting

Binder jetting is a powder based additive manufacturing process in which powder feedstock materials are bonded via a liquid binder selectivity deposited by an inkjet printhead to fabricate the part geometry. The printed green parts are then often subjected to thermal post processing to increase part strength and (possibly) densify [21]. Compared to the traditional pharmaceutical processes, as well as other AM technologies, binder jetting method offers unique opportunities to create highly intricate and complex tablet formulations through modifying the powder materials and binders. Binder jetting (BJ) can process a wide range of materials including metals, ceramics, and polymer [22-25]. Many different binders have been utilized in binder jetting, including various solvents, colloids, and polymers [26]. In most of the previous studies, the binder solution, deposited to bond the powder particles together, acts as a solvent for the powder in which the powder is dissolved upon contact with the binder [26, 27]. After binder deposition, the binder-powder mixture may then dry to form a solid part, or the saturated areas may react to cause localized polymerization causing particle bonding, and thus part formation.

One of the major advantages of utilizing binder jet technology for pill printing is its ability to produce highly porous and fast dissolving tablets with high drug loadings [28]. In BJ, the powder bed plays a role of physical support for the printed parts, eliminating the requirement of brackets or rafts, which further enables advanced tablet design and structure production not feasible via other fabrication processes. Moreover, precise control of the tablet composition distribution is also achievable by mixing functional nanoparticles with the binder. The combined use of a powder bed and jetting-based deposition enables the BJ process to be scaled quickly as the powder provides support for printing unique tablets throughout the entire build volume without needing secondary supports and additional jetting nozzles can be added to the system to reduce the number of printing passes required per layer.

However, within BJ technology, various fabrication parameters affect the printed part quality including powder material characteristics, droplet size of the binder solution, binder viscosity, the concentration of the binder solutions, and the thickness of each powder layer [29].In the context of binder jetting pharmaceutical printing, variety of powders including soluble polymers, plastics and starches and different binders such as chloroform, water, and solvents have been investigated for pill printing. Wilts et al. investigated the effect of the powder composition. They added 5wt% silica of the lactose powder and 20wt% powdered sugar as a flow modifier to improve spreadability [30].

In 2015, a modified binder jet printing process was used to manufacture the first FDA-approved 3D printed tablet, Spritam R (levetiracetam), by Aprecia Pharmaceuticals [31], for the treatment of the epileptic seizures [7]. Spretam is an oral suspension that rapidly

dissolves when exposed to a small amount of liquid. The use of Spritam shows the potential of individualized medication to improve chronic disease management [5].

The tablets fabricated by this technology suffer from high structural porosity, which is attributed to the low packing density of powder beds in BJ process [32] . Although the high porosity may increase the pill dissolving rate, it constrains mechanical strength of the products. Due to the poor mechanical strength and fragility of the binder jetting pills, they are not currently suitable for pill handling or packaging processes [33].

1.3 Research Objectives/Questions

The main objective of this research is to investigate the effects of different material selection of the powder binder pair on tablet strength of 3D printable pills with various geometries, while maintaining sufficient compression strength and desired dissolution rate. In this study, we conducted a comprehensive investigation on the compression strength of the BJ printed pills with tailored dissolution rates with different binder-powder material pairs. Moreover, through modifications of the binder and powder material system, we studied and optimized the composition of the solutions to improve the pill mechanical properties. Figure 1 illustrates the schematic of the binder jetting process studied in the study, including all the materials systems (i.e., binders and powders).

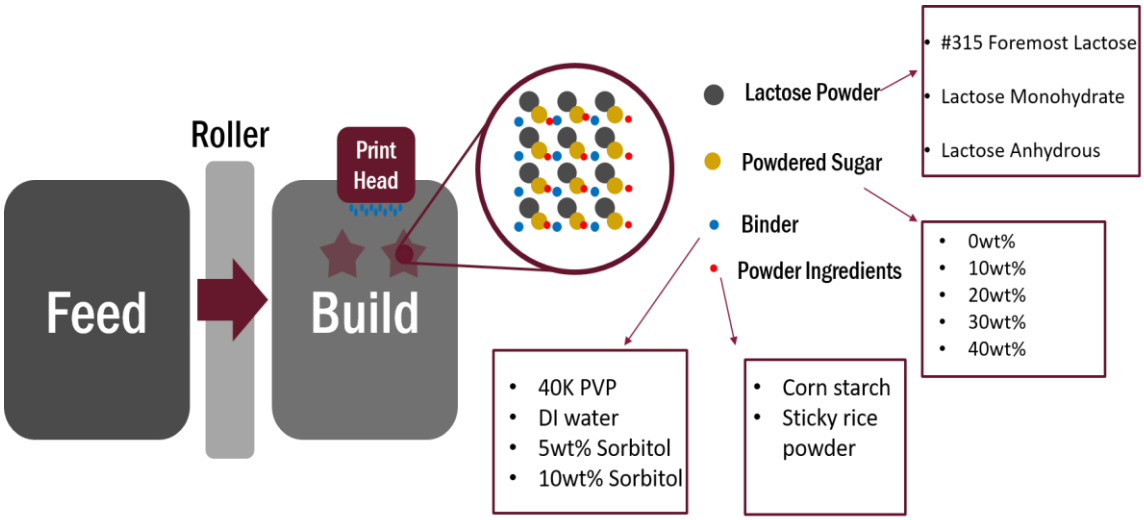


Figure 1. Illustration of binder jetting process with all the material systems explored

The specific objectives of the current research are as follows:

(i) to investigate the effect of type and concentration of powdered binding agent on the strength and dissolution rate of the printed tablet,

(ii) to explore the effect of lactose powder/binder on strength, and

(iii) to study the effect of power ingredients composing the powder bed on the strength and dissolution.

In Chapter 2, the experimental methods are presented, including material preparation (Section 2.1), fabrication process parameters (Section 2.2), and analytical characterization (Section 2.3). The evaluation of the as-fabricated parts is presented in Section 3. In Section 4, the results of printed tablets' dissolution rate and compressive strength are analyzed. Summary and proposed future work are presented in Section 5.

2. Experimental Procedures

The overall goal of this work is to explore the effects of a variety of binder and powdered materials on printed tablet compressive strength and dissolution rate. As early experiments demonstrated that printed polymeric / food-safe binders did not result in tablets with sufficient compressive strength, it was decided to explore the impact of a variety of powdered 'binding agents' that could be incorporated with the excipient powder in the powder bed. Section 2.1 describes the materials used in this work, including excipients (e.g., lactose powder) and binding powders (e.g., powdered sugar, corn starch, sticky rice powder) and liquid binders. BJ printing parameters and specimen fabrication processes are described in Section 2.2. The characterization methods used to analyze the resultant printed pills are described in Section 2.3.

2.1 Materials

2.1.1 Powders

Three different lactose powders were selected for this study to determine their effect on the final part strength and dissolution. The Lactose powders (#315 Foremost Lactose, NF lactose monohydrate impalpable 312 powder, and Lactose anhydrous NF IMP) were provided by Zoetis, the industrial sponsor of this study. The characteristics of these lactose powder are shown as follows:

1. *315 Foremost Lactose*: #315 Foremost Lactose is a white, crystalline powder used primarily for direct compression tablets and in capsule filling. It is a product composed of a spray-dried mixture of crystalline and amorphous Lactose Monohydrate. This

pharmaceutical grade product is currently used in infant formulas and nutritional supplements, capsules, tablets, and powders.

2. *NF lactose monohydrate impalpable 312 powder*: Foremost NF Lactose, Product Code 312 is a crystalline, 200 mesh size, impalpable lactose monohydrate. This pharmaceutical grade product finds its use in infant formulas and nutritional supplements, capsules, and tablets. The NF lactose monohydrate impalpable 312 powder is white to cream colored powder. It is used in direct compression of tablets (tablet binder).

3. *Lactose anhydrous NF IMP*: This powder is used as a tablet diluent in the pharmaceutical industry.

All the lactose powders were dried at 60° C under vacuum for 24 h and sifted to break up aggregates before further processing.

A central hypothesis of this research is that combining the excipient (lactose) powders with a powdered binding agent will increase the strength of the printed pills. Multiple powdered binding agents were evaluated to determine their affect on printed tablet strength:

1. *Powdered sugar*: Powdered sugar has a mean particle size of 5-30 μm, which is acquired by grinding sugar into fine powder. It usually comes with a small quantity of anticaking agents to prevent caking and improve liquidity. Powdered sugar is a safe ingredient often used in industrial food production when it is needed to dissolve sugar quickly. Although adding powdered sugar into the powder bed can increase the pills'

strength because of the physical interaction between the binding base and powdered sugar, powdered sugar can also increase the chance of diabetic illness and different types of cancer, such as the esophagus, small intestine, colon and breast cancers. To study the effect of the binding powders on pill strength, four different powdered sugar concentrations (i.e., 0wt%, 10wt%, 20wt%, 30wt%, and 40wt%) were examined among all three excipient powders.

2. *Corn starch:* Corn starch is a common food ingredient. It is widely used, easy to modify, and has many industrial applications such as in adhesives, paper products and textile manufacturing [34]. This powder is also used as a glucose source for patients with glycogen storage disease in the medical field [35]. Corn starch is a carbohydrate, gluten free powder substance with small particle size that can fill into the pores of the lactose powder to increase the powder packing density and potentially the strength of the pills.

3. *Sticky rice powder:* Sticky rice powder contains a very low amount of amylose that becomes very sticky when it cooks. It is viewed as a safe food ingredient in many recipes, and is grounded from stick rice into the powder.

The powder ingredients were placed in a cylindrical container and mixed on a Waverly TR-E roller for 20 to 45 min. After mixing, the powders were placed in a ZCorp Spectrum Z510 BJ printer for pill fabrication.

