An Analysis of Differences in Glass Cartridge Siliconization Parameters and Processes for Manufacturing of Pharmaceutical Cartridges

By

Alexandra M. Unger

B.S. Mechanical Engineering
Northeastern University, 2012

Submitted to the MIT Sloan School of Management and the Department of Mechanical Engineering in Partial Fulfillment of the Requirements for the Degrees of

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Signature of Author Signature redacted
MIT Sloan School of Management, Department of Mechanical Engineering
May 11, 2018

Certified by Signature redacted
Jung-Hoon Chun, Thesis Supervisor, Professor of Mechanical Engineering

Certified by Signature redacted
Thomas Roemer, Thesis Supervisor, Professor of Management

Accepted by Signature redacted
Maura Herson, Director of MIT Sloan MBA Program MIT Sloan School of Management

Accepted by Signature redacted
Rohan Abeyaratne, Chairman, Committee on Graduate Students, Department of Mechanical Engineering

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Abstract

The application of silicone inside of glass insulin cartridges helps reduce injection forces during drug delivery. This is important for a less painful patient experience. Insulin pen designs are increasingly reliant on consistent and repeatable injection forces as mechanized injection replaces manual injection. A minimum silicone layer thickness of 40nm is required to produce low gliding forces of approximately two Newtons with little variability. Differences seen in final gliding forces across production areas at Sanofi Insulin Frankfurt are small, but this variation makes it difficult to design for set-force mechanical injection. While the minimum silicone layer thickness required is established, how to achieve it consistently is less understood.

This project looked at three insulin packaging lines at Sanofi Insulin Frankfurt that use different methods for siliconization. Differences between these lines were investigated in order to understand which parameters are the most important for creating an acceptable silicone layer thickness. First, each production line was mapped from loading of empty cartridges through the end of the heating tunnel, before insulin is packaged. Differences in the process were found in cleaning procedures, silicone application methods, and production settings. Points for potential variability were found at silicone mixing steps and during start/stop conditions. Lab experiments were developed to test cleaning procedures, heating time, standing time, air pressure of silicone blowout, and silicone concentration.

Results from these experiments showed that some production processes have a greater effect than others on silicone layer thickness and subsequent gliding forces. Differences in cleaning procedures on each of the lines have little effect on overall silicone layer thickness and gliding forces. Time in the heating tunnel and standing time have a moderate effect. The largest effects were seen from silicone emulsion concentration and air blow out pressures in the flushing method of silicone application. The following recommendations are given to improve performance consistency across production areas: (1) standardize processes across production areas where possible, (2) reduce air pressure in the flushing process, and (3) eliminate process steps that can lead to several of these effects occurring in the same cartridge.

Thesis Supervisor: Thomas Roemer
Title: Professor of Management Science, MIT Sloan School of Management

Thesis Supervisor: Jung-Hoon Chun
Title: Professor of Mechanical Engineering, MIT

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1.1 Siliconization for Insulin Products

1.1.1 Project Context

The force required to move a rubber stopper down a glass cartridge to expel medication is an important factor in insulin pen design and subsequent drug delivery. Patients using current insulin delivery systems, such as insulin pens, typically use the force from their thumb at the top of the pen to inject a dose of insulin. The required manual force can affect customer experience during drug delivery and have an impact on customer satisfaction. Even a small improvement in customer satisfaction could drive overall business growth for the Insulin Division at Sanofi. As of 2015, consumers spent $673B on diabetes care globally, and health trends indicate this will increase 19% in the next 25 years [1].

Sanofi hopes to improve customer experience by looking at the possibility of transitioning the insulin pen design from a manual injection to an automated injection. Instead of the thumb, a mechanism such as a spring would drive the rubber stopper down the cartridge for drug delivery. This spring must exert an appropriate force to overcome the both the break loose and gliding friction forces and deliver the dosage in a timely manner. The force cannot be so strong that it delivers the medication too quickly resulting in a painful experience for the patient.

This project is important because there is a limited force range in which engineers can design a spring to deliver a force that is timely but not painful. This is highly dependent on consistent friction forces along the entire length of the cartridge and between cartridges produced not only on the same production line but across different production areas. Current forces seen in production areas at Sanofi Frankfurt Insulin are currently all acceptable for manual injection, but the variation in forces between production areas could be a challenge for designing a consistent spring-driven insulin pen.

A large factor contributing to forces in insulin pens is the silicone layer. The processes used to apply silicone can affect the performance of these forces in a significant way. Baked-in siliconization in pharmaceutical applications is a method that consists of applying a layer of silicone via a silicone-water-substrate emulsion and then baking off the excess water and substrate in a high temperature oven. This creates a thin layer of silicone that acts as a lubricant between a glass cartridge containing liquid medication, such as insulin, and the rubber stopper that caps the end of the cartridge. In order to disperse the medicine, pressure is applied to the rubber stopper to move it down the glass cartridge and out through an attached needle at the other end of the capped cartridge. Figure 1 shows an image of a common 3.0mL volume cartridge used at Sanofi. The bottom, or flange end, of the cartridge is on the left with the black rubber stopper. The top, or needle end, is at the right with the yellow metal cap.

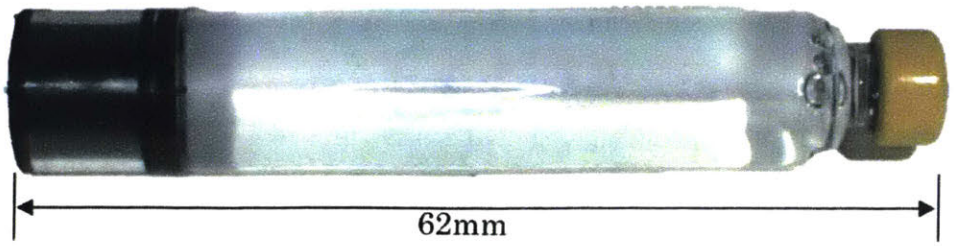

Figure 1: Insulin Cartridge [2]

The focus of this project is to understand what production parameters affect silicone application and subsequent friction forces and to make recommendations to improve consistency across all production areas. Siliconization involves several process steps, each of which are evaluated for overall contribution to the final force outcomes.

1.2 Project Overview

Academic research, including previous projects done at Sanofi Deutschland GmbH, have established a relationship between silicone layer thickness and friction forces. In general, as long as there is a sufficient silicone layer thickness, gliding forces are relatively low and consistent. The manufacturing and production processes required to establish a quality silicone layer are less known.

This project first looks at past research in this area, both inside and outside of Sanofi, to determine what constitutes a "quality" silicone layer. Layer thickness and coverage percentage are common metrics that contribute to friction forces. This project will explore these metrics by looking in closer detail at specific areas of the cartridge that display higher forces, such as the top, or needle end.

The second phase of the project establishes what production steps are involved in siliconization and how those differ across production areas, particularly at Sanofi Deutschland GmbH. There are several process steps surrounding the actual application of silicone including surface preparation, application, and heating time. There are also factors that can affect the silicone layer such as the concentration of the applied silicone emulsion and time between process steps.

Finally, analysis of experiments designed to test production parameters will evaluate what effect each factor has on silicone layer quality and subsequent friction forces. This portion of the project will look at overlapping factors and how they can affect the overall silicone layer and force result. From these results, process-specific recommendations are proposed to improve performance.

2 Background

2.1 What is Diabetes?

Diabetes is a disorder affecting the pancreas's production of insulin or the body's ability to use insulin effectively. In a body's healthy operation, carbohydrates are broken down to glucose in the bloodstream. Insulin helps this glucose pass from the blood into cells where it is converted into the energy necessary for the cell, and therefore the body, to function. A lack of insulin or inability to utilize it results in high blood sugar levels, which can cause severe damage to the body in the form of heart conditions, complications with the blood vessels, eyes, kidneys, nerves, and teeth, and an increase in the risk of infections in general. Complications often include cardiovascular disease, heart attack, stroke, kidney failure, blindness, nerve disease, infection, and even amputation.

There are two types of diabetes. Type I is not preventable, and the causes of the onset of Type I are currently not well understood, though some links have been made to genetic or environmental causes. Type I diabetes is characterized by an auto-immune reaction where the immune system destroys the cells that produce insulin. Typically, this type of diabetes develops in children and young adults. If left untreated, the condition is fatal since there is no way to feed the body's cells with glucose from the bloodstream. Without insulin, the patient cannot survive.

Type II diabetes is much more common than Type I and accounts for approximately 90% of all diabetes cases. Type II is characterized by an insulin resistance or deficiency. Often this disease is considered preventable, as it is brought on by a sedentary lifestyle and poor diet. The onset of the condition can usually be managed through diet and exercise, but most patients will eventually require medication such as insulin to manage the disease sooner or later [3].

There are also other types of diabetes including gestational diabetes (GDM), which results in elevated blood glucose levels for mother and baby during pregnancy only, but elevates risk for both mother and baby for later onset of Type II diabetes. GDM can generally be managed through diet and exercise, though in 10-20% of cases, insulin is required [4].

The first and preferred initial method of treatment for Type II diabetes is generally a recommended change in lifestyle to eat healthier and exercise more. When this is not enough to maintain adequate blood sugar levels, various medications can be prescribed to help the body produce more insulin and use it effectively. Generally, insulin injections are often necessary to maintain glucose levels in Type II diabetes [5]. The effects of Type I diabetes can be aided by a careful diet, but insulin injections are required to ensure patient survival [6].

Insulin was initially made from cow or pig insulin since it was almost identical to human insulin. Eventually, synthetic human insulin was created through enzyme modification. Insulin can be formulated to be quick-acting or long-acting and are used to manage insulin levels through glucose-heavy times such as mealtimes and glucose-light times such as sleep [7].

2.2 Scope

As of 2015, an estimated 415 million adults worldwide have diabetes. That equates to 1 in 11 adults worldwide with the disease. This is projected to rise to over 640 million over the next 35 years. Diabetes treatment and complications from the disease account for up to 12% of global healthcare costs, or an estimated $827 billion USD annually in direct costs [8]. Since up to half of people with diabetes are undiagnosed, many people experience expensive and dangerous complications while the condition is untreated. In 2015, an estimated 5 million people died from complications caused by diabetes [3], [9].

As a result of the prevalence and projected growth of diabetes globally, the markets for monitoring and treatment of diabetes together were estimated to be over $140 billion as of 2015, and projected to grow to over $180 billion by 2021 [7]. Low-income and middle-income countries will see a larger diabetes growth trend and, therefore, increased healthcare costs compared to high-income countries [8].

Sanofi's main products are Lantus® and Toujeo®, long-acting insulins at different concentrations that regulate glucose levels for diabetes patients over the day. Sanofi also offers a rapid-acting insulin called Apidra®, among other products [10]. The diabetes franchise in Sanofi accounted for 21.7% of Sanofi's total net sales in 2016 [11]. Sanofi's business strategy includes sustaining leadership in diabetes treatment through developing its insulin franchise with Lantus® and Toujeo® and shifting market focus to managing diabetes outcomes by partnering with Verily (formerly Google Life Sciences) [11].

2.3 Medical Devices for Insulin Delivery

In addition to the different medication options, Sanofi also offers different methods of insulin delivery. The main packaging option available and the focus of this project is insulin pens, but a brief overview of alternatives is described in the following section.

2.3.1 Medical Devices to Deliver Insulin

Insulin is injected via syringe and needle, insulin pump, or insulin pen. *Syringe and needle delivery* is the most common method of insulin injection due to its widespread availability and low cost. This method can be uncomfortable and time consuming as it requires careful measurement of the dose and regular replacement of needles. Disposable syringes with pre-fixed needles are an advancement on this basic method [7].

Insulin pumps are more advanced methods of delivering insulin. They generally consist of a device about the size of a deck of cards that contains an insulin cartridge. A tube attached to the cartridge has a needle at the end that is inserted under the patient's skin. The pump delivers insulin constantly throughout the day at a rate determined and set by the patient. This is the most expensive method of treatment with pumps that last 5 years costing up to $5,000. [7].

Insulin pens are considered more user-friendly. They tend to be more expensive than the traditional syringe and needle system, but they are much easier to use and more comfortable. The pen portion of the device can be reusable with the patient replacing the cartridge of insulin when it is empty, or the

pen as a whole can be disposable where the whole device is discarded when the cartridge inside is empty. There is no clear advantage of disposable versus reusable pens besides patient preference, cost depending on insurance coverage, and perhaps concern for sustainability and environmental impacts [12].

2.3.2 Insulin Pens

Insulin pens generally consist of a plastic housing around a glass cartridge filled with insulin. There is a mechanism such as a dial to control the dosage amount, which is determined and set for each delivery by the patient. Finally, there is an injection feature, such as a button, which the patient presses to deliver the insulin.

Before injection, the patient removes the cap from the pen. The patient then attaches a disposable, single-use needle to the end of the pen and performs a safety test to ensure the insulin is able to leave the needle end and that there is no air in the system. The patient dials in the correct dose. Finally, in manual dosage pens, the patient presses the button with a finger or thumb to deliver the insulin. Once the dial returns to zero, the patient removes the needle and the delivery of insulin is complete [13].