2.1.2 Liquid Binders

To explore the effect of liquid binder on the printed tablets' strength, three different binders were evaluated:

1. *Deionized water*: Deionized water, commonly known as DI, DIW or deionized water , is the water in which almost all mineral ions such as sodium, calcium, iron, copper, chlorides and sulfates have been removed. Deionization is a chemical process that uses specially manufactured ion exchange resins to exchange hydrogen and hydroxide ions into dissolved minerals and then combine to form water.
2. *4-arm star polyvinylpyrrolidone (40K PVP)*: 4-arm star polyvinylpyrrolidone (40K PVP) s a most common polymeric binder in aqueous binders used in binder jetting AM due to its biocompatibility, water-solubility, and high glass transition temperature [36, 37].
3. *Sorbitol*: Sorbitol is a sugar alcohol with a sweet taste which is slowly metabolized in the human body. Most sorbitol is commonly made from corn syrup, and can also be found in nature, for example in apples, pears, and peaches [32].

The preparation of the binder starts with the dissolving of the 40K PVP and sorbitol binders into DI water at various concentrations (5wt% 40K PVP, and 5wt% and 10wt% sorbitol) by stirring with a magnetic stir bar at 350 R.P.M. for 10-15 min until the polymer was fully dissolved. To adjust the surface tension of the mixtures, 1wt% Tween 20 [38], a nonionic detergent widely used in biochemical applications, was added to the binder compositions and stirred for an additional 30 minutes. The binder was then delivered to mixing, to dissipated air bubbles, and filtered through a 2.2 μm filter. The filtered binders

were then used either immediately, or kept in cold storage for no greater than 24 hours before jetting.

2.2 Specimen Fabrication via Binder Jetting

2.2.1 Binder Jetting and Printhead Preparation

All printing trials were conducted on a ZCorp Spectrum Z510, which features HP11 C4810A printheads. This printhead has nozzles of 11μm in diameter, and operates via thermal jetting technology in the temperature range between 5 to 40° C [38] . Before using the custom binders, the printheads' remaining ink was cleaned from the printhead by soaking in hot water for at least 8 hours. The printheads would often clog after 20 trials during experimentation, as such they were frequently cleaned by soaking them in ethanol to dissolve the dried binder.

2.2.2 Printing Parameters

Experimental specimens were designed to mimic cylindrical pharmaceutical tablets with a dimension of 12 mm diameter and 5 mm height. The resulting .STL file was imported to the Z-Corporation print software, and the layer thickness was set as 0.127 mm. The specimens were printed with 100% saturation level (due to the Z-Corp printer limitation) at shell and 100% saturation level at the core with bleed composition model for all evaluated powder and binder combinations.

For each printing trial, 15 pills were printed along the fast (traverse) axis of the print head. After printing, the parts were kept in the powder-bed for 40 min at 60° C to allow the binder to dry/cure. They were then removed from the printer and placed into the vacuum

oven (Isotemp Vacuum Oven model 282A, Fisher Scientific) for further drying at 40° C across different time spans. To evaluate the effect of drying time on part strength, we examined three different drying times (4 hours, 24 hours, and 48 hours).

2.2.3 Powder and Binder Combinations

Table 1 presents a summary of the combinations of excipient powders, binding powders, and liquid binders explored to identify their impact on printed tablet strength and dissolution rate.

Table 1: wt% of powdered sugar concentration level with each type of binder combination

BINDERS(100% SARYRATION RATIO USED)	WT% OF ADD POWDER SUGAR
DI WATER	0%, 10%, 20%, 30%, 40%
5 WT% 40k PVP	0%, 10%, 20%, 30%, 40%
5 WT% SORBITOL	0%, 10%, 20%, 30%, 40%
10 WT% SORBITOL	0%, 10%, 20%, 30%, 40%

Lactose Powders: #315 Foremost Lactose, NF lactose monohydrate impalpable 312 powder, and Lactose anhydrous NF IMP

2.3 Materials and Printed Part Characterization Techniques

2.3.1 Powder Particle Size Analysis

Powder particle size distribution affects the layer recoating quality in the binder jetting process, as well as the drug release rate in the printed pills [39]. Fine powders result in pills with rapid drug release owing to their higher surface area; however, the poor flowability presents a challenge in the layer recoating of the fine particles. In contrast, coarse particles

are desired for smooth layer recoating in binder jetting processes, while it leads to tablets with slow drug release rate. Hence, it is important to quantify the powder particle size distribution to ensure the powder printability as well as drug delivery efficiency.

In general, there are several approaches to evaluate powder particle size: (i) dynamic light scattering, (ii) scanning electron microscopy, (iii) transmission electron microscope, and (v) atomic force microscopy. Transmission electron microscope (TEM) was chosen to characterize the powder particle size and shape. The lactose powders were dissolved in the ethanol (since lactose powder has lower solubility in alcohol), and characterized using a ZEISS microscope.

2.3.2 Characterization of Printed Tablet

One of the key metrics for evaluation of the traditionally manufactured tablets is compression testing, and the target compression strength for these pills is above 5 kp (kilopond, or kilogram-force, equal to 9.8 N), provided by industrial collaborator Zoetis. Following printing, the pills' compression strength was evaluated via a Instron 5944, based on ASTM standard. Compression testing was conducted at 1.3 mm/min strain rate with a 2 kN load cell.

2.3.3 Evaluation of Dissolution Rate

In the pharmaceutical industry, drug dissolution rate is a valuable metric as it provides key insight into both quality control (i.e., pill quality consistency over different batches) and also the drug release rate curve *in vivo* [40]. There are three typical situations where dissolution testing plays a vital role in: (i) helping the product formulation and optimization; (ii) determining the equivalence between the reference product and its generic or modified

products for regulatory approval decisions; (iii) guiding the product release decisions during routine manufacturing [41-43].

The dissolution evaluation can be accomplished either by partially immersing the tablets in a water bath solution or by heating them in a dry container. In this work, the printed pills were delivered to a water bath (glass beaker containing 40mL of DI water), and a digital camera was used to record real time imaging of the tablet's dissolution. Subsequent video analysis provided the total time for the pill dissolution, from the time the pill starts to dissolve until it fully dissolves in the water.

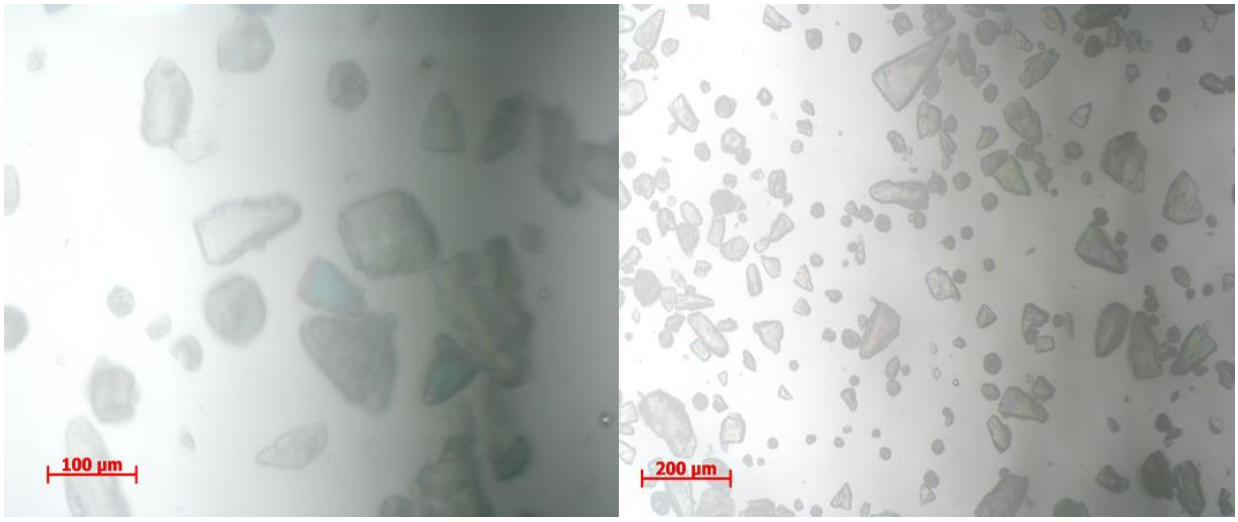
3. Results and Discussion

3.1 Powder particle size

To investigate the correlation between powder size and compression strength, the particle size of the excipient powders used in the experiments was first analyzed via optical microscopy (OM).

3.1.1 #315 Foremost Lactose

Figure 3 illustrates OM images of #315 Foremost Lactose powder under different magnification scales. As shown in the figure, the #315 Foremost lactose particles are crystalline powder with irregular shape, and the size of the powder particles ranges from 75μm to 135μm.

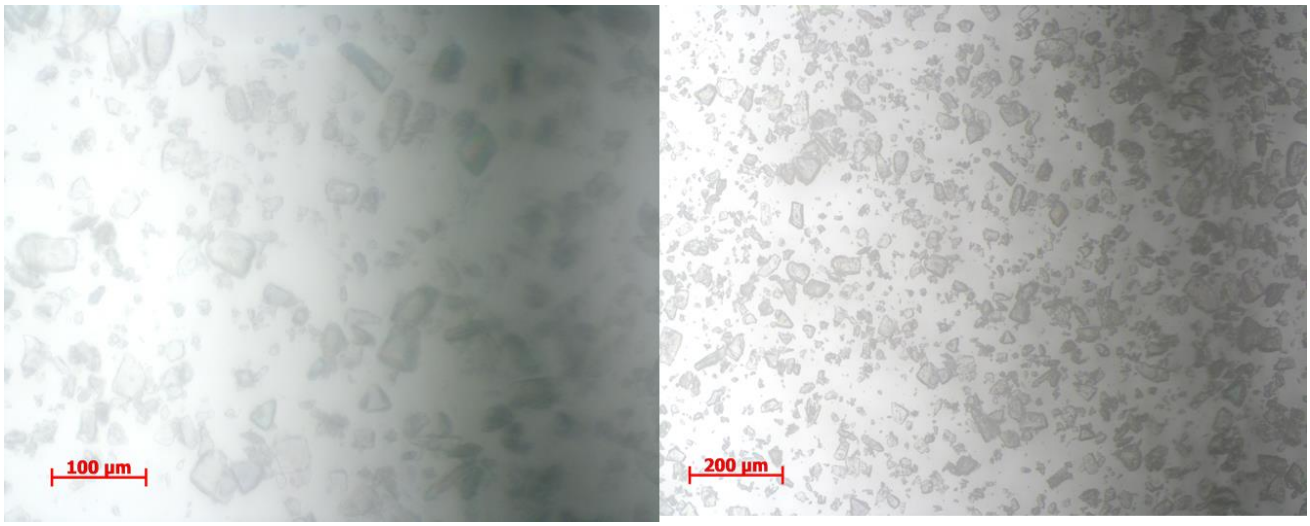


(a) (b)

Figure 3: (a) #315 Foremost Lactose powder under 100μm(b) #315 Foremost Lactose powder under200μm

3.1.2 NF lactose monohydrate impalpable 312 powder

Figure 4 presents the NF lactose monohydrate impalpable 312 powder particles at different magnifications. The NF lactose monohydrate impalpable 312 powder particles are crystalline powder with irregular shapes. The powder particle size ranges from 15µm to 106µm

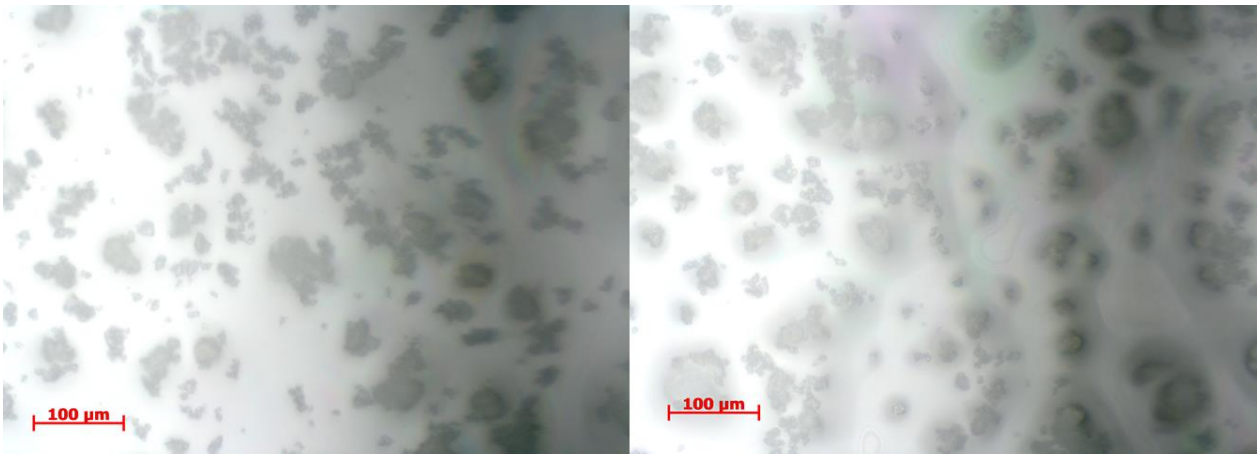


(a) (b)

Figure 4: (a) NF lactose monohydrate impalpable 312 powder under 100 µm,(b) NF lactose monohydrate impalpable 312 powder under higher magnification at 200µm

3.1.3 Lactose anhydrous NF IMP

Figure 5 shows the microscopy images of Lactose anhydrous NF IMP powder at the same magnification but different angles of the lactose powder. The powder particle shapes are irregular with particle sizes ranging from 15µm to 75µm.



(a) (b)

Figure 5: (a) Lactose anhydrous NF IMP under 100 µm (b) Lactose anhydrous NF IMP under 100 µm at different angle

3.2 Powdered and liquid binder effect on the compressive strength of the printed tablets

3.2.1. Binder effect on the strength of the pills printed with different powder materials

3.2.1.1 #315 Foremost Lactose powder

Figure 6 presents the compressive strength of the pills printed with #315 Foremost Lactose powder mixed with different concentrations of the powdered sugar (i.e., 0%, 10%, 20%, 30%, and 40%). The liquid binder was selected from: DI water, 40K PVP, 5wt% sorbitol, and 10wt% sorbitol. At least five tablets were printed for each set of these experiments.

Eliminating the powdered binder (i.e., 0wt% powdered sugar) results in the lowest strength of the printed pills as compared to the other pills. This observation is explicit since the powder binder directly affects the binding strength of the fabricated samples. The measured values of the strength are: 1.03 ± 0.21 Kp, 1.5 ± 0.51 Kp, 1.3 ± 0.42 Kp , and 1.7 ±

0.1 Kp (10wt% sorbitol) printed via DI water, 40K PVP, 5wt% sorbitol, 10wt% sorbitol, respectively. On the other hand, a 40wt% sugar concentration yielded strongest printed pills; the corresponding featuring compressive strengths are 11.88 ± 0.11 Kp (DI water), 18.61± 0.7 Kp (40K PVP), 14.35 ± 0.18 Kp (5wt% sorbitol), and 16.24 ± 0.2 Kp (10wt% sorbitol), respectively.

Based on the results, adding 10wt% sugar to the #315 Lactose powder seems to provide the desired strength (i.e., >5kp) when printing with 40KPVP, 5wt% sorbitol, and 10wt% sorbitol. Meanwhile, 30wt% sugar is required to provide sufficient strength when printing with DI water. From the collected data, both powdered and liquid binders significantly affect the strength of the printed tables.

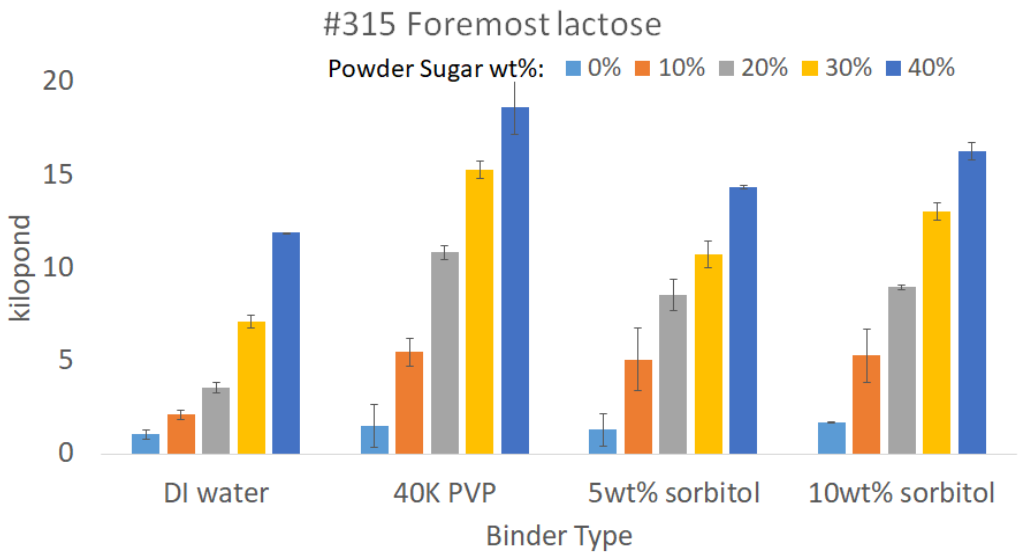


Figure 6. Compressive strength of pills printed with #315 Foremost Lactose and varying amount of % sugar powder using 40K PVP, DI water binder,5wt% sorbitol, and 10wt% sorbitol as liquid binder

3.2.1.2 NF lactose monohydrate impalpable 312 powder

Figure 7 presents the compressive strength of pills of NF lactose monohydrate impalpable 312 powder, when printed with 40K PVP, DI water, 5wt% sorbitol, and 10wt% sorbitol binders. As shown in Figure 7, increasing the concentration of the powder sugar yields the enhanced strength of the tablets printed with all types of liquid binder. This is attributed to the increased packing density as a result of the additional powder sugar in the printing feedstock. Fabrication of the tablet without the powdered binder leads to pill strength of 1.3 ± 0.21 kp (DI water), 0.7± 0.0.41 Kp (40K PVP), 1.2 ± 0.38 Kp (5wt% sorbitol), and 0.9 ± 0.64 Kp (10wt% sorbitol), which is significantly lower than the target compressive strength of 5 Kp. The 40 wt% sugar concentration results in the strongest printed pills, featuring 6.94 ± 0.21 Kp (40K PVP) and 5.56 ± 0.5 Kp (DI water) compressive strength.

According to the experiment measurement, a 10wt% sugar is sufficient to satisfy the strength requirement (>5kP) of the NF lactose monohydrate impalpable 312 powder with the 40KPVP liquid binder. Regarding general scenarios, a 20wt% sugar is required to provide sufficient strength when printing with all binders. Based on the previous results and analysis, it is concluded that (i) introducing an additional powder phase binding agent within the composite of the feedstock significantly improves the compressive strength of the printed tablet, and (ii) with 30wt% sugar concentration level, there is a negligible difference in the compressive strength for the tablet printed with the NF lactose monohydrate impalpable 312 powder, when the concentration of the liquid binder sorbitol are 5wt% and 10wt%.

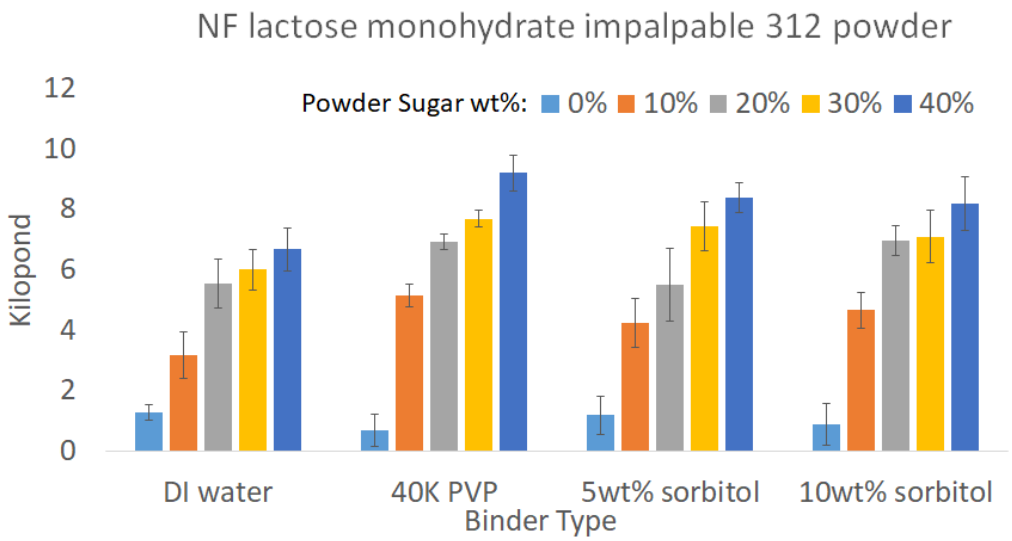


Figure 7. Compressive strength of printed NF lactose monohydrate impalpable 312 pills made via 40K PVP, DI water binder,5wt% sorbitol, and 10wt% sorbitol