When the patient presses on the button to inject the dose, several mechanical interactions occur. The patient's thumb or finger applies force to the button, which delivers that force to move a rubber stopper down the glass cartridge to inject the insulin. This rubber stopper is used to push out the insulin and seal the insulin in the cartridge, so there is a very delicate balance between the dimensions of the stopper and the glass cartridge. It needs to ensure that there is enough contact area to create a safe, leak-proof seal, but not so much pressure between the stopper and the glass such that it is too difficult to move down the barrel of the cartridge. In order to aid this interaction, a layer of silicone lubrication is applied to the glass.

The patient is able to control the speed of the injection based on the pressure applied by the thumb. If the injection is going too quickly, which can be painful, the patient can reduce the force the thumb applies to the injection button, slowing down the injection. Conversely, an increased force applied to the button can speed up injection if it is not too painful and the patient wants it to go faster. With this type of manual pen device, the patient has complete control over the force, speed, and therefore comfort of the injection.

Next generation insulin pens are moving away from this manual injection and toward an automatic injection driven by a mechanical force such as a spring. This change has been driven partially by patient dislike of the experience of applying force throughout the injection. It can be an uncomfortable and even painful sensation especially if there is a higher force required to administer the dosage. In newer pen designs, the patient would select the dosage and simply click a button once to activate a force mechanism such as a spring, and the insulin would be injected automatically without applying pressure manually. The goal of this is to increase patient comfort and experience during injection, but this can be a difficult balance to meet. The force provided by an automatic pen to move the rubber stopper must be strong enough to deliver the insulin in a timely manner and in the full dosage amount.

However, the force cannot be too strong, or the insulin will inject too quickly, causing excessive pain to the patient. This leaves a narrow range of force in which the pen must perform, which means there must be low variability in all the forces that occur in an insulin pen.

2.3.3 Insulin Pens at Sanofi

Sanofi offers both disposable and reusable insulin pens. These different products and the cartridges that go in them are manufactured across several production lines at Sanofi; some products are made on multiple lines across different production areas, and others are made only in one production area among other products.

Sanofi produces many brands of insulin pens. Figure 2 shows a diagram of a SoloSTAR® pen. The "insulin reservoir" indicated in the figure is the focus of this project, but understanding its role in the context of the pen as a whole is important.

Figure 3 shows a diagram of the current injection procedure. First (1), a patient dials in a dose. Next (2), the patient inserts the needle through the skin. Finally (3), the patient presses the button with the thumb until the button is fully depressed. The patient must hold this for 10 seconds after injection to ensure full delivery of the medication. Note that this is only the injection portion of the total insulin pen usage procedure and does not include attaching and replacing the needle or pen care.

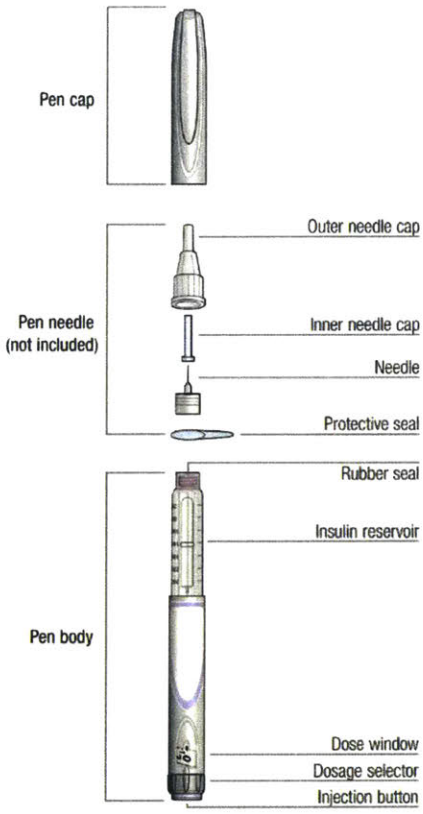

Figure 2: Sanofi SoloSTAR(R) Insulin Pen [30]

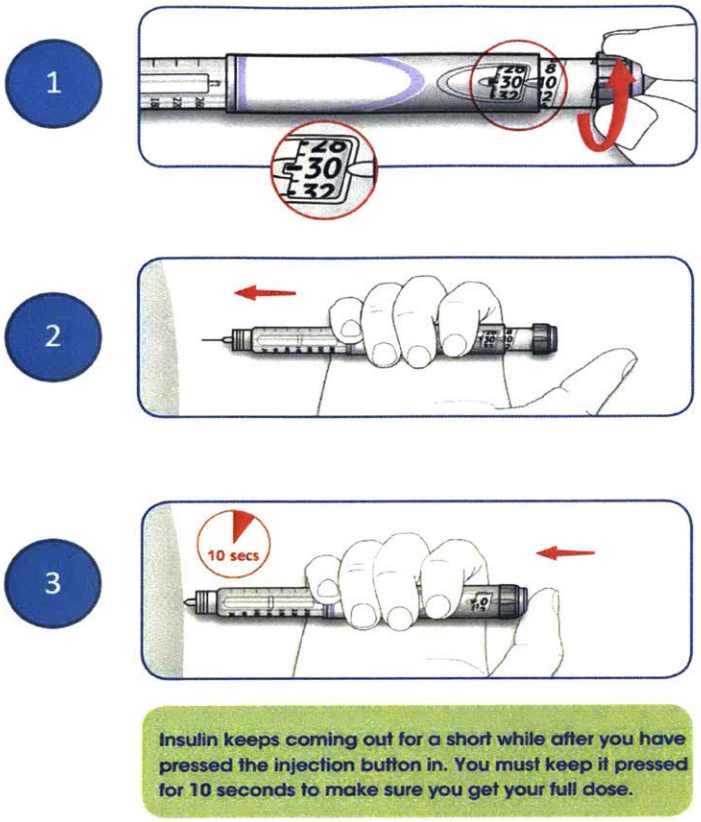

Figure 3: SoloSTAR (R) Injection Procedure [30]

Though not prohibitively painful, the procedure can be uncomfortable for a patient, and this injection must sometimes be done multiple times a day. An improvement in friction forces can help lead to better patient comfort. Additionally, an improvement in force consistency would allow for a more comfortable automatic-inject pen to be developed.

3 Literature Review

3.1 Baked-in Siliconization of Glass Cartridges

3.1.1 Silicone

Application of silicone oil to the inside of glass cartridges is an important part of the production process to create a quality, functional insulin pen. Without enough silicone, the rubber stopper can be difficult to move down the barrel leading to an uncomfortable or incomplete injection experience. In order to diminish the effect of the dimensions and tolerances of the rubber stopper and glass cartridge, a layer of silicone is sprayed on the rubber stopper before production and on the glass cartridge before filling. This lubrication reduces the friction between the rubber and the glass, thereby lowering the force required to administer the insulin and decreasing variability in delivery. This practice has been widely used in the pharmaceutical industry for over fifty years, but until recently has not been explored in much technical detail in regards to the application of silicone [14]. It has become the focus of more

scrutiny due to the advancement of pen devices and the increased need to control forces and variability.

Though application of large amounts of silicone can be a tempting solution to the friction problem, there are two problems with this. A very high layer of silicone can actually create an elevated force due to the buildup of silicone in front of the stopper as it moves down the barrel, referred to as a "plowing effect" [15]. Secondly, too much silicone can lead to protein aggregation and visual contamination of the drug, which may limit or eliminate a medication's effectiveness [16]. It is beyond the scope of this project to explore the potential interactions between silicone and drug substrate, but it should be considered before any changes that increase silicone in the cartridge are implemented.

The process for applying silicone to glass cartridges in production is influenced heavily by the manufacturing equipment available, but the general process is similar everywhere. The silicone is mixed with water for injection (WFI) to a concentration recommended by the supplier, generally 1% to 5% [17]. The concentration of the solution will affect the viscosity of the fluid and the amount of pure silicone applied. The viscosity of the solution is important in regards to the flow of the emulsion during and after application. Specifically, the film flow due to gravity may cause thinner coatings near the top of the cartridge as gravity pulls the solution down. Lower surface tension film coatings will be more affected by the effect of gravity after application [18].

The solution is applied to a cleaned and rinsed glass cartridge. The manner of this cleaning and application varies across production areas and will be explored further in this paper. After application in some processes, the excess internal silicone is removed. In other processes, silicone is also applied on the outside of the glass to improve contact between cartridges and reduce glass breakage. The coated glass is then put through a heating tunnel to evaporate excess water and remove surfactants from the solution and form the chemical bonds between the silicone and glass. After the baking-in process is complete, the glass cartridge has a stopper inserted in the end and is then filled with insulin or other medication.

3.1.2 Baked-in Siliconization

Baked-in siliconization refers to the process in which the silicone is applied to the glass surface and then baked at high temperatures to improve the durability of the coating by the formation of hydrogen and covalent bonds between the glass and the silicone. This creates a layer thickness of 15-50nm as opposed to unbaked silicone layer thickness of 500-1000nm [14]. The baked-in layer is more resistant to removal than unbaked silicone when the rubber stopper moves down the glass cartridge. This keeps the silicone in place for lubrication and decreases the effect of protein aggregation due to silicone contamination. The manufacturer recommends baking the silicone at no higher than 200 degrees Celsius, but the process is routinely carried out in production at 300 degrees Celsius or slightly higher for short amounts of time. This part of the process not only bakes in the silicone, forming a chemical bond between the silicone and glass layer, but also sterilizes the unfilled cartridges in the heating tunnel [19]. Studies also show that the amount of time spent baking at high temperatures can have an

effect on forces seen in the cartridge; baking times beyond 1 hour can cause higher forces in drug delivery [20].

3.1.3 Silicone Application Process Factors

There are several different methods for applying silicone including time-pressure, flushing, and microdosing. The mechanics of these processes are described in Section 4.2.3. In general, there is little research for the improvement of silicone application since as long as silicone is applied, forces are reduced significantly enough for an acceptable manual injection. However, with the rising need for tighter tolerances, a deeper understanding of silicone application is required.

There are several factors that can affect the application of substrates on surfaces. The cleanliness of the surface is generally important for any coating application. Cleaning removes contaminants that could block or impede the adhesion of silicone to the surface of the glass. It also increases surface energy and wettability. The surface energy is the sum of intermolecular forces on the surface of a material, or the degree of attraction or repulsion force that a material surface exerts on another material [21]. Wettability is the degree to which a liquid spreads or adheres to a surface and can be observed by measuring the contact angle of a liquid droplet placed on the substrate [22]. Surface energy and wettability are proportional to one another, as surface energy increases, so does wettability. Silicone will adhere better to a cleaner surface.

There are various methods used for the application of silicone. They range from applying a fine mist of silicone emulsion to dousing the cartridge with liquid emulsion and blowing out the excess. The application nozzle can move into the cartridge for application- called "diving" nozzles- or be stationary beneath the cartridge. Stephanie Funke, et. all (2016) conducted a study on stationary time-pressure method nozzles and showed that geometry could have a large impact on siliconized cartridges. Based on diameter and spray pattern geometry, covering the entire cartridge can be difficult with a stationary application nozzle [20].

3.1.4 Air Pressure and Nozzle Geometry

Air pressure factors into silicone application in two ways. For microdosing and time-pressure procedures, air is blown with the silicone in a mist to apply atomized silicone emulsion to the cartridge. This air pressure can affect the geometry of the spray stream and thickness of application.

In the flushing procedure, silicone is applied as a liquid stream sprayed in excess inside the cartridge. The coated cartridge then moves to an air nozzle where the excess liquid is blown out. In this step, the air nozzle geometry and air pressure likely have a large impact on the silicone remaining in the cartridge. A simplification that can be used to understand the impact of air pressure on the silicone inside the glass is the application of fluid dynamics considering flow within a tube as depicted in Figure 4.

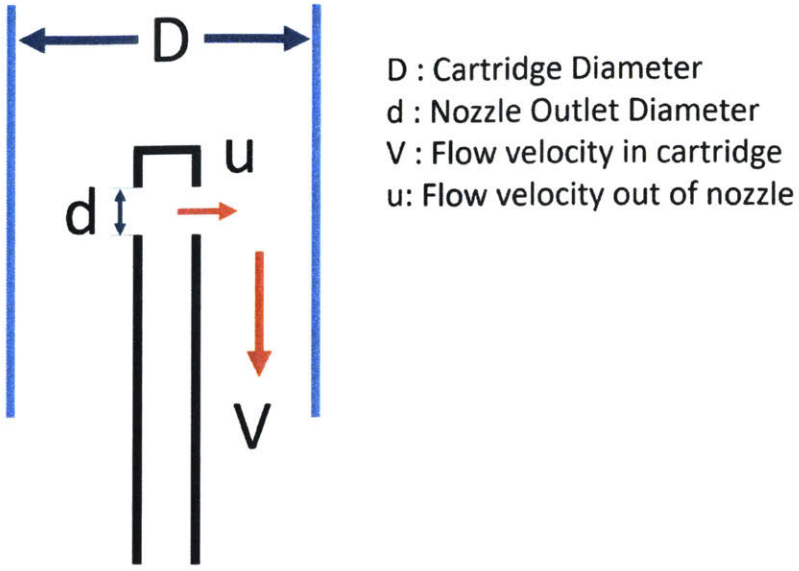

Figure 4: Drawing of Airflow in a Cartridge

Given that an ideal pressure setpoint can be found for a cartridge of a certain diameter, D_1, the pressure for a different diameter, D_2, can be scaled using the relationship between the change in air pressure ΔP in each cartridge as shown in Equation 3.1.

$$\Delta P_2 = \Delta P_1 \times \left(\frac{D_2}{D_1}\right)^2 \tag{3.1}$$

The full derivation is in Appendix A.