3.2.1.3 Lactose anhydrous NF IMP powder

Figure 8 demonstrates the compressive strength of pills printed with various concentrations of sugar, for Lactose anhydrous NF IMP powder mixed with the liquid binder 40K PVP, DI water, 5wt% sorbitol, and 10wt% sorbitol binders. Similar to previous results for the NF lactose monohydrate impalpable 312 powder, increasing the concentration of the powder sugar yields increased strength of the tablets printed with the mixture of Lactose anhydrous NF IMP powder and the liquid binder. Fabrication of the simple mixture of Lactose anhydrous NF IMP powder and liquid binder yields the strength of 0.5 ± 0.21 Kp (DI water), 0.52 ± 0.21 Kp (40K PVP), 0.3 ± 0.15Kp (5wt% sorbitol), and 0.4 ± 0.13 Kp (10wt% sorbitol) respectively, which are one order of magnitude lower than the compressive strength target of 5kP. The 40wt% sugar concentration results in the strongest printed pills, featuring 2.69 ± 0.63 Kp (DI water), 3.36± 0.78 Kp (40K PVP), 2.91 ± 0.68 Kp (5wt% sorbitol),

and 3.01 ± 0.54 Kp (10wt% sorbitol) compressive strength. However, the highest 40wt% sugar could not provide sufficient strength (>5kP) with any binder type.

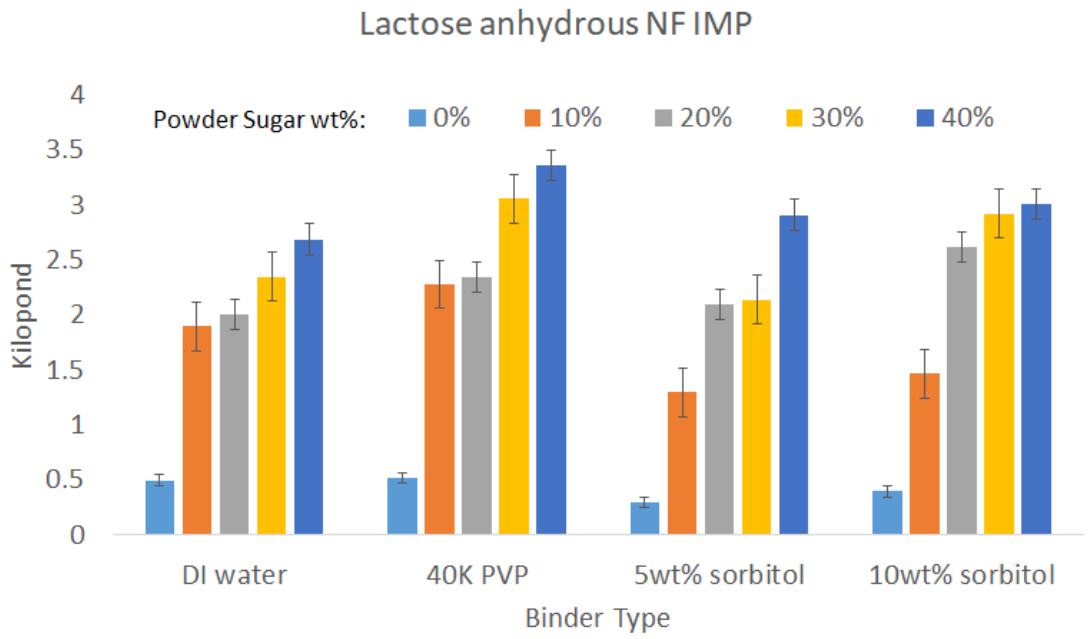


Figure 8. compression strength of printed Lactose anhydrous NF IMP pills made via 40K PVP, DI water binder,5wt% sorbitol, and 10wt% sorbitol

3.2.2 Powder effect on the strength of the pills printed using different liquid binders

3.2.2.1 40K PVP binder

The average compressive strengths of the pills printed with a mixture of 40K PVP binder and various combinations of lactose powder and solid phase binder (powder sugar) are shown in Figure 9. The Lactose anhydrous NF IMP powder resulted in the lowest strength pills used compared to the other two types of lactose powder for all concentration ranges of powdered sugar, while #315 Foremost lactose powder yields the highest compressive strength of the printed tablets. For all lactose powder materials.

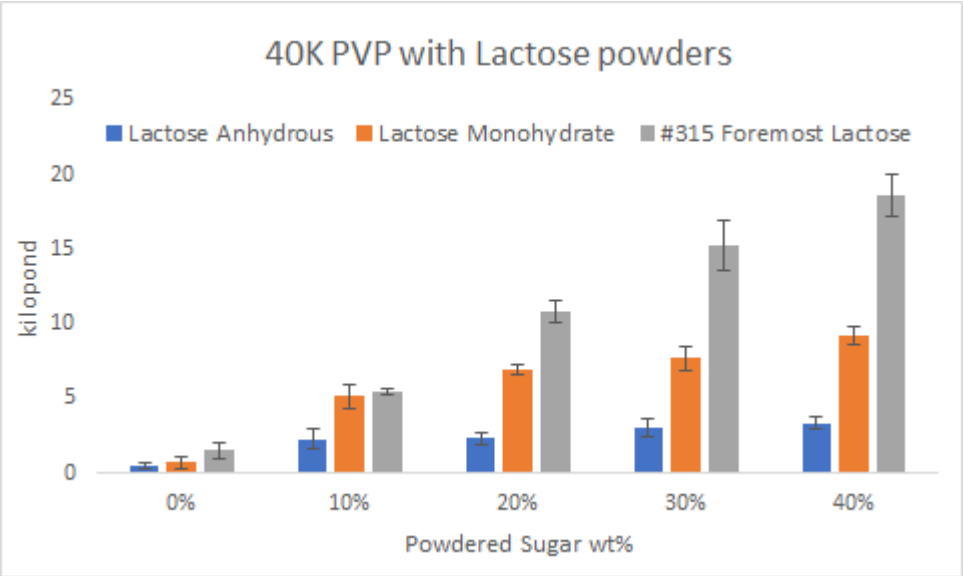


Figure 9, #315 Foremost lactose, NF lactose monohydrate impalpable 312 powder, and Lactose anhydrous NF IMP pills printed via 40K PVP binder and varying quantity of powdered sugar

3.2.2.2 DI water binder

Figure 10 presents the average compressive strength of the pills printed with a mixture of DI water binder and various combinations of lactose powder and solid phase binder (powder sugar). Similar to previous results, the lactose anhydrous NF IMP resulted in the pills with the lowest compressive strength compared to that fabricated with the other two lactose powders. However, when the sugar concentration levels are between 0wt% and 20wt%, the NF lactose monohydrate impalpable 312 powder outperformed the #315 Foremost lactose powder with DI water as the liquid binder.

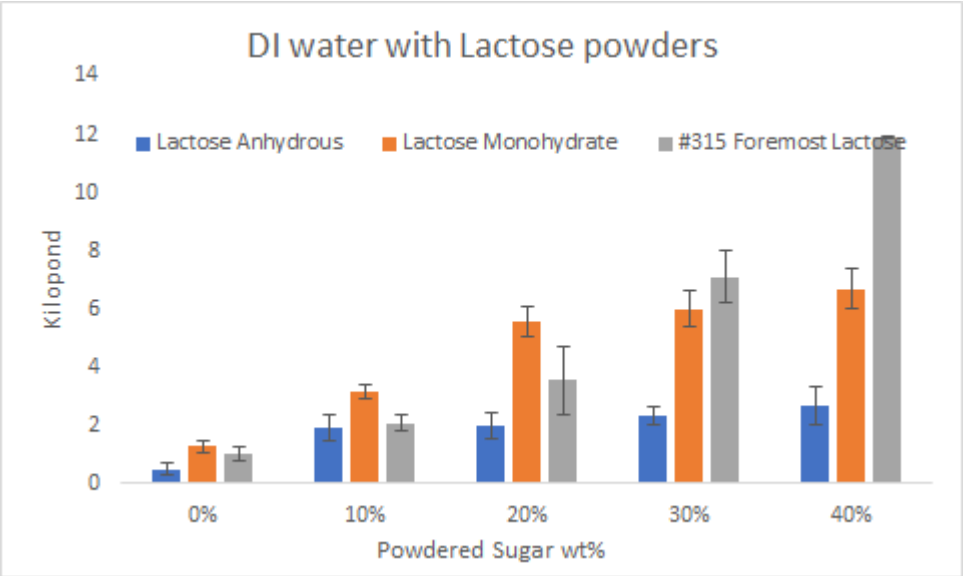


Figure 10, Compressive strength of pills printed with #315 Foremost lactose, NF lactose monohydrate impalpable 312 powder, and Lactose anhydrous NF IMP and DI water binder

3.2.2.3 5wt% sorbitol binder

The average compressive strength data for the pills printed with the mixture of 5wt% sorbitol binder, different concentrations of powdered sugar and all types of lactose powders is shown in Figure 11. From this figure it is clear that lactose anhydrous NF IMP powder containing 0% powder sugar printed with DI water presents lowest strength overall. For powdered sugar concentrations higher than 20 %, the pills printed with the #315 Foremost Lactose and NF lactose monohydrate impalpable 312 powder both satisfy the target compressive strength requirement of 5 kp for this study. Furthermore, the results indicate that increasing the power sugar concentration level significantly increases the strength of the printed pills, which is consistent with previous measurement results.

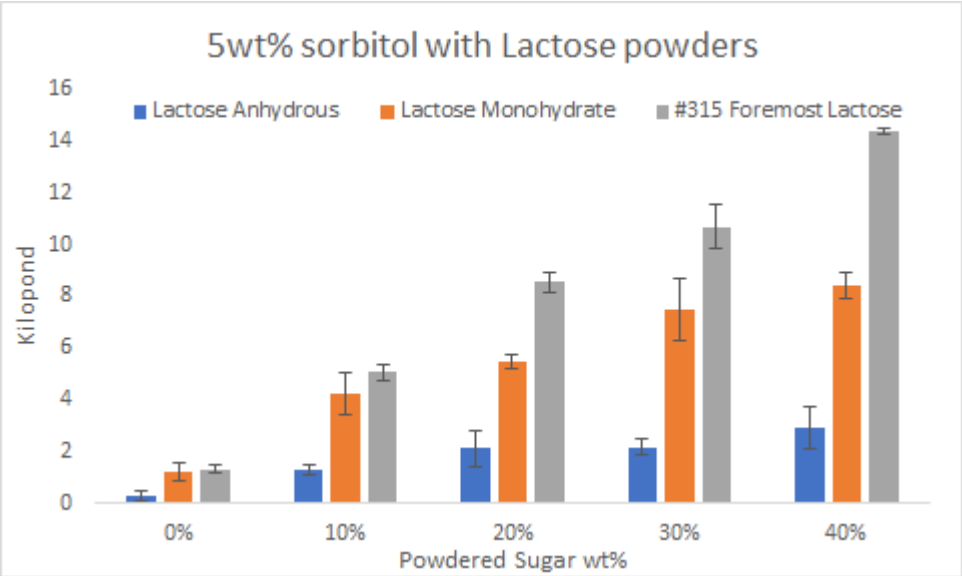


Figure 11, #315 The compressive strength of Foremost lactose, NF lactose monohydrate impalpable 312 powder, and Lactose anhydrous NF IMP pills made via 5wt% sorbitol binder

3.2.2.4 10wt% sorbitol binder

Figure. 12 shows overall compressive strength of pills printed with 10wt% sorbitol binder for all powder material configurations. As can be observed, increasing the concentration of the powder sugar enhances the compressive strength of the as-fabricated pills.

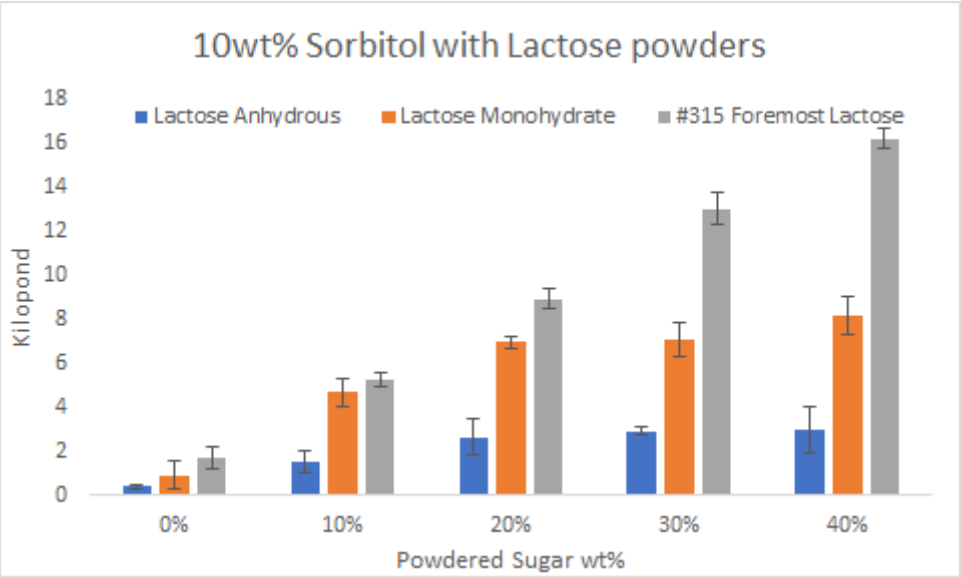


Figure 12, Compressive strength of *#315 Foremost lactose, NF lactose monohydrate impalpable 312 powder, and Lactose anhydrous NF IMP pills printed via 5wt% sorbitol binder*

3.2.3 The effect of different powder configurations and pill drying time on the compressive strength of the printed pill

3.2.3.1 The effect of corn starch and different drying times

Figure 13 illustrates the compressive strength of pills made via NF lactose monohydrate impalpable 312 powder mixed with 30wt% of corn starch and 20wt% powder sugar, along with different liquid binders (40K PVP and DI water) and different drying conditions. The drying conditions are: air-dry for 24hrs at room temperature, in a vacuum oven at 40 C for 4 hours, 24 hours, and 48 hours, respectively.

The compressive strength of the pills dried in air is 7.87 ± 0.61 Kp and 2.36 ± 0.29 Kp for 40K PVP and DI water binders, respectively. Although the air-dry condition results in comparatively higher compressive strengths for both binders, it should be noted that a portion of the liquid binding agent remains in the pill after air drying. Consequently, the pills dried in air do not exhibit brittle breaks under compressive stress (shown in the Figure. 14)

as opposed to the pills dried in the vacuum oven, which contributes to the higher strength of the air-dried pills.

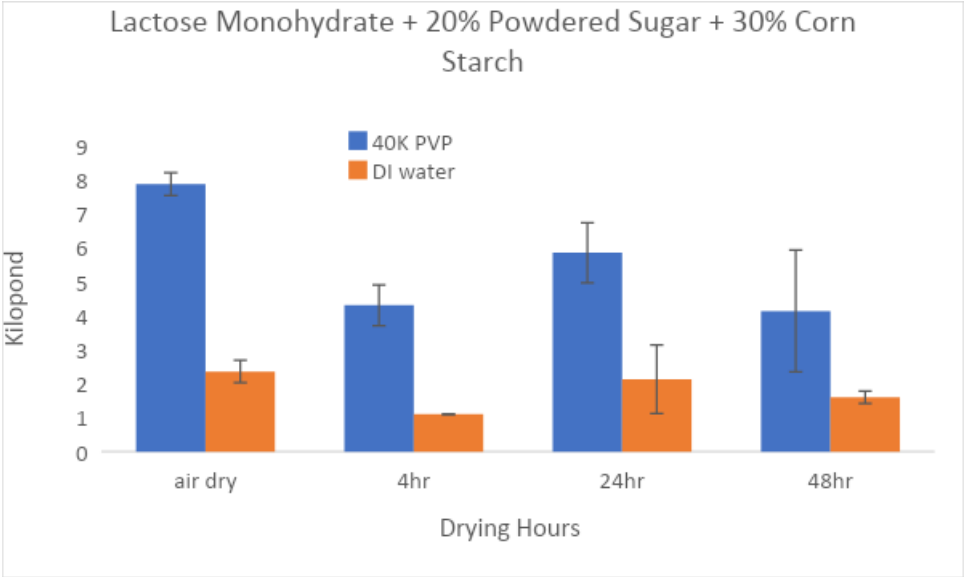


Figure 13, NF lactose monohydrate impalpable 312 powder combined with the 30wt% of corn starch and 20wt% of powdered sugar to printed with 40K PVP and DI water binder. Compression strength at different drying time

3.2.3.2 The effect of sticky rice powder and different drying times

The overall compressive strength data of the pilled printed with 40K PVP and DI water binders drying at different drying hours in vacuum oven (4hr, 24hr, and 48hr) are shown in Figure 14. From the figure, we observed that the strongest pills' compressive strength is 8.28

± 0.86 Kp (40K PVP) and 3.64 ± 0.31 Kp (DI water) with the dying condition of 24 hours in a vacuum oven. The pills printed with 40K PVP and dried in the vacuum oven for 24 hours are the combination of lactose, powdered sugar, and powder ingredients that yields the strongest compressive strength. Overall, pills printed with 40K PVP binder has higher compressive strength among all the drying times in the vacuum oven. Furthermore, further increasing the drying time in the vacuum oven has minimal effect on the compressive strength of the printed pills.

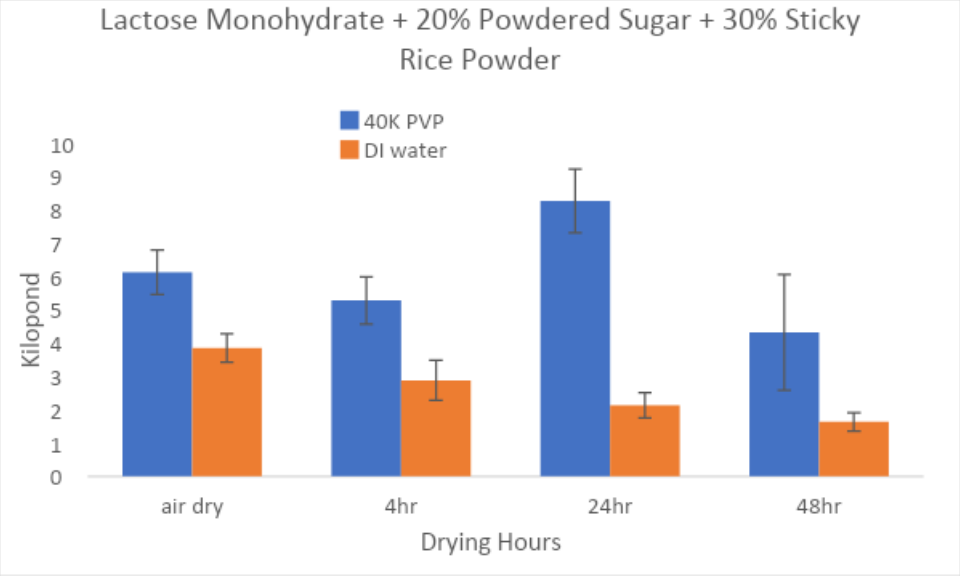


Figure 14, compressive strength of the pills printed with NF lactose monohydrate impalpable 312 powder combined with the 30wt% of sticky rice powder and 20wt% of powdered sugar and 40K PVP and DI water binders at different drying time

3.3 Summary

In summary, the #315 Foremost lactose powder printed with 40K PVP binder resulted in the tablets with the highest compressive strength. The 40K PVP presents biocompatibility, water-solubility, and high glass transition temperature. Meanwhile, DI water leads to the weakest pills compared to other polymeric binders, due to lack of any polymeric binding agent in DI water. The DI water does not contain any polymer to increase the descent

compressive strength. Regarding the sorbitol binders, increasing the sorbitol amount in the binder will slightly increase the strength of the printed tablets along with the sugar alcohol percentage in binder. Furthermore, the results indicated that adding cornstarch into the powder bed configuration results in higher compressive strength in the pills compared to those printed with the sticky rice powder.