3.2 Force Considerations in Insulin Pens

3.2.1 Pen Dynamics

There are many sources of force variability that can arise from different parts of an insulin pen. First, there are the mechanical forces in the button mechanism of the pen. For manual pens this might simply be the friction of the button shaft along the body of the pen as it drives the rubber stopper down the glass cartridge. More advanced mechanical devices used in automated pens might add various forces. There are also fluid dynamic forces at play as the insulin moves through the cartridge and the smaller-diameter needle. Finally, there is the interaction between the rubber stopper and the glass cartridge as the stopper slides down the glass during insulin delivery. This stopper not only serves as the mechanism to force the insulin out of the pen, but also is a seal against the glass to prevent the drug from leaking out of the cartridge. A balance between the seal formed and the force to travel down the cartridge must be met. A larger diameter rubber stopper ensures a better seal, but the larger the diameter, the greater the normal force of the rubber against the glass, and the higher the contact area between the rubber and glass. The fundamentals of these friction forces can be described by Equations 3.2 and 3.3, where μ is the coefficient of friction which is constant for a specified set of materials

under specified conditions, τ_C is the yield stress during sheer and, A_{real} is the real contact area between the two substrates on a nanoscale level [23].

$$F_{friction} = \mu F_{normal} \tag{3.2}$$

$$F_{friction} = \tau_C A_{real} \tag{3. 3}$$

These equations show the important relationship between the dimensions of the stopper and glass cartridge, since a higher normal force and greater contact area result in higher friction forces. The variation in dimensions was investigated briefly by McArthur (2017) [2]. His investigation discovered there can be as much as a 50% deviation in either direction from the minimum to maximum interference of the specifications of the stopper and glass dimensions. Though this interaction is an important contributor to overall forces, it is not the main focus of this project.

3.2.2 Lubrication

Since silicone is serving as lubrication between the glass and rubber stopper, the principles of hydrodynamic lubrication are important to consider. Typical lubricant layers are around 1μm thick, which provides enough liquid thickness to avoid direct contact between the two surfaces. Friction in these cases is related to fluid viscosity [23]. The silicone layer thickness in this study is on the scale of .05-0.1μm or ~50-100nm, so the lubrication might be viewed more as a boundary layer interaction between the chemically bonded silicone layer on the glass and the rubber than through the interface of a silicone lubricant. Boundary lubrication friction coefficients are much higher than those under hydrodynamic lubrication, but still smaller than for dry friction. The surfaces are still wetted by molecular layers of lubricant, and the friction depends more on the constitution of the lubrication layer than on its viscosity [23]. In Figure 5, the Stribeck Diagram plots friction coefficient, μ, versus v/F, where v is the velocity, and F the contact force. From left to right there are three different friction regimes: boundary lubrication with high friction and wear, mixed lubrication with medium friction and wear, and hydrodynamic lubrication with low friction and wear [23].

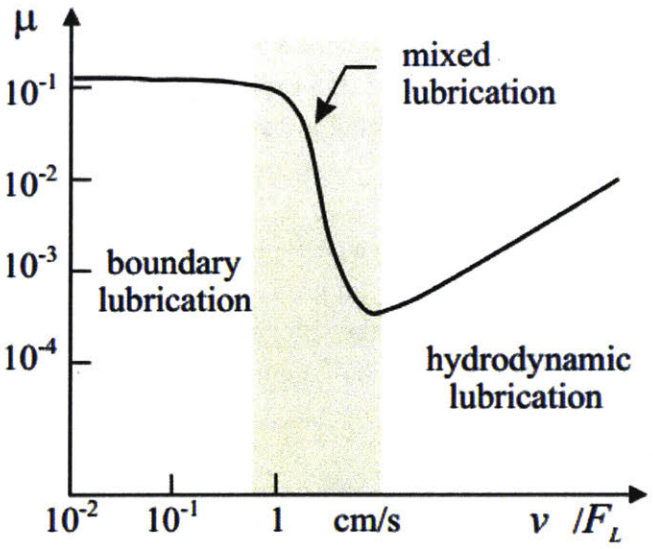

Figure 5: Stribeck Diagram [23]

In addition to the friction equations described in Section 3.2.1, the principles that govern the interaction between rubber, glass, and silicone are described by Reynolds's classical theory of hydrodynamic lubrication:

$$F_F = \frac{A}{d} \times \eta \times v \tag{3.4}$$

where v is the relative speed, η is the viscosity of the lubricant, A is the area and d the diameter of the cylinder. This assumes that the flow of lubricant is laminar [23]. Laminar flow is when a fluid flows in parallel layers and does not mix between those layers.

Though this principle helps gain better insight into the friction properties observed throughout this project, it is difficult to fully explain the phenomenon, especially when getting into extremely thin lubrication layers on the nanometer scale. Research continues to be done on thin film lubrication, but these principles can be used as a base upon which to build understanding.

3.3 Previous LGO Projects

Prior to this project, there were two other LGO projects based at Sanofi looking at siliconization and friction forces. Schacherl (2016) investigated silicone applied to flat plate glass. His studies showed that silicone application and force were related. To a certain extent, thicker layers of application did not yield lower forces down to a certain threshold. Dry spots showed a dramatic effect on force [15]. Other research supports this conclusion that higher silicone layers do not necessarily provide better functionality, but a minimum threshold should be met [20]. McArthur (2017) continued to investigate this layer thickness and dry spot definition and defined an acceptable thickness level and dry spot

amount that yielded the lowest forces at the most repeatable levels. Using Rap.ID imaging technology and force testing, he was able to suggest a minimum layer thickness of 60nm over the whole cartridge and less than 20% dry spots [2]. Dry spots were defined as areas with less than 30nm of silicone layer thickness. Figure 6 and Figure 7 show the correlation between layer thickness and force and dry spots and force, respectively.

Knowing that siliconization and dry spots can cause high forces in insulin pens shifts the focus from friction forces to silicone application especially in production conditions. As highlighted by the process description above, there are many variables in the siliconization process, but it is not entirely clear which ones are the most essential to the creation of a uniform silicone layer of appropriate thickness and minimal dry spots.

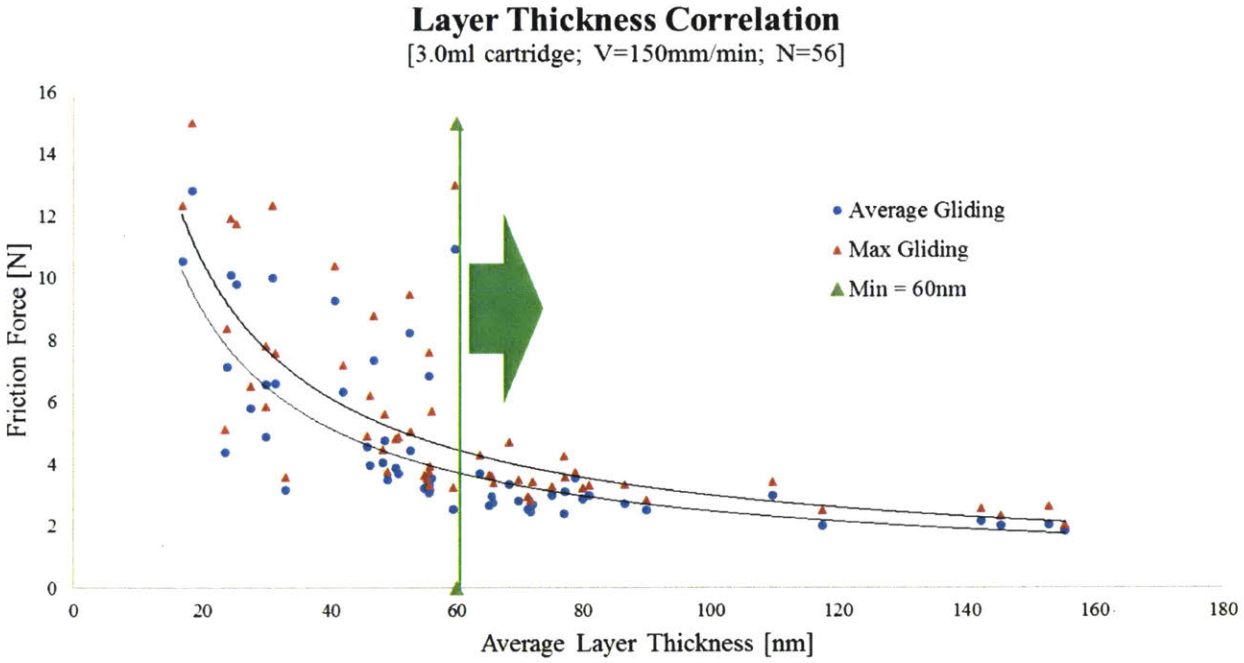

Figure 6: Layer Thickness Correlation - McArthur [2]

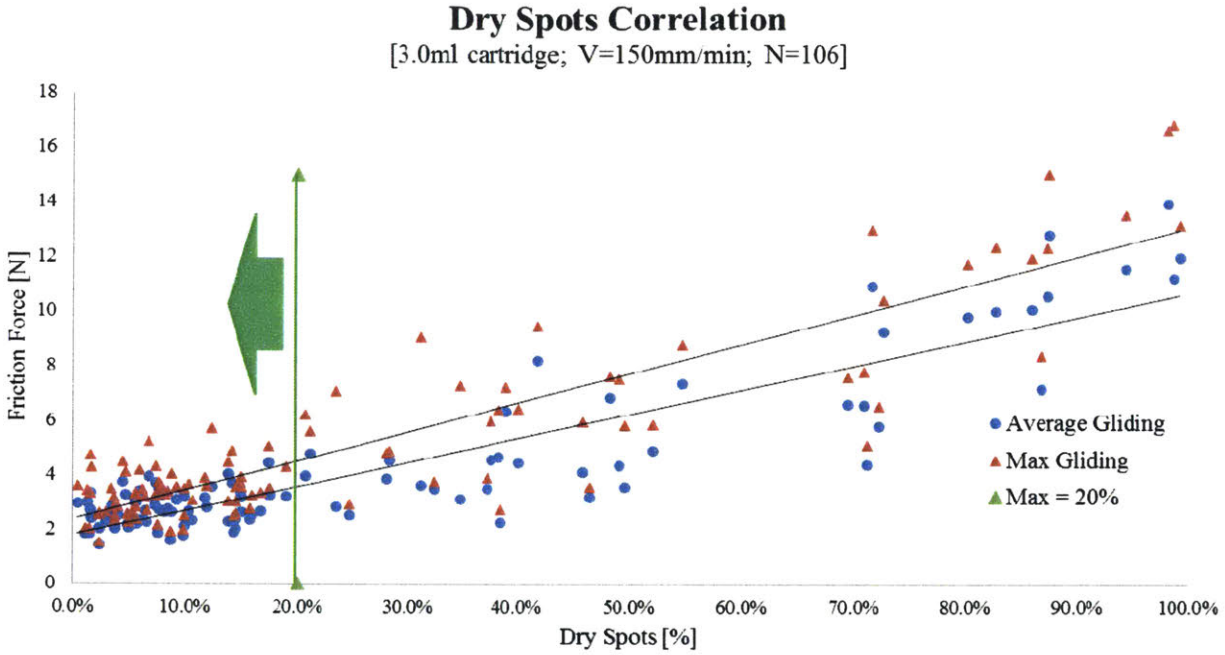

Figure 7: Dry Spots Correlation - McArthur [2]

4 Current State of the Process at Sanofi

4.1 Friction Testing at Sanofi

The friction forces in pre-filled cartridges are evaluated by in-process control testing using a force instrument. This instrument travels at a constant speed and measures the force required to move the rubber stopper along the cartridge. The resulting forces can be broken down into two parts. *Break loose force* is the force required to start the stopper moving, and it is essentially static friction. *Gliding force* is the force required to keep the stopper moving, and it is generally known as kinetic friction. A normal friction test profile will appear as in Figure 8 below, with a peak for the break loose force, a decrease in force after the stopper starts moving, and a level or a slightly positive-sloped gliding force until the end of the test. The diagram below was taken from a lab test of five siliconized cartridge samples. "Kraft in N" translates from German to Force in Newtons, and "Standardweg in mm" to distance in millimeters. Though there is some deviation from this smooth gliding force in one or two of the samples, this generally describes a typical ideal break loose and gliding force profile.

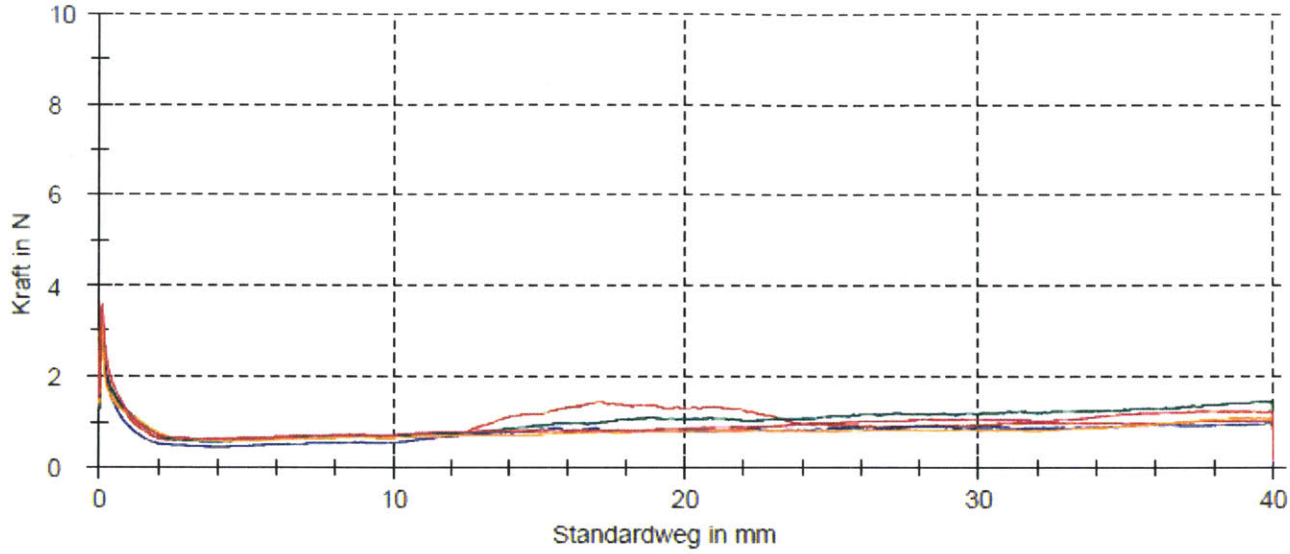

Figure 8: An example of a typical force profile including break loose and gliding forces

Break loose force can increase over time as the rubber stopper can actually push silicone away from the glass surface lowering the lubrication locally as it sits for longer periods of time. See Appendix C for break loose force over time test setup and results. Although break loose force is important to overall pen design, the focus of this project is on the parameters that primarily affect gliding force.

4.2 Process Description

This project studied three main production areas with two different methods of siliconization. The overall process is diagrammed in Figure 9.

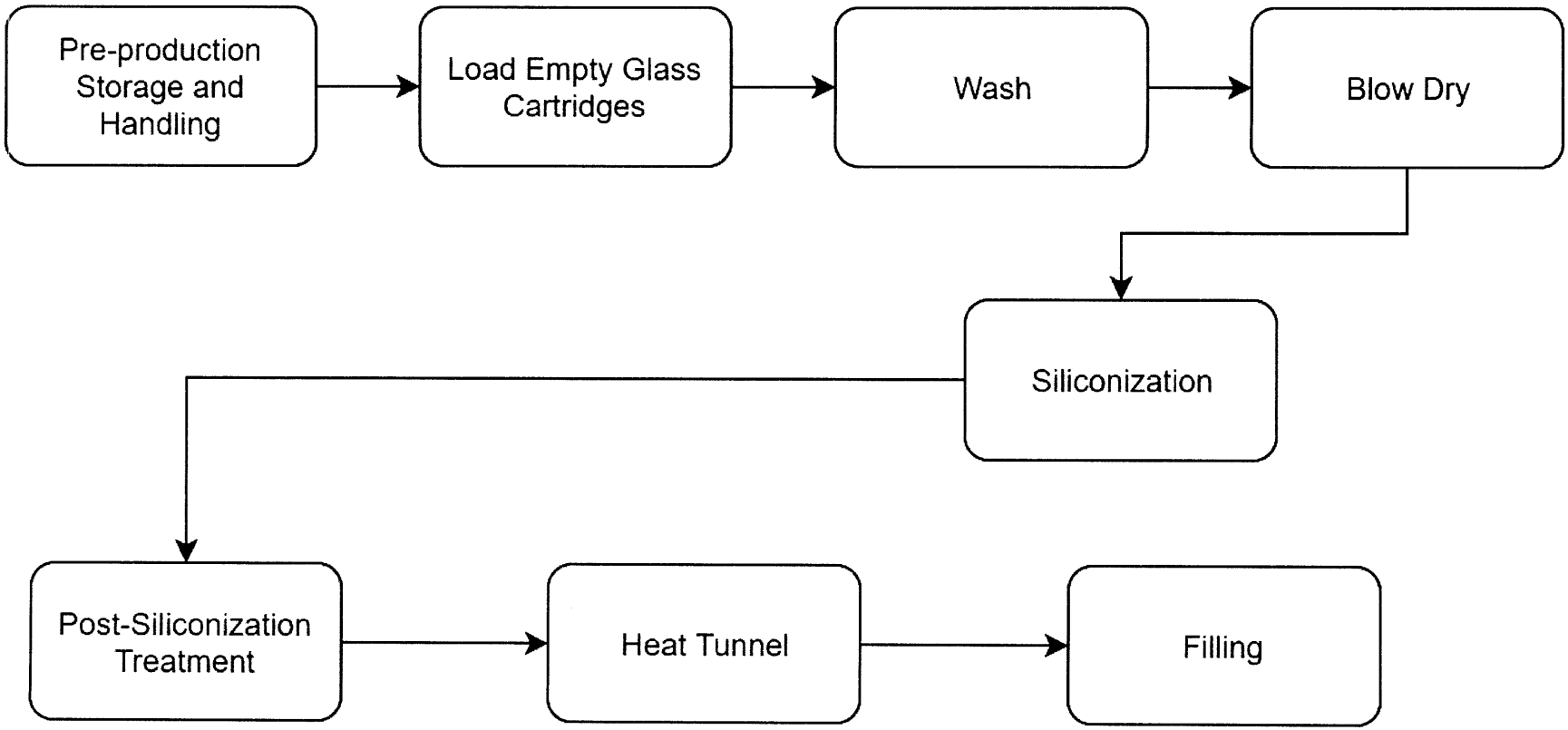

Figure 9: Process flow diagram of insulin cartridge production

4.2.1 Loading

The first step of the process for producing insulin-filled cartridges is loading the glass cartridges onto the line. The glass cartridges are stored on pallets which are brought to the line when needed. For the purpose of this project, the focus was on 3mL glass cartridges, but there are various sizes of cartridges both smaller and larger than the 3mL, all of which are run on the same production lines. In production areas B and C, an operator removes the plastic from around the pallet, and then flips the box over onto a conveyor to load the cartridges or breaks open the side of the box and pushes them out, based on cartridge orientation in the box. In production area A, an operator loads an entire pallet onto the production line. A robot then lifts a box off the pallet and loads the glass onto the conveyor. The glass cartridges are loaded in bulk and then sorted by a corkscrew-shaped cylinder, generally called a worm, into single file for the rinsing and siliconization processes. In processes with a bath, this separation into single file occurs after the bath.

4.2.2 Cleaning

The next step in some production setups is a bath. Production Area A does not have this step. In Production Area B there is a bath with warm water. In Production Area C the bath with warm water also has ultrasonic cleaning. Production Area B has ultrasonic capability, but it is not in use. In all three production areas, the next step is a double rinse. The first rinse is done with recycled water from the second rinse. For the second rinse, the water for injection (WFI) is heated to 80C. The glass cartridge is then blown dry with compressed air by an air nozzle inserted into the cartridge.

4.2.3 Siliconization Methods

After cleaning and drying, the cartridge is ready for siliconization. There are three methods of siliconization used at Sanofi. The first, which is not the focus of this project, is known as time-pressure. A description of this system is still worthwhile to include since another process, microdosing, is similar in performance, and there are a few research studies that have been performed using the time-pressure system to optimize performance of siliconization. There is also a third, very different process called flushing that is used at Sanofi.

4.2.3.1 Time-Pressure

In the time-pressure method of siliconization, a nozzle of fixed height sprays air and silicone together for a set amount of time to coat the inside of a glass cartridge. The glass is presented over the nozzle. The nozzle is then moved into place a set height below the cartridge. In a study of the optimization of the process of siliconization via the time-pressure method, the placement of this starting height was found to be a critical parameter [24]. Once spraying begins, the nozzle stays fixed in place, so if the area of the spray pattern is not ideally placed, it can be applied unevenly or not at all in some areas.

Once the nozzle is fixed in place, the siliconization process begins. This starts first with only compressed air, then the silicone spray is turned on for a duration. After that set amount of time,

the silicone turns off, but the air is still spraying. After another set amount of time, the air then turns off. This pattern of *air, silicone/air, air* creates a fine mist of micro-droplet silicone solution. This small particle size helps create an even coating with no large drops or unevenness [24]. Having the air remain on longer than the silicone spray helps continue to distribute the silicone mist on the glass after the silicone stream stops. See Figure 10 for a diagram of the time-pressure siliconization process.

There are many important variables to adjust that can affect the quality of siliconization. In particular, the placement of the nozzle is important. Additionally, the pressure and duration of the air spray especially in relation to the pressure and duration of the silicone spray is a key parameter to optimize.

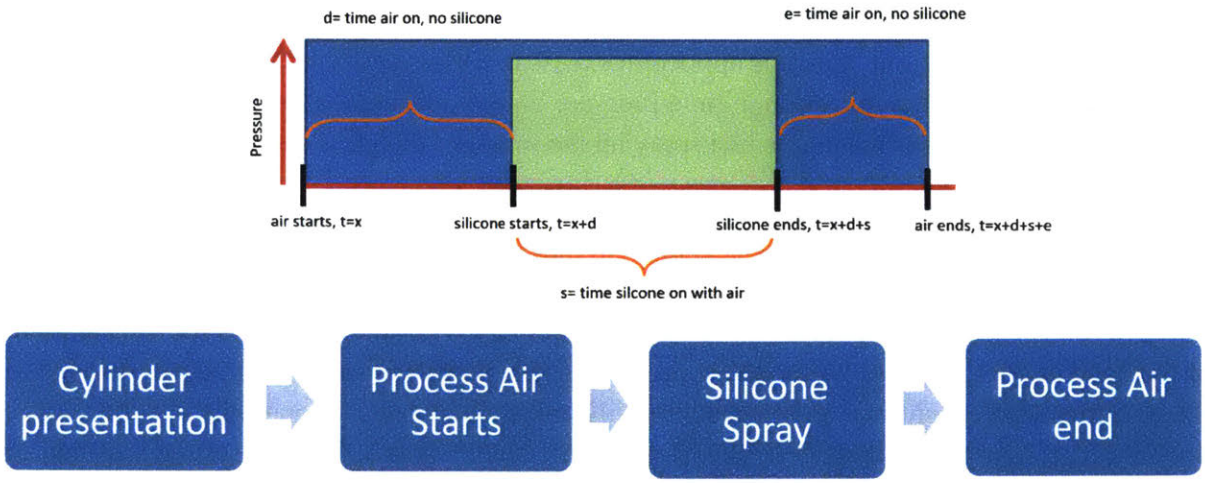

Figure 10: Time-Pressure Siliconization

4.2.3.2 Microdosing

Microdosing is similar to time-pressure in that it applies a mist of micro-droplet silicone solution to the inside of the glass cartridge. The difference is that the air and silicone starts and stops simultaneously and the application nozzle moves along the length of the glass cartridge to create an even coating as the silicone and air spray. Each nozzle has its own microdosing pump that disperses a set amount of silicone.

The key parameters that affect this method of siliconization are the height at which the nozzle starts and stops for the spraying process, the nozzle speed, air pressure, silicone pressure, the amount of silicone dosed, and the process time. The process time for microdosing is fixed, so each step always takes a set amount of time no matter what speed the production line runs at. This process is also highly reliant on a clean surface before application since there is so little silicone applied. Any contamination could easily block the adhesion of the silicone to the glass and create dry spots after the contamination is burned away in the baking process.

Since the microdosing process is very precise, little silicone escapes the inside of the cartridge during spraying. This is more precise than the time-pressure method where a cone of overspray escapes from the bottom, or the flushing method where there is so much solution applied that it spills out the top and bottom. In the two messier processes, silicone from the internal coating often ends up on the outside of the glass cartridges. External siliconization is helpful in reducing glass breakage since the cartridges can then slip past one another on the line easier. Because this does not happen in microdosing, there is actually a step after siliconization where silicone is applied to the outside of the cartridge as well.

Microdosing is used in Production Area C.

4.2.3.3 Flushing

Flushing is a very different siliconization method used at Sanofi in production areas A and B. In the flushing system, a fluid stream is applied in excess to a glass cartridge to ensure complete coverage. Instead of the application in time-pressure or microdosing that might be compared to a mist from a spray bottle, flushing is like spraying the inside of the glass cartridge with a garden hose.

In the flushing process, the nozzle is inserted into the cartridge so that the top of the nozzle is about half a centimeter below the shoulder of the needle end, or top, of the cartridge. The nozzle is kept at this position for the duration of the silicone spray. The silicone sprays for a set amount of time and at a set pressure. When the spray stops, the nozzle is removed from the cartridge. Excess silicone is caught in a tray beneath the siliconization nozzles. Though there is the opportunity to reuse this silicone, neither flushing production area at Sanofi uses the recycled silicone solution. Recycled silicone emulsion could lead to issues with dilution resulting in lower concentrations of silicone applied to the cartridge.

After the silicone is applied, the cartridges move to the air station to have the excess silicone blown out. The air nozzle moves up into the cartridge to a similar height the silicone nozzle had been placed. The air turns on and the nozzle moves down the cartridge with the air on, similar to the microdosing process. When the nozzle reaches the bottom, the air turns off. There is still some excess silicone dripping from the flange end of the cartridge, so after air blow-out, the cartridge moves past an external air nozzle that blows the excess silicone off the bottom of the cartridge. Finally, the cartridge moves past an external blow-off station, where excess silicone that had been applied to the outside of the cartridge during the process is reduced.