4. Dissolution rate of the printed tablets

4.1. Binder effect on dissolution rate of the pills printed with different powder materials

4.1.1. #315 Foremost Lactose

Figure 14 presents the dissolution results of the pills printed with 40K PVP, DI water, 5wt% sorbitol, and 10wt% sorbitol binders and using #315 Foremost Lactose mixed with varying amounts of powdered sugar. For all dissolution measurements, at least five tablets were fabricated and tested for each powder and binder configuration.

The dissolution data indicates that the pills fabricated with 0wt% powdered sugar results in the shortest dissolution times for all types of the liquid binders examined. Generally, increasing the powder sugar amount in the powder bed seems to significantly increase the pill dissolution time, regardless of the liquid binder type. The 40wt% sugar concentration results in the longest dissolution times of 12 ± 1 s, 14 ± 1 s, 14.8 ± 1 s, and 16 ± 1 s for pills printed via DI water,40K PVP,5wt% sorbitol, and 10wt% sorbitol liquid binders, respectively. From these results, 30wt% sugar is required to provide sufficient dissolution time when printing with 5wt% sorbitol binder. Utilizing 10wt% sorbitol binder provides faster dissolution rate than DI water, 40K PVP, and 5wt% sorbitol binder for #315 Foremost Lactose powder.

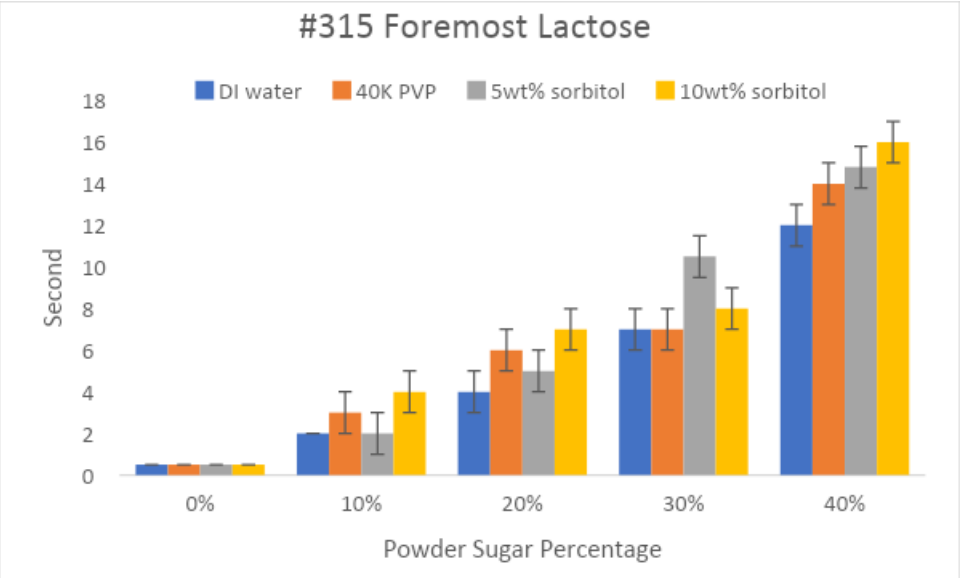


Figure 14. Dissolution data of the tablets printed via 40K PVP, DI water, 5wt% sorbitol, and 10wt% sorbitol binders and using #315 foremost lactose powder mixture with different wt% of powder sugar

4.1.2. NF lactose monohydrate impalpable 312 powder

Figure 15 presents the dissolution of the pills printed with 40K PVP, DI water, 5wt% sorbitol, and 10wt% sorbitol binders and using NF lactose monohydrate impalpable 312 powder mixed with varying amounts of powder sugar. For these experiments, five tablets were tested to determine the average dissolution rate.

Similarly, eliminating the powdered binder (0wt% powdered sugar) in the powder bed results in pills with the lowest dissolution time of 2 ± 0.1 s (DI water), 2 ± 0.1 s (40K PVP), 2 ± 0.1 s(5wt% sorbitol), and 2 ± 0.1 s (10wt% sorbitol). The 40wt% sugar concentration results in the longest dissolution for printed pills, featuring 15 ± 1 s (DI water), 16 ± 1 s (40K PVP), 16 ± 1 s (5wt% sorbitol), and 17 ± 1 s (10wt% sorbitol) dissolution time. Clearly, increasing the powder sugar concentration in the powder bed significantly increases the dissolution time of the printed pill regardless of the binder type. These results indicate that

the 10wt% sorbitol binder has the longest dissolution time regardless of the amount of binding agent in the powder.

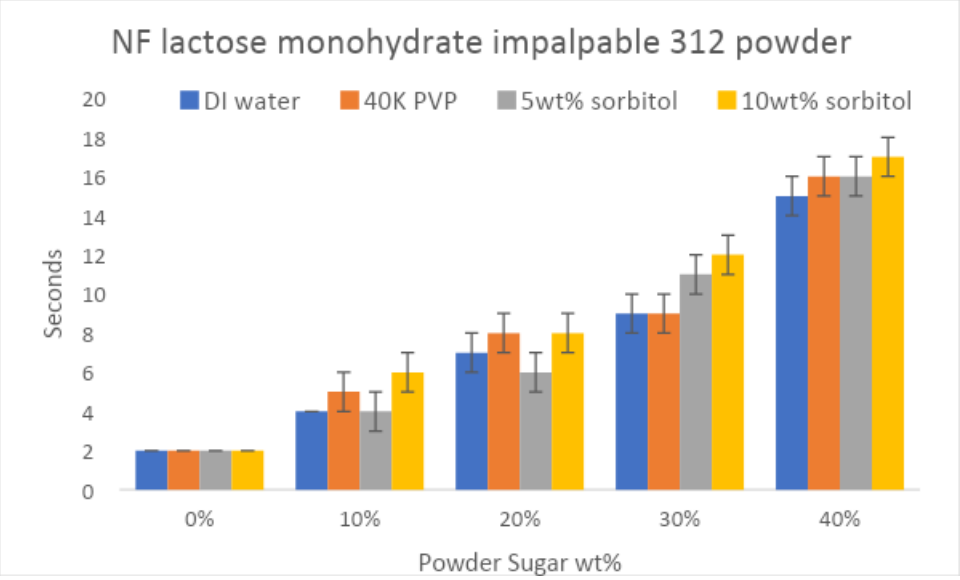


Figure 15, Dissolution data of the tablets printed via 40K PVP, DI water, 5wt% sorbitol, and 10wt% sorbitol binders and using NF lactose monohydrate impalpable 312 powder mixture with different wt% of powder sugar

4.1.3. Lactose anhydrous NF IMP

Figure 16 illustrates the dissolution time of the pills printed with Lactose anhydrous NF IMP powder mixed with different powder sugar concentration levels and with 40K PVP, DI water, 5wt% sorbitol, and 10wt% sorbitol as liquid binders. From Figure 16, it is seen that the lowest dissolution time is observed in the pills with 0wt% powdered sugar regardless of the binder type used for pill printing. Based on the experimental measurement, it is concluded that the 40wt% sugar concentration results in the longest dissolution for printed pills, targeting at 8 ± 1 s (DI water), 10 ± 1 s (40K PVP), 12 ± 1 s (5wt% sorbitol), and 11 ± 1 s (10wt% sorbitol) dissolution time. Starting at 10wt% powder sugar concentration level, the Lactose anhydrous NF IMP powder printing with 40KPVP, DI water, 5wt% sorbitol, and 10wt% sorbitol dissolution time slightly increases. While 40wt% sugar is required to

provide sufficient dissolution time when printing with 5wt% sorbitol binder. Therefore, we draw two from these experiments: (i) the dissolution time will increase along with the powder sugar concentration; (ii) as the compressive strength increase additional binding agents in the powder bed significantly improves the dissolution rate of the printed tablets.

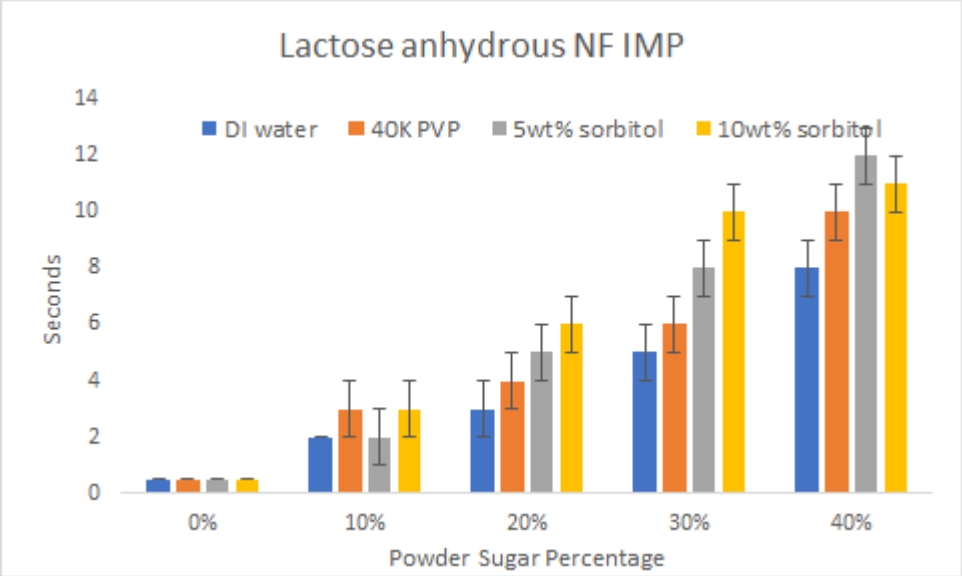


Figure 16, Dissolution data of the tablets printed via 40K PVP, DI water, 5wt% sorbitol, and 10wt% sorbitol binders and using Lactose anhydrous NF IMP mixture with different wt% of powder sugar

4.2. Effect of the different liquid binders on the dissolution rate of the pills printed using different powder material configurations

4.2.1. 40K PVP liquid binder

Figure 17 illustrates the dissolution time of pills made via 40K PVP liquid binder along with different powder material configurations. As shown in the figure, the Lactose anhydrous NF IMP demonstrated the fastest dissolving rate within the DI water as compared with other lactose powder, among all of the powder sugar amounts in the powder bed. ANOVA indicates that increasing the powder binding agent (powdered sugar) amount expediates the dissolution time of the printed pills for all types of the lactose powders. Based

on these data, NF lactose monohydrate impalpable 312 powder interacts better than #315 Foremost Lactose, and Lactose anhydrous NF IMP powder. This is attributed to the large quantity of crystalline in the NF lactose monohydrate impalpable 312 powder.