The key parameters in the flushing method of siliconization are the time and pressure of the silicone spray and the time and pressure of the internal air blow down. Nozzle geometry is also important; where it is placed and the size, shape, and number of holes plays a role in the final silicone application.

It is also important to note that in the flushing process in Production areas A and B, the timing of the siliconization process is tied to the line speed. This means that the duration of the

siliconization and air blow off can vary based on the machine state. This is particularly obvious in start-stop conditions. When the machine stops, the needles are all up in the glass cartridges. The machine stops in such a way that the silicone sprays, but the air has not started to blow yet. When a stop occurs, fully-siliconized but not-yet blown-out cartridges stand and wait over both the siliconization station and the air station. When the machine starts again, it ramps up slower than full production speed, so the air turns on to its set air pressure and blows out as the needle slowly exits the cartridge. Each cartridge is subjected to the siliconization and blow out steps during start-stop conditions, but when the machine runs slower, the glass cartridges at the air station are blown out for a longer amount of time than compared to steady-state run conditions. The machine slows down when downstream processes back up and stops when buffer areas are full of product or the line goes down for some sort of mechanical issue.

4.2.4 Silicone Solution

The silicone material used in all production areas is Dow Corning® 365, 35% Dimethicone NF Emulsion, which is described by the manufacturer as a hydrophobic lubricant for medical devices. It is diluted to approximately 2.1%, within the manufacturer's recommended range of usage [17]. On each production line, an operator measures out the diluted solution by volume according to line-specific standard operating procedures. First, the operator fills a small container with 35% silicone emulsion up to a level marker. This level marker indicates the amount of 35% silicone needed to add to a water tank to achieve a final dilution of 2.1%. Next, the operator fills water for injection (WFI) in a mixing tank. There is a fill line that marks the level at which enough water has been added to the silicone emulsion to achieve the correct dilution. The water is filled a few inches below this line, then the undiluted 35% emulsion amount is placed into the mixing tank. The operator tops off the level in the water tank to the line with WFI to ensure that the correct volume of water has been added to meet the desired concentration. Some procedures call for the operator to add the silicone emulsion first before adding water to ensure good mixing throughout the solution, but if this is done, the water causes too much agitation and the surfactants in the emulsion overflow the tank. For this reason, the operator generally does not add the emulsion until close to the end of the tank filling. Finally, the operator opens a valve at the bottom of the tank which transfers the solution to another tank below for storage until it is applied. In production areas A and B, there is a circulation loop in this tank that mixes the solution while it is waiting to be used. Production Area C uses a continuous mixer in this tank.

4.2.5 Heating Tunnel

After siliconization, the glass cartridges move from the rinsing and siliconization unit, where they were moving through production in single file, back into bulk transport. Cartridges can actually move past one another and do not necessarily finish the entire process in the order in which they were loaded onto the line or worked through the rinsing and siliconization process. The glass cartridges then move into the heating tunnel. The heating tunnel has three stages, a warm up, a sterilization stage, and a cool down. In the warm up phase, the temperature is raised from ambient to warm, but not hot in order to protect the glass from thermal shock. This stage

lasts only a few minutes. In the sterilization stage, the temperature of the oven is around 300C, but the exact set point varies by 30 degrees across the three production areas. In typical production conditions, the glass cartridges travel through this portion of the heating tunnel in approximately 20 minutes. The purpose of this section of the heating tunnel is twofold. First, it creates the covalent bond between the silicone and glass. Second, it sterilizes the glass to remove any contamination or harmful microbes from the cartridge to ensure completely clean and safe medication. After this step, the rest of the production line through filling and capping is closed to prevent external contamination. Finally, the sterilized cartridges enter the cooling zone where they are gradually lowered in temperature to again prevent breakage from thermal shock. They are released from the tunnel generally above ambient temperature but cool enough to touch or to prevent damage to the insulin that will be filled in it shortly.

The sterilization temperature of 300C is higher than the recommended baking temperature of 200C for the silicone emulsion, but Dow clearly states that the purchaser can also determine the end-use suitability and application and that it makes no recommendations for particular processes [17]. Additionally, another white paper produced by Dow indicates that temperatures exceeding 250 degrees C have been used at much shorter time spans than two hours [25]. The relationship between baking time and temperature is also used as a standard accepted process across the industry and experimentation has been done to verify the solution's acceptable performance at these temperatures [20]. Manufacturing line verification at Sanofi has also determined that this baking temperature is suitable for this shorter amount of time and does not adversely affect the siliconization enough to increase the break loose and gliding forces.

Each production area has a different maximum allowable time in the heat tunnel when the production line halts. For Production Area A, it is 3 hours, B allows 4 hours, and C up to 6 hours. After this amount of time has passed on each line, the cartridges are removed from the hot zone all the way back through the rinsing and siliconization stations. The standing time in the tunnel has been previously verified to not adversely affect the break loose and gliding forces on the lines, but the difference in maximum heat tunnel time varies widely between production areas. The parameters that can affect the heating tunnel process are time and temperature, maximum standing time, and air velocity in the tunnel.

4.2.6 Post-Tunnel and Filling

After the cooled cartridges exit the tunnel, they once again are sorted single-file. A rubber stopper is inserted in the flange end of the cartridge. This rubber stopper is also siliconized. The siliconization of rubber stoppers can take place at the manufacturer or in-house. The stoppered cartridges then move to a two-part filling station. The first fill is a rough fill that makes up most of the volume. The second fill tops off the insulin level to an exact amount, leaving no space in the glass cartridge for air pockets. The filled cartridge then receives a cap, which is crimped on creating a seal. The final product then passes through inspection for excess air or contamination, and quality cartridges are packaged in boxes to move on to the next stage of assembly into the pen.

There are not many variables that can affect siliconization during this final filling process. When the stopper is inserted, it can push some of the silicone from the end of the cartridge up as well as deposit some silicone from the stopper itself since this silicone is not baked on the rubber like the glass. Additionally, the fill level is an important factor post-production. Excess headspace can cause turbulence in the cartridge. If there is headspace, the liquid can move around in a turbulent way during handling and shipping. This turbulence can actually cause silicone to leave the internal surfaces and migrate into solution [26]. Though this effect is more pronounced in unbaked siliconization, the phenomenon can still be seen in baked-in cartridges, especially since the rubber stopper also contains silicone.

4.3 Comparison of Production Processes and Parameters across Production Areas and Lines

At the time of this study there were three production lines producing 3.0mL cartridges in Production Area A, two in Production Area B, and one in Production Area C. In general, for production areas with multiple lines, the lines have the same setup across all lines in that area. There are small exceptions in regards to silicone and air nozzle heights on one line in Production Area A which gets changed from 3.0mL to 1.5mL cartridges. A summary of the major production area processes is shown in Table 1.

Table 1: Summary of Major Processes in Production Areas

Production area:	**A**	**B**	**C**
Loading	Robot	Manual	Manual
Bath	No	Yes	Yes- Ultrasonic
Rinsing	Two station	Two station	Two station
Siliconization Method	Flushing	Flushing	Microdosing
Silicone	Mixed	Mixed	Mixed
Max Heating Time	3 hours	4 hours	6 hours

It is important to note that even though the standing times in the heat tunnel are different across all three production areas, the heating tunnels operate the same, so it is not clear why area A can only stay in the tunnel for 3 hours when C can remain for 6 hours. Furthermore, even though areas A and B both use the flushing siliconization process, there are different set points and acceptable performance ranges for silicone application and air pressure for blow out after siliconization. A list of some of the differences between each line is summarized in Table 2.

Table 2: Parameter Settings Across Production Areas

	Production Area		
Process Parameter	A	B	C
Loading	Robot	Manual	Manual
Bath	No	Yes	Yes-Ultrasonic
Post-Rinse Drying Air Pressure (bar) (min/max)	2.0/NA	0.9/NA	1.5/4.0
Siliconization Method	Flushing	Flushing	Microdosing
Siliconization Pressure (bar)	0.3	0.2	NA
Siliconization Needle Movement	Stationary	Stationary	Diving
Air Blow Out Post-Siliconization (bar) (min/operating/max)	1.4/1.4/1.7	0.5/1.7/2.0	NA
Heat Tunnel Temperature (C)	290	320	300
Max Tunnel Time (hr)	3	4	6

Additionally, though production settings are generally the same across lines in the same production area, there can be small differences in the exact set points for some parameters from line to line in addition to small setup differences due the to change over between different sized cartridges for different production runs or for different products.

4.4 Influences on Production Differences

When confronted with some of these differences between production areas, the question of how such situations arose is a logical one. Some of the obvious differences in production are due to equipment such as microdosing in production area C and flushing in areas A and B. Although similar flushing equipment is installed in production areas A and B, they were installed at different times and in different areas with different clean room standards. Some other production variances, such as maximum heating time, are less easy to explain. One factor that could influence production area segregation is the organizational structure at Sanofi Frankfurt. The production areas A, B, and C are organized into three separate departments. The employee structure of each department is very similar with similar roles and processes throughout. There are few obvious channels of communication across the departments or with other departments outside production and outside the SFI group. The siloed structure makes it understandable that differences between production parameters could develop and perpetuate.

4.5 Differences in Silicone Performance

Given the many differences between equipment and settings in different production areas, it is little surprise that there are differences in the average break loose and gliding forces. In-process control tests are taken approximately every half an hour of run time on the production lines. Each production area follows the same SOP for break loose and glide force testing. The testing is performed on a force testing instrument. This instrument records the force required to move the

rubber stopper a certain length down the cartridge at a set speed. Generally, these production tests are performed in two movements to simulate how the cartridge might be used by a patient, so the test will run half the length of the cartridge, stop, then start again to complete the rest of the test. The tests are performed with insulin still in the cartridge, but with the cap removed and no needle to restrict flow. This isolates the impact of the siliconization and eliminates any influence from the needle performance and fluid dynamics.

An analysis of in-process control data from the lines in all three production areas from August 2016 through March 2017 shows that there are differences in what each line produces for break loose force, gliding force, and the standard deviations in each. Data from the second line in Production Area B was not available for 3mL in this time frame since it only ran 1.5mL cartridges. There is very little difference between the minimum values across all lines for both gliding and break loose forces, suggesting that all lines are capable of performing at low break loose and gliding forces.

4.5.1 Break loose Force

As seen in Figure 11, the standard deviation for break loose force is similarly low across all production lines. Additionally, there is no significant difference between Production Area A and C in regards to the average break loose force, though area B appears a bit higher on average. Since production areas A and B use flushing and production area C uses microdosing, this points away from the siliconization method's influence on the break loose force. In regards to the requirements for the automated insulin injection pen, the break loose force is less of a focus for this project than the gliding force.

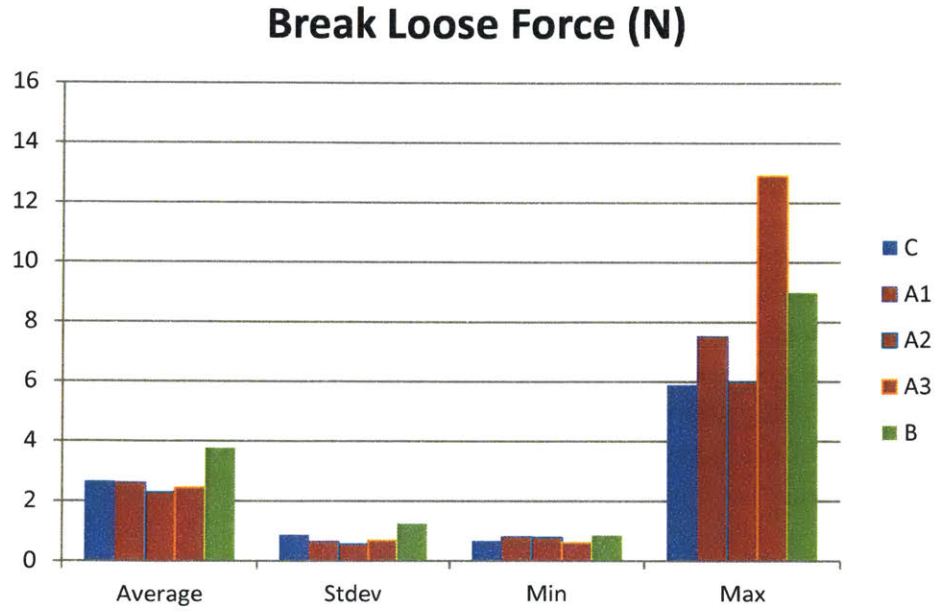

Figure 11: Break Loose Force Comparison between three production areas

4.5.2 Gliding Force

For the gliding force, there are a few key takeaways from the in process control test data that suggest there are critical process differences affecting siliconization. One thing to note in Figure 12 is the difference between the maximum gliding force recorded between Production Area C (lowest maximum force) and one line from Production Area B (highest maximum force). All three production lines in Production Area A are at least twice as high as the maximum for Production Area C. Though it appears small, the standard deviation is twice as high on the flushing lines (A,B) as compared to the microdosing line (C), indicating that these high maximum values occur more frequently in the flushing production areas.

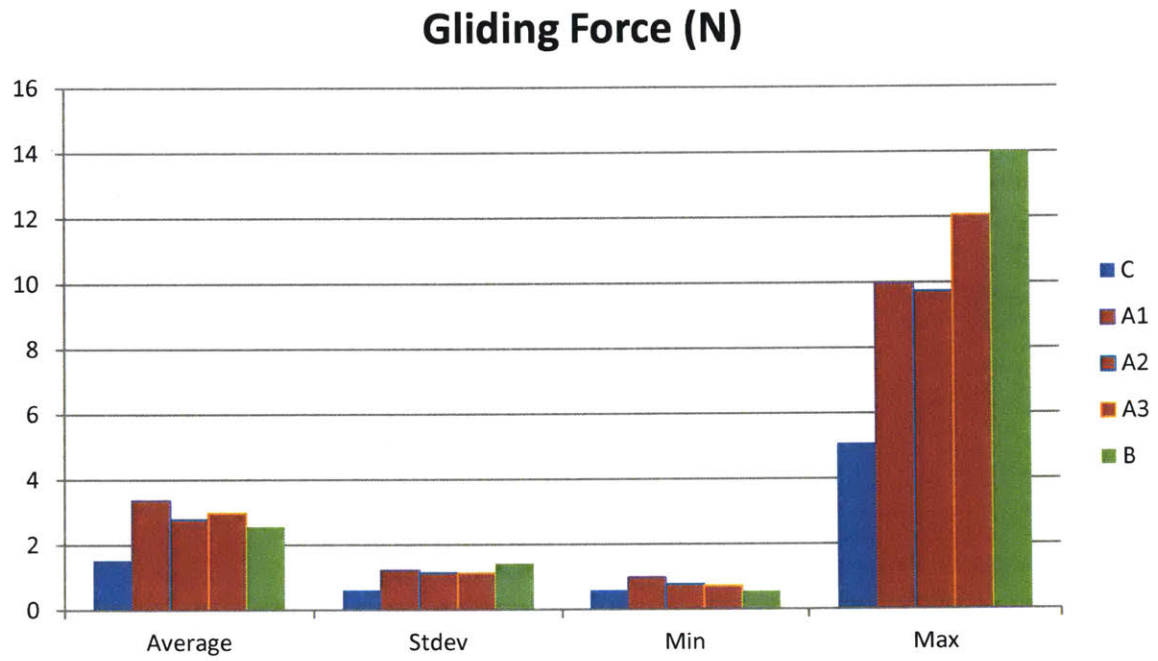

Figure 12: Gliding Force comparison across three production areas

4.5.3 Comparison Across Production Areas

Further investigation into this data showed an interesting pattern regarding the performance of break loose and gliding force in Production Area A. As shown in Figure 13, on average the gliding force is actually *higher* than the break loose force in Area A. This presents a challenge for designing for pen automation. It is much more difficult to design a pen that can perform reliably when the break loose and gliding forces are unpredictable in regards to which will provide the higher force.

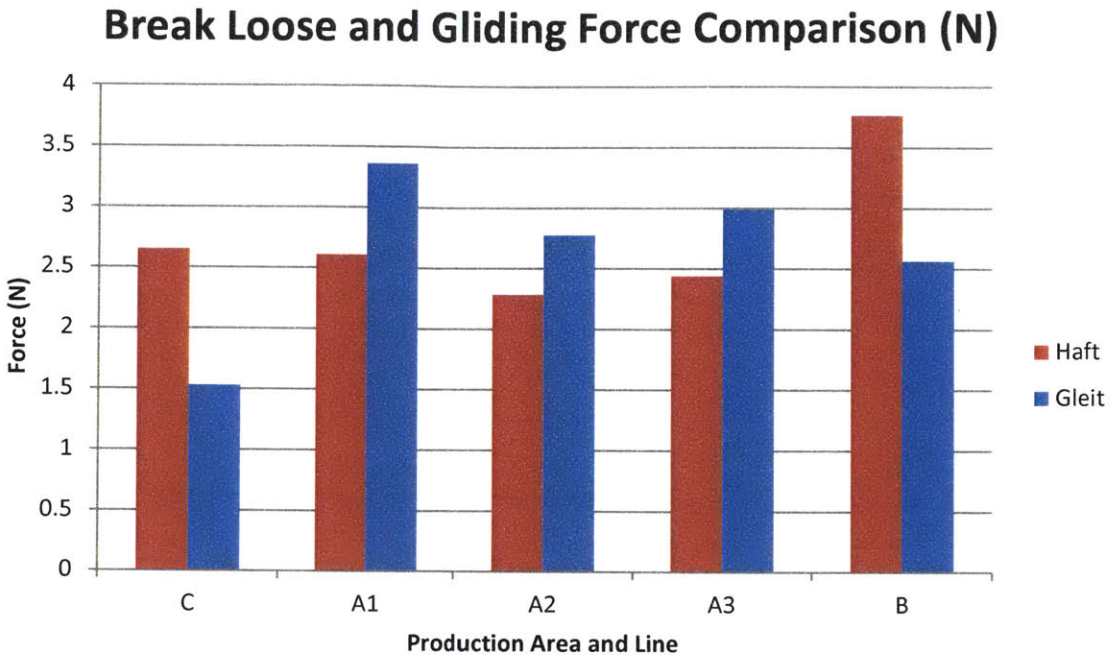

Figure 13: Break Loose and Gliding Force Comparison Across Three Production Areas

There are two common ways in which the gliding force can end up higher than the break loose force. In one scenario, the break loose force is within normal range, and the gliding force starts low, but then rises significantly as the stopper travels down the glass cartridge. This can happen immediately as shown in Figure 14 or at some later point in the cartridge as the stopper approaches the needle end of the cartridge as shown in Figure 15.

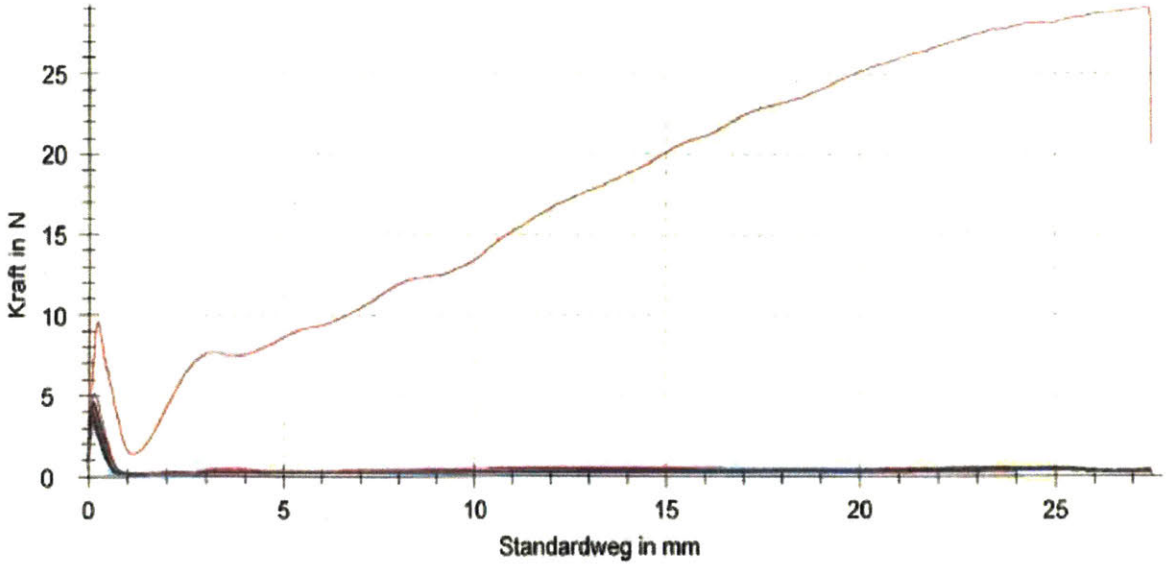

Figure 14: High Gliding Force Sample – Steady Increase

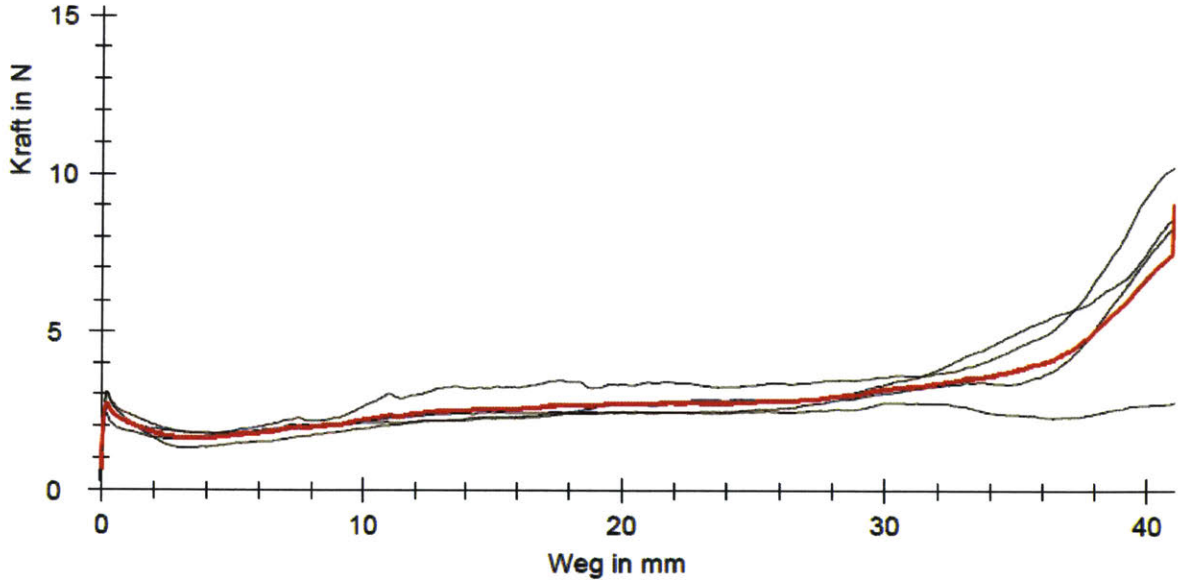

Figure 15: High Gliding Force Sample - Increase at End

Another way a higher gliding force can occur is if the break loose force never has a peak. In this case, the force to move the stopper keeps rising without ever decreasing after breaking loose. In Figure 16, taken from a 12 sample in-process control test on production area A, there are a few samples that behave in a normal fashion. They break loose before 0.5mm and then the force declines. However, many samples in this test show no break loose and simply arch up continuously without ever reducing after the stopper starts moving.

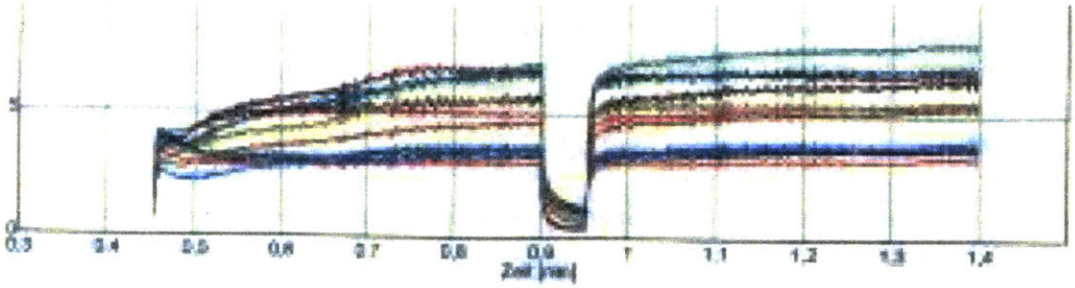

Figure 16: In process control test showing no break loose and high gliding forces

The cause of such behavior is difficult to diagnose. Differences in tolerances in glass and rubber stoppers could cause increased forces, and this is more likely if seen over a large number of samples especially in the same lot number from the glass or rubber stopper manufacturer. Ignoring this potential for defect, another reasonable assumption is that such increases in forces are due to differences in silicone layer thickness along the cartridge leading to higher forces in some places, particularly the top of the cartridge. This is the assumption explored in this project through evaluation of production parameters that affect siliconization.

5 Analysis Methods

Silicone applied to the inner surface of glass cartridges can be very difficult to measure. There are a few methods in common practice such as weight before and after silicone application and powder coating with talc powder to highlight where silicone is applied. Developments in reflectometry for this application are also starting to be used.

The method of weight measurement requires that the glass cartridge be weighed before silicone application and then after to see how much silicone was applied. Generally, this weight is used as an understanding of how much silicone is in the cartridge with the assumption that it has formed a uniform layer along the surface. This gives an indication of the amount of silicone applied, and this method is frequently used in reference to concerns about the effects of silicone mixing with a medication and potentially interacting with protein structure [16]. It does not give a good indication of layer thickness along the cartridge or how that might affect injection forces.

5.1 Measurements of Silicone Presence, Layer Thickness, and Force

5.1.1 Powder Coating

Powder coating is a destructive method of silicone application analysis. It consists of coating the inner surface of a siliconized syringe with fine glass powder or talcum powder. The powder sticks to the silicone layer and generally falls away from the untreated glass, showing precisely where the silicone has been applied. This can be useful in visualizing silicone distribution. There are limitations to the usefulness of this method. Since the powder cannot be removed without disturbing the silicone layer, the sample cannot be used for additional testing such as force

testing. Currently, there does not appear to be a measurement that can be used to indicate the actual amount of silicone on the cartridge from the powder coating. A thicker, more opaque coating indicates a thicker silicone layer, but there is no current metric for definitively measuring the silicone layer thickness using this method.