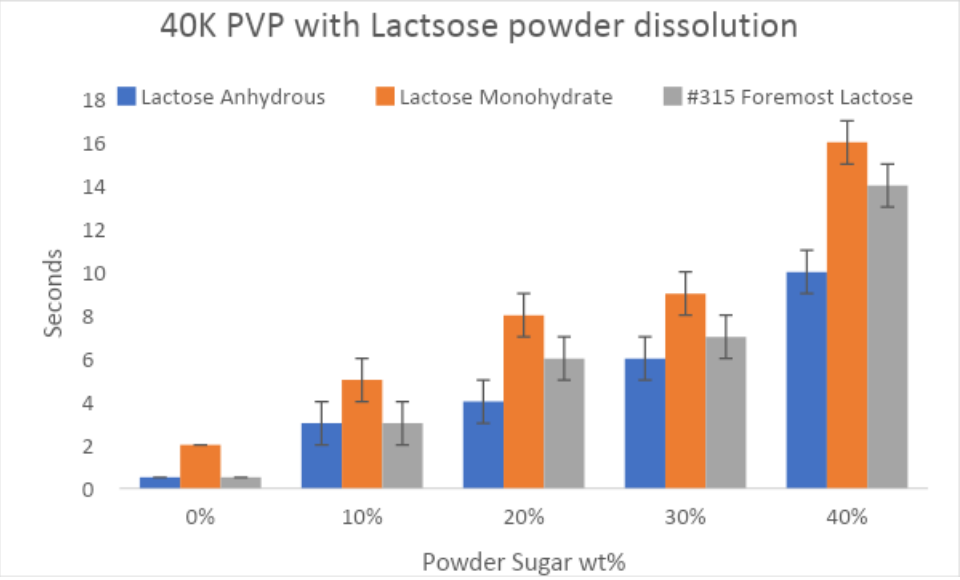


Figure 17. Dissolution data of the tablets printed 40K pvp binder via Lactose anhydrous NF IMP, NF lactose monohydrate impalpable 312 powder, and #315 Foremost lactose mixture with different wt% of powder sugar

4.2.2. DI water liquid binder

The overall dissolution time data of the pills printed with DI water are shown in Figure 18. From the figure, utilizing the NF lactose monohydrate impalpable 312 powder resulted in pills with the longest dissolution time for all powder sugar levels, as compared with other lactose powder materials.

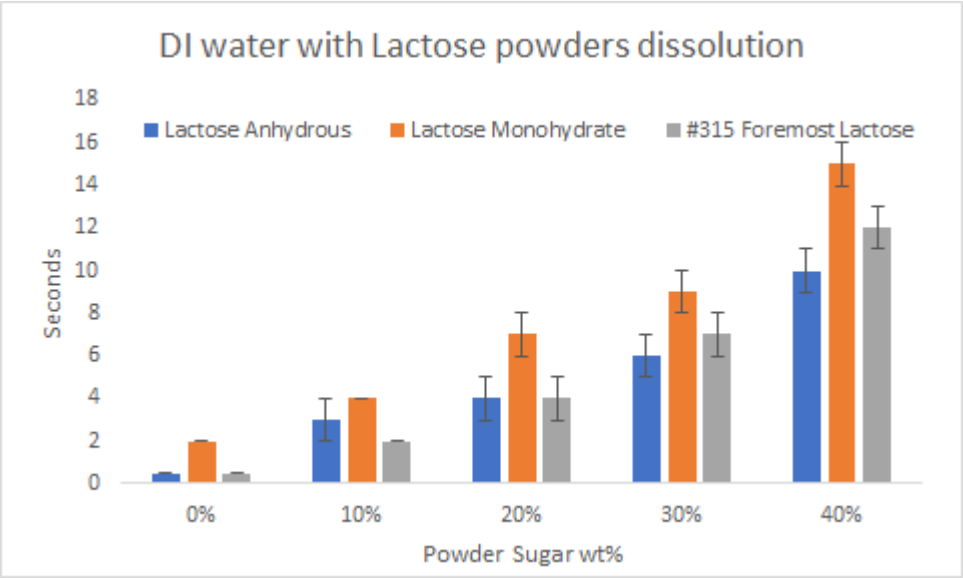


Figure 18. Dissolution data of the tablets printed DI water binder via Lactose anhydrous NF IMP, NF lactose monohydrate impalpable 312 powder, and #315 Foremost lactose mixture with different wt% of powder sugar

4.2.3. 5wt% sorbitol liquid binder

To summarize the #315 Foremost Lactose, NF lactose monohydrate impalpable 312 powder, and Lactose anhydrous NF IMP powder dissolution data via 5wt% sorbitol binder. The overall dissolution time data with 5wt% sorbitol binder were shown in figure 19. From Figure 19, due to the lactose powder size, as-fabricated tables with lactose anhydrous NF IMP powder dissolves faster than those printed with the other two types of lactose powder. In the figure, we are able to draw conclusion from these experiments with 5wt% sorbitol binder: (i) at 20wt% powder sugar concentration level, the pills printed with #315 Foremost Lactose is weaker than those fabricated with the other two types of lactose powders; (ii) the pills printed with NF lactose monohydrate impalpable 312 powder dissolves slower than those of the others among all powder sugar concentration levels.

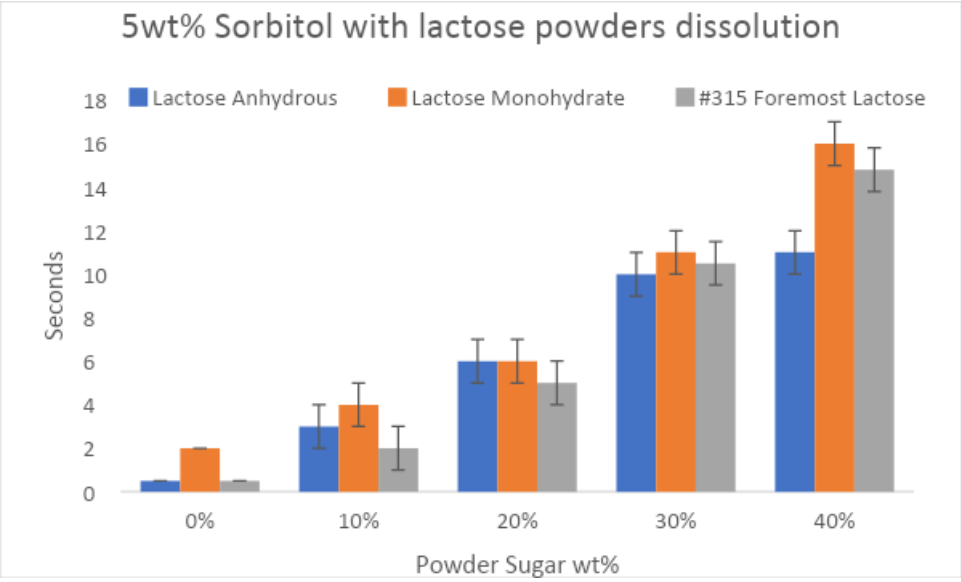


Figure 19. Dissolution data of the tablets printed 5wt% sorbitol binder via Lactose anhydrous NF IMP, NF lactose monohydrate impalpable 312 powder, and #315 Foremost lactose mixture with different wt% of powder sugar

4.2.4. 10wt% Sorbitol liquid binder

The overall dissolution time data with 10wt% sorbitol binder are shown in Figure 20. As the weight amount of powder sugar increases, the dissolution time increases as well. Respectively, starting at 0wt% powder sugar concentration level, the pills printed with NF lactose monohydrate impalpable 312 powder present longer dissolution than those fabricated with other two lactose powder. At this point, we can conclude: (i) the pills printed with Lactose anhydrous NF IMP powder and #315 Foremost Lactose powders are both weaker than that of NF lactose monohydrate impalpable 312 powder; (ii) the tablet fabricated with NF lactose monohydrate impalpable 312 powder with 40wt% powder sugar has the longest dissolution time around 17 seconds among all combinations of powder and sugar concentrations.

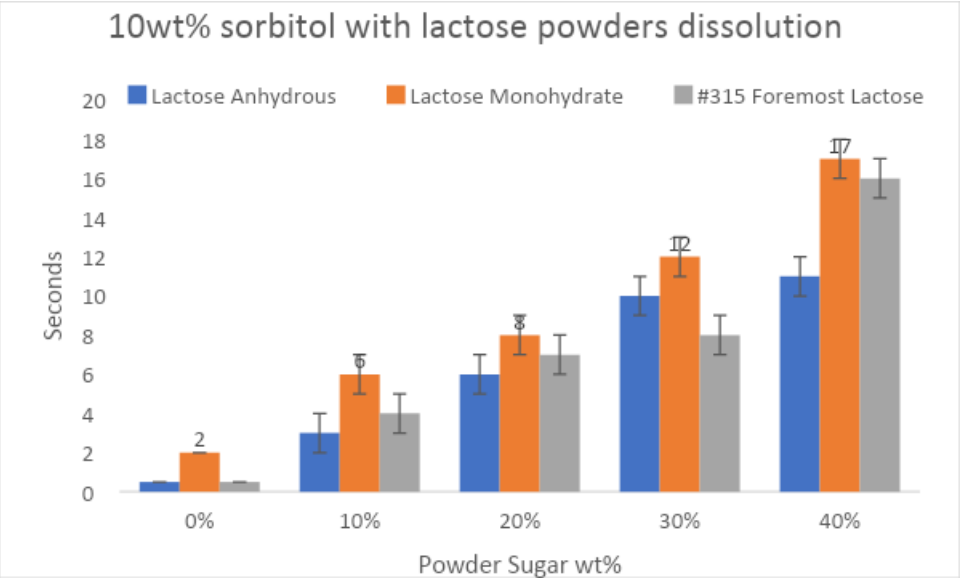


Figure 20. Dissolution data of the tablets printed 10wt% sorbitol binder via Lactose anhydrous NF IMP, NF lactose monohydrate impalpable 312 powder, and #315 Foremost lactose mixture with different wt% of powder sugar

4.3. Effect of cornstarch and sticky rice powder on pills dissolution time

Figure. 21 illustrates the dissolution times of the pills printed with the mixture of NF lactose monohydrate impalpable 312 powder, 20wt% powdered sugar, and 30wt% corn starch/sticky rice powder using 40K PVP and DI water binders. To evaluate the effect of cornstarch and sticky rice powders on pill's dissolution time, at least five tablets were printed with each powder configuration (i.e., (i) NF lactose monohydrate impalpable 312 powder, 20wt% powder sugar, and 30wt% corn starch, and (ii) NF lactose monohydrate impalpable 312 powder, 20wt% powder sugar, and 30wt% sticky rice) using DI water and 40K PVP binder. Herein, based on the dissolution time rate and powder particle size, we picked the NF lactose monohydrate impalpable 312 powder. From the figure 21, when

compared with pills printed using the cornstarch and sticky rice powder, 40K PVP binder printed pills were stronger than the DI water printed pills.