Figure 17, created using samples from Sanofi production areas A and C, shows a series of siliconized cartridges that are powder coated.

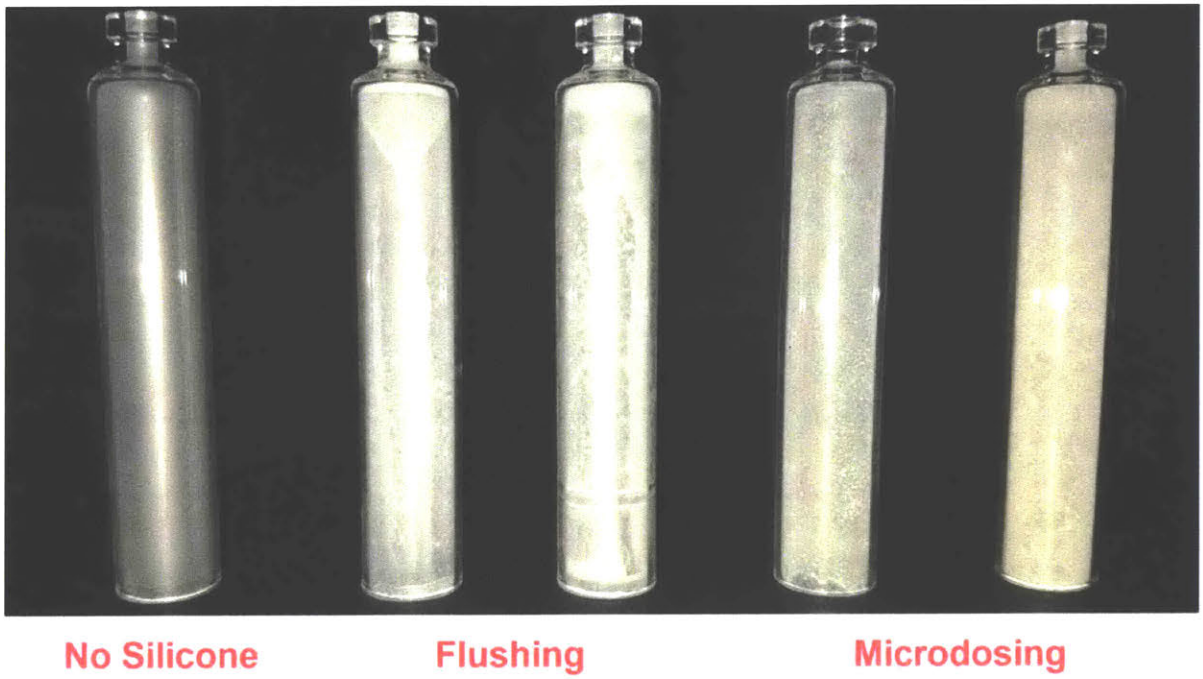

Figure 17: Powder Coated Samples

5.1.2 Rap.ID

5.1.2.1 Rap.ID Technology

LayerExplorer Software by Rap.ID uses white light reflectometric interference spectroscopy to measure the layer thickness of silicone oil on the glass surface. Based on the refractive index of the glass cartridge and silicone oil, the thickness of the silicone layer can be determined using the returned spectrum. This can measure layer thicknesses down to approximately 80nm. For layers thinner than 80nm, which often occur in baked-in siliconization, the Rap.ID Layer Explorer uses laser inferometry. Using a monochromatic laser, the machine can detect layer thicknesses down to 20nm [27]. This is depicted in Figure 18. The equipment uses two sources of light. For thin silicone layers less than 100nm, the machine relies on a laser for measurement. These layer thicknesses are commonly found in baked on siliconization. The laser can measure down to 20nm thickness, after which it returns a 'limit of detection' reading.

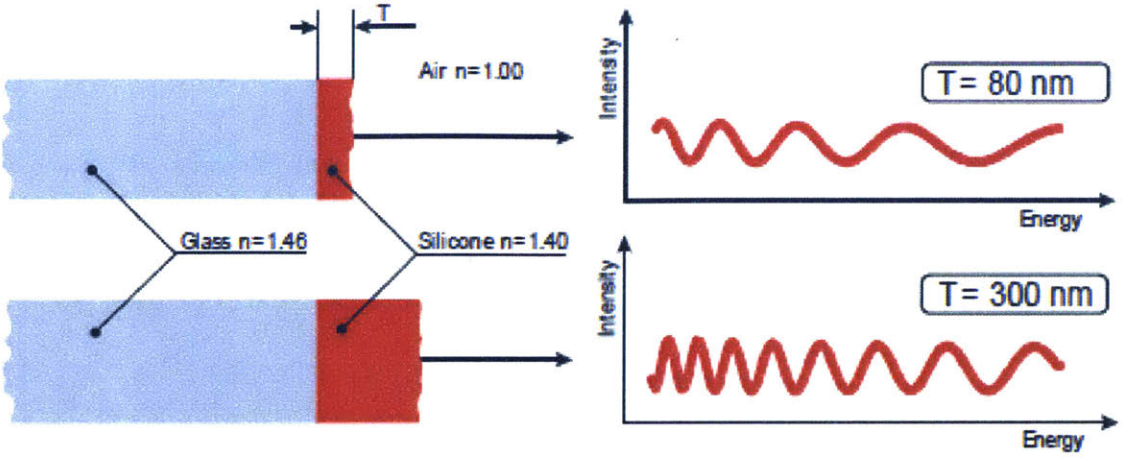

Figure 18: Reflectometry wave length readings to determine layer thicknesses [28]

5.1.2.2 Measurements and Analysis Using Rap.ID

The Rap.ID Layer Explorer uses refracted light to determine layer thickness at a particular location on the sample. The user can set sampling frequency along different parameters, length and rotation. Length describes how far down the sample the Rap.ID will measure and how many sample points it will take. For instance, most samples in this study were done at 35-40mm lengths with 100 measuring points along that distance. Second, the user selects the rotational degrees at which the Rap.ID takes measurements along the circumference of the sample. The minimum is 4 points of measurement, or 90 degrees between measurement points. The maximum is 36 measuring points or 10 degrees between each point. The Layer Explorer then generates a report detailing the layer thickness at each point on each line and assembles a sort of topographic map to show the layer thicknesses. Figure 19 shows the topographic image of layer thickness for three measurements of the same sample at 36 lines, 12 lines, and 8 lines. The sample was also measured at 4 lines, but an image is not generated at this resolution.

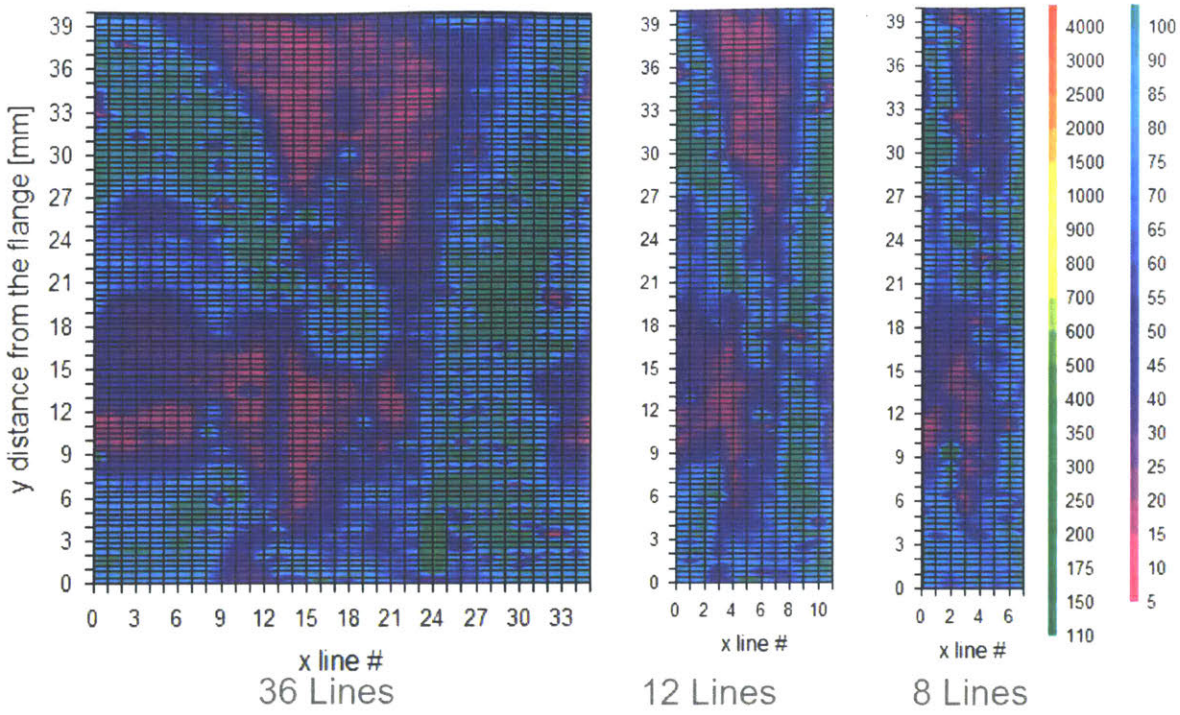

Figure 19: Rap.ID resolution comparison

The selection of resolution was important because of the time required to take such measurements. A sample with measurements at 30 degrees (12 lines) and 100 points over 40mm took about 45 minutes to complete. A sample with measurements at 10 degrees (36 lines) and 100 points over 40mm took 2.5-3 hours to complete. These measurement times were a large consideration for assessment in this project. In samples where a clearer visual picture was required, the more thorough analysis at 36 lines was performed. This was particularly useful in evaluating sample "streakiness" as discussed in Section 6.5. In tests where a simple overall average was required, fewer lines were read, generally 8 to 12 maximum.

For the sample shown in Figure 19, the mean thickness, percent dry spots, and other important measurements that indicate sample quality were generated from further analysis of the rap.ID output. These results are in Table 3. The results show that using 8 or more lines produces similar results for these important measurement factors, but going down to 4 lines is not representative of the other sample measurements.

Table 3: Analysis of One Sample at Different Line Resolutions

Sample Lines --->	36L	12L	8L	4L	Average All
Overall mean:	69.8	68.5	70.1	77.1	71.4
Percent dryspot	17.6%	17.6%	15.8%	10.2%	15.3%
Bottom (stopper) average	71.4	69.9	69.9	83.1	73.6
Middle avg.	71.8	70.2	72.9	77.4	73.1
Top (Flank needle end) avg	66.4	65.5	67.6	70.7	67.5
%dry bottom	16.3%	13.8%	15.7%	6.2%	13.0%
%dry middle	8.4%	7.6%	8.7%	3.3%	7.0%
%dry top	27.9%	31.3%	23.0%	20.6%	25.7%
Difference from Average					
Overall mean:	-1.5	-2.9	-1.2	5.7	
Percent dryspot	2.3%	2.3%	0.5%	-5.1%	
Bottom (stopper) average	-2.2	-3.7	-3.7	9.5	
Middle avg.	-1.3	-2.9	-0.2	4.4	
Top (Flank needle end) avg	-1.2	-2.1	0.1	3.2	
%dry bottom	3.3%	0.8%	2.7%	-6.8%	
%dry middle	1.4%	0.6%	1.7%	-3.7%	
%dry top	2.2%	5.6%	-2.7%	-5.1%	
Difference from 36L Results					
Overall mean:		-1.33	0.30	7.21	
Percent dryspot		0.0%	-1.8%	-7.4%	
Bottom (stopper) average		-1.48	-1.52	11.73	
Middle avg.		-1.65	1.06	5.63	
Top (Flank needle end) avg		-0.90	1.25	4.32	
%dry bottom		-2.5%	-0.7%	-10.1%	
%dry middle		-0.8%	0.4%	-5.1%	
%dry top		3.4%	-4.9%	-7.3%	

5.1.2.3 Important Analysis Measurements

When samples are analyzed on the Rap.ID, the Layer Explorer generates a report as well as a series of files with the raw data. This data was imported to Microsoft Excel® and analyzed using a custom built macro. This program analyzed the results for any errors. Occasionally a false high reading around 240nm occurred due to a decision point in the Rap.ID software that defaulted to this value under certain conditions. In such cases, these values were either converted to their proper value using the data or classified as "n.d." or "not determined."

The macro also calculated the following information from the raw data:

Overall Mean: The average layer thickness across the entire measured portion of the sample.

Percent Dry Spot: The percentage of readings below a designated thickness. This could be selected by the user. The Rap.ID cannot measure below 20nm, so anything registering below that automatically comes back as LOD, limit of detection. This dry spot measurement accounts for

LOD and any values below the specified value. In all tests performed in this paper, the specified value was 30nm as it was used as the baseline for other LGO projects [2]. At 30nm as a dry spot, the data tends to show significant changes in performance when this level of percent dry spots exceeds 20%.

Bottom/Middle/Top Average: There can be large differences in average layer thickness between the top and the bottom of the cartridge. This average designation helps identify specific problem areas in cartridge coating thicknesses.

Percent Dry Spots Bottom/Middle/Top: Similar to the average bottom/middle/top, there can be large differences in the percentage of "dry spots" in different areas of the cartridge.