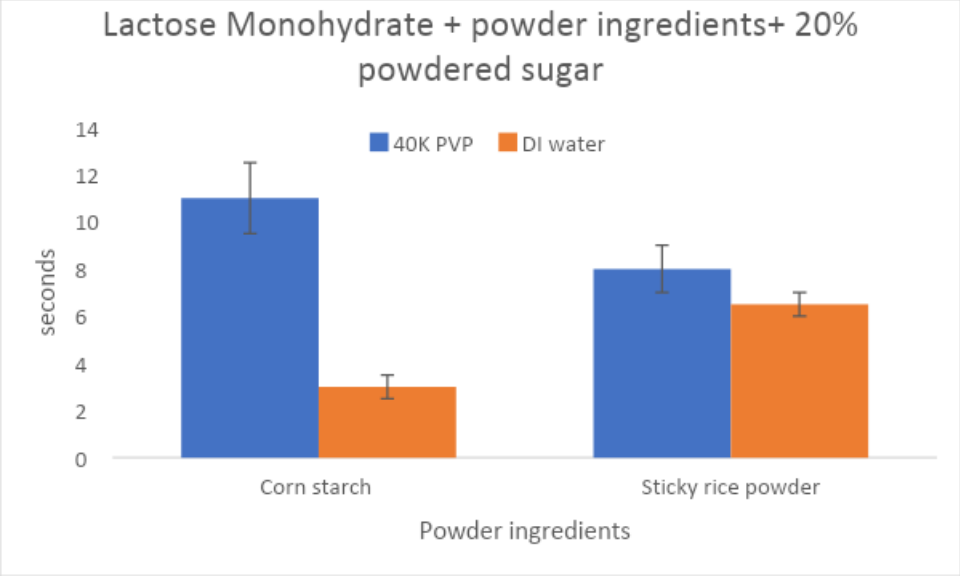


Figure 21 Dissolution data of the tablets printed 40K pvp binder and DI water binder via NF lactose monohydrate impalpable 312 powder mixture with different 20 wt% of powdered sugar + cornstarch

4.4 Effect of multi-binder on the dissolution time of the printed pills

To investigate the effect of using multi-binder on printed pills dissolution, 50-layer pills were fabricated using the mixture of the NF lactose monohydrate impalpable 312 powder and 40wt% powder sugar. As shown schematically in Figure 22, ten top and ten bottom layers of the pills were printed via 10wt% sorbitol binder whereas for the middle layers (i.e., layers 10-40) 40K PVP binder was used for the pill fabrication.

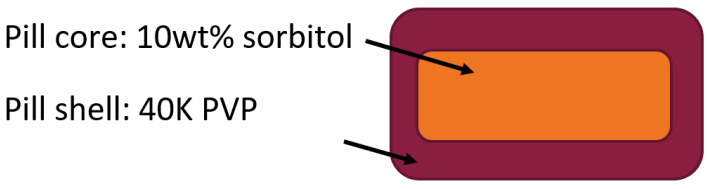


Figure 22. Schematic illustration of the pills printed with multi-binder

From the previous data, the mixture of the NF lactose monohydrate impalpable 312 powder with 40wt% powder sugar and pills printed with 40K PVP and 10wt% sorbitol binder results in dissolution times of 16 seconds and 17 seconds, respectively. While the shell layers (i.e., the layers printed with sorbitol binder) were printed with 100% binder saturation level, 50% saturation level was used for printing of the inner layers (i.e., the layers printed with 40K PVP). The dissolution experiments suggest that these pills dissolved at different time ranges as shown in Figure 23. Because of the difference in the layer binder, we hypothesize that the inner section of printed pills dissolves first, which causes the pills to float to the top and slowly dissolve the shell after three minutes. This hypothesis will need to be tested directly in future experiments.

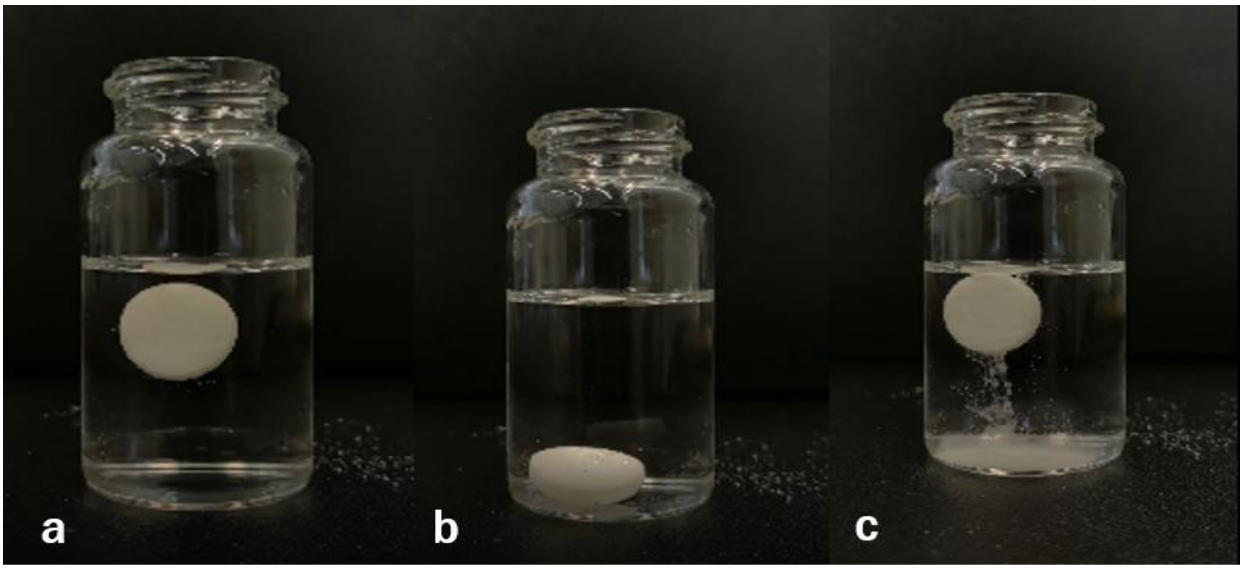


Figure 23. (a)Multi-binder printed pill dropped into DI water t=0s (b) the pill stayed at the bottom within the first 10 seconds t<10s. (c) after 10 seconds, the pill floated to the top t>10s.

4.5. Summary

From the experimental measurements, it was discovered that:

1. DI water, 5wt% 40K PVP, 5wt% sorbitol, and 10wt% sorbitol are all applicable binders for the different lactose powders to fabricate tailored pills. To satisfy the 5kp compressive strength requirement, additional binding agents are required to be mixed into the powder bed.

2. Introducing additional powder binding agents into the powder feedstock enables tailoring the compression strength of the as-fabricated tablets. The compressive strength and dissolution time increase with an increase in concentration of the powder sugar.

3. Based on the analyzed dissolution data, the powdered sugar will affect the pills dissolution time range as the sorbitol concentration amount increases. The pills can dissolve from 0 *second* to 17 *seconds*. The higher the sorbitol concentration within the binder, the longer the dissolution time.

4. The powder particle size also affects the compressive strength. The larger size of the lactose particle will provide better strength along with either 40K PVP binder or 10wt% sorbitol binder.

In general, the analyzed properties are observed to consistently increase the pills' compressive strength by adding the different amount of powdered sugar into the all lactose powders. By using the binder jetting method, we can manipulate the sugar concentration to

tailor the dissolution time of the printed pills. This allows the precise control of the medication treatment according to the requirement of health conditions for each individual patient.

5. Summary and Future Work

The overall goal of this work was to increase the compressive strength of tablets fabricated via binder jetting AM. The feasibility of manipulating the mixture of the powder and binder feedstocks to increase the pharmaceutical pills' compression strength and to control the dissolution time was explored. To examine the powder/binder effects on part strength and dissolution, a variety of different excipient (lactose) powders were combined with different concentrations of a variety of powdered binding agents (e.g., powdered sugar). The results of this study indicated that using the Z-Corp Spectrum Z510 printer and the suitable lactose powders and binders would allow the fabrication of pharmaceutical pills to have strength above 5 kilopond and dissolution time over 17 seconds. The following are the main findings based on the experimental results of this work:

- Each lactose powder tested can be combined with different concentrations of powdered sugar to increase the pills strength and the dissolution time.
- Incorporating polymeric binders (40K PVP or sorbitol) into DI water binder provides an increased compression strength and the dissolution time with increasing concentration.
- A multi-binder BJ system can be used to produce pharmaceutical pills with features that have different dissolution times within a single printed pill.

Prospective pathways for future works identified in this research include: (i) incorporating multiple binders and powders to create multifunctional drug delivery systems with accelerated release characteristics, (ii) studying adjustable and personalized dosage forms through binder jetted pills, and (iii) exploring the impact of adding active ingredients into the powder and binder materials.

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