LOD: Limit of Detection- Layer Explorer generates this output when it measures a thickness below 20nm. The evaluation tool developed in Excel® can also assess the number of LOD points and generate a percentage.

n.d.: Not detectable – Layer Explorer generates this output when it fails to get an accurate measurement for a point. The evaluation tool in Excel® can also assess the number of n.d. points and generate a percentage. If that percentage is above 5%, the sample likely does not have enough data to generate an accurate reading and should be re-run. Often times this is caused by a sample that has not been cleaned properly prior to measurement.

5.1.3 Zwick Force Testing

Force testing was performed on a Zwick instrument. This instrument measured the force required to move the rubber stopper down a cartridge at a constant speed. The testing parameters used in all tests in this project were done over 40mm at 50mm/s. The raw data contains point by point force measurements at approximately 0.01mm intervals. The speed setting was selected to match in-process control testing in all production areas. The distance of 40mm is 5mm longer than the in-process control tests in production, but was chosen to reflect the standard measurement distance in the Rap.ID analysis and get data closer to the shoulder of the cartridge.

5.2 Creation of Lab Samples

There were two main methods used to produce silicone-coated cartridges in a lab setting. The main instrument was a test setup machine that allowed for the programming of microdosing settings. The amount of silicone applied, the silicone pressure, air pressure, cycle time, etc. could all be adjusted to create samples with different silicone layer thickness or different treatment. This setup was used to create samples for several experiments in this project.

The testing equipment was also modified to simulate the flushing siliconization setup. A peristaltic pump connected to a spare siliconization nozzle from one of the flushing lines was set up in the main siliconization test chamber. This was not an exact replication of the flushing process since the pump could not control the pressure. In order to increase siliconization pressure in this setup, a clamp was placed on the tubing. The pump ran for 3 seconds, building up

pressure in the silicone line. The clamp was released, and the silicone sprayed out through the nozzle to cover the inside of the sample. The sample was then removed from the test stand and moved to the microdosing equipment. The machine was programmed to only spray air, not silicone. An air nozzle from the flushing lines was substituted for the traditional microdosing nozzle. Though there was a greater time delay between silicone application and air blow out than on the lines, it was the closest lab replication possible given the available equipment. Pictures of the lab equipment setup are in Figure 20. Results from the lab setup and actual line samples were compared for replication accuracy, and these results can be seen in Section 6.5.

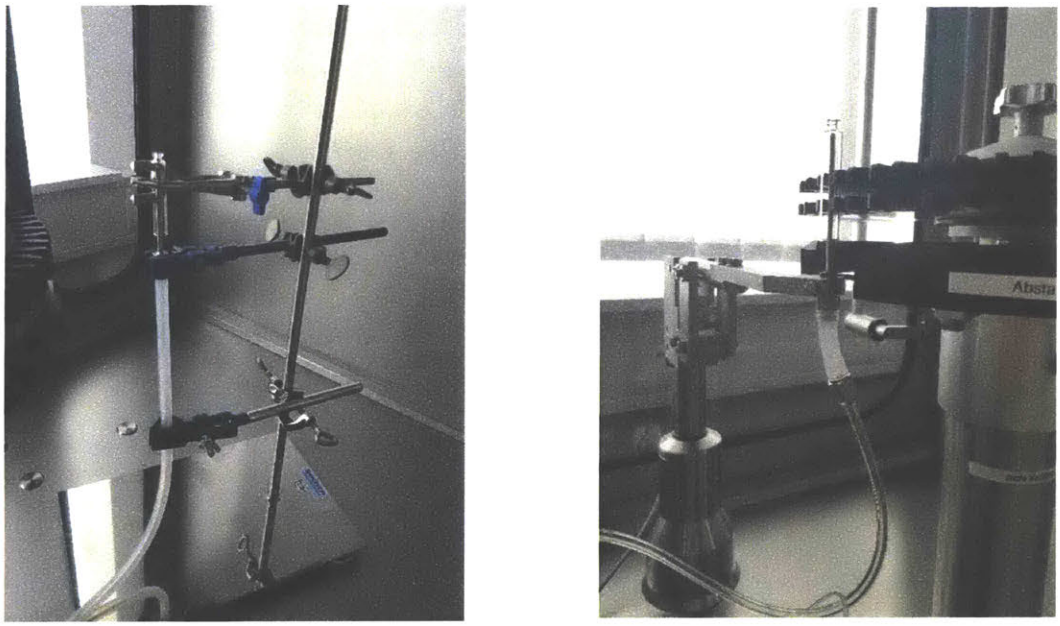

Figure 20: Flushing Siliconization Test Setup – Flushing (Right) and Air Blow Out (Left)

6 Production Parameter Study

This section will begin with another look at the relationship between layer thickness and friction forces. Data from all experiments and line samples were compiled along with previous research data from McArthur (2017). This was to compare results and continue the establishment of a minimum layer thickness. After this analysis, the project moves forward to compare results from different production settings.

There are many variables that could affect siliconization in production processes, and there are some obvious differences between production areas that could cause inconsistencies. There are major differences in the three production areas in regards to cleaning and surface preparation, silicone application, and baking procedures.

Surface preparation and cleaning are important in the application of coatings. The three production areas have three different cleaning procedures. They have similar rinsing steps before

the siliconization step, so it is not clear how important the initial cleaning step is. A comparison of cleaning methods is used to determine the importance of surface preparation to silicone layer thickness.

For the heating tunnel, the most obvious difference is the maximum time that siliconized glass cartridges stay in the tunnel in the event of a line shutdown. The manufacturer recommends that the silicone emulsion not be exposed to high heat for long periods of time [17]. Further studies show that an increase in friction forces can result from exposures longer than an hour in these high temperatures [20]. Line verifications in the three production areas at Sanofi have demonstrated acceptable force thresholds at extended holding periods in the heating tunnel, but it is not clear why there is such a difference in allowable times between production areas. The extended time in the heating tunnel affects not only the samples in the tunnel, but also the samples that are standing on the line post-siliconization and before the heating tunnel. Silicone can migrate down the glass barrel before it gets baked in place, potentially leaving an uneven coating with thinner layers at the top end of the cartridge and thicker layers at the bottom.

For siliconization, there are process differences between the microdosing line and the flushing production areas. Inherent differences in how the silicone is applied in these two methods cannot be made similar without replacing equipment. The microdosing production area has lower overall gliding forces, and more importantly the lowest standard deviation in gliding forces. The microdosing process appears to repeatedly make a consistent silicone coating with low forces and low standard deviation. The silicone layer produced by microdosing is very uniform. Between the small particle size dispersed as a fine spray to the needle movement distributing the spray evenly down the barrel of the glass, uniformity is inherent in the microdosing process. Alternatively, the flushing process douses the barrel with silicone solution. After application, an observer can visibly see the silicone still moving around on the cartridge and dripping out with some small air bubbles clinging to the side. The excess is then blown out with compressed air, but patterns in the silicone after blow out suggest this process may not always leave a uniform coating.

6.1 Layer Thickness, Dry Spots, and Force

The previous LGO project at Sanofi recommended a minimum of 60nm layer thickness with less than 20% dry spots to ensure consistently low forces seen in drug delivery. There is a strong relationship between layer thickness and dry spots suggesting that there are more dry spots with lower layer thickness. This makes intuitive sense; if you apply more silicone, you would expect to get a higher layer thickness and fewer dry spots. Figure 21 shows that as layer thickness decreases, the percentage of dry spots increases.

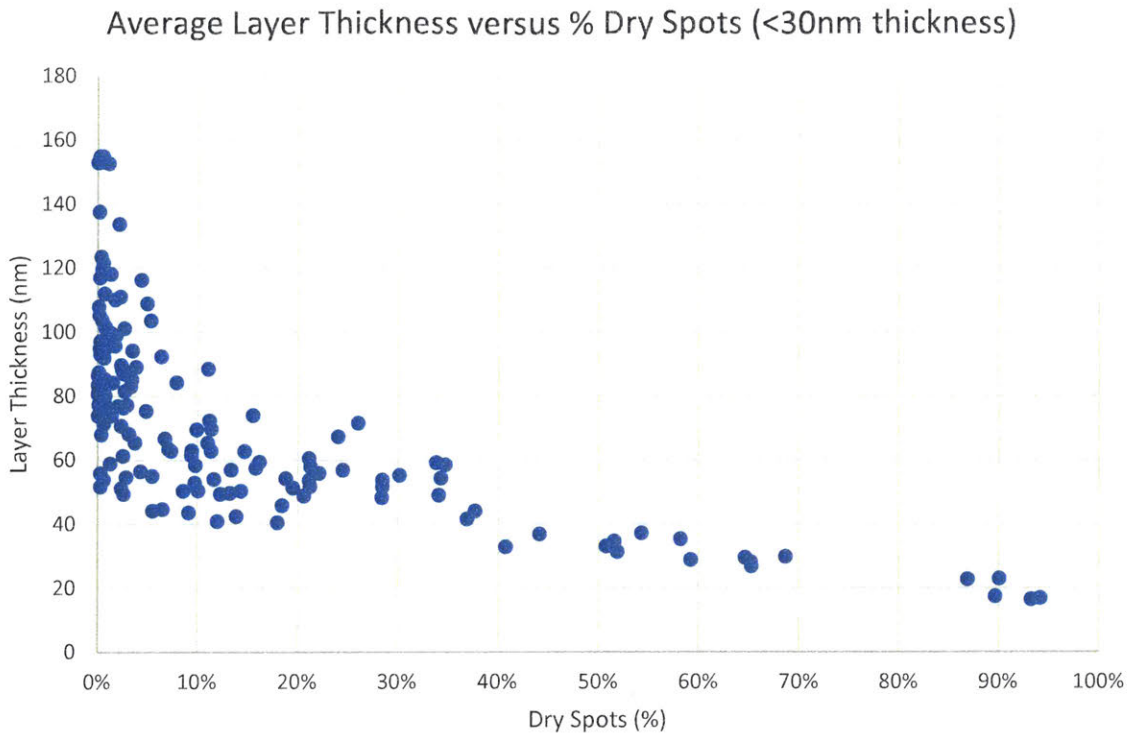

Figure 21: Average Layer Thicknesss versus % Dry Spots

Since fewer dry spots are seen with higher layer thickness, the focus of the rest of this project is primarily aimed toward assessing layer thickness with the assumption that the coatings are generally uniform and dry spots will decrease with increased layer thickness.

As experiments testing production parameters were performed, the data was added to the original set of force data from the previous project. The new data was broken down by location in the cartridge – top, middle, and bottom. Given that this analysis was more local, an adjustment could be made to the minimum layer thickness required to achieve low, repeatable forces.

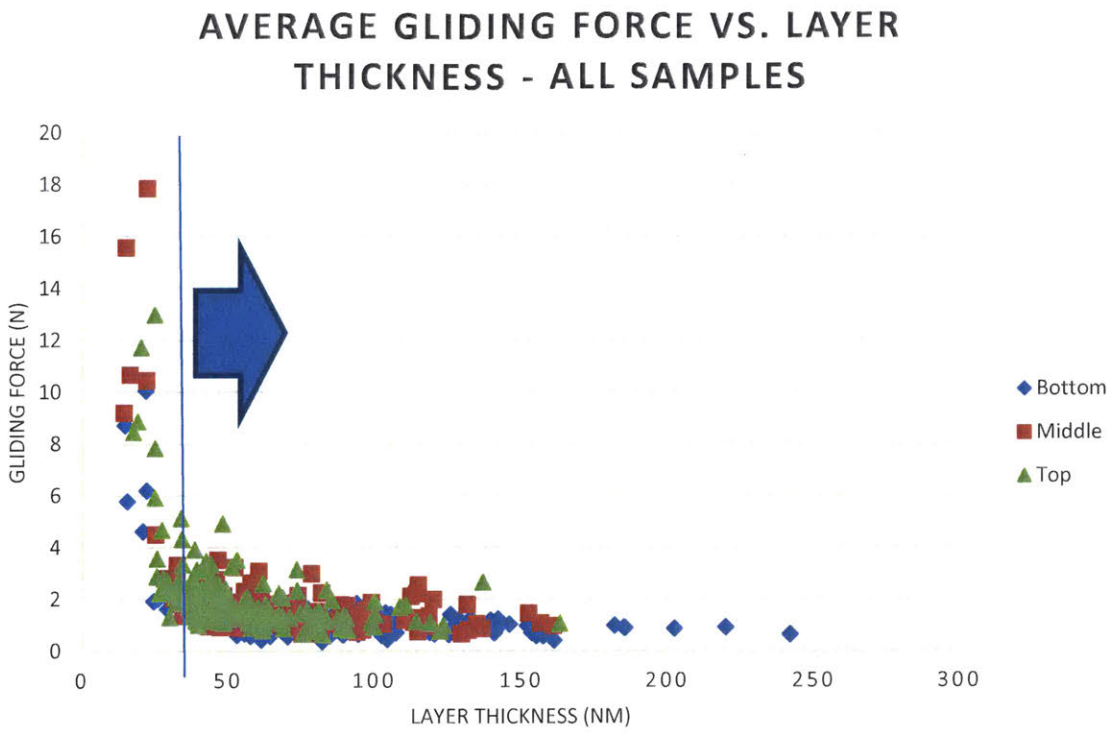

Figure 22: Average Gliding Force vs. Layer Thickness - All Samples

When broken down by area, the minimum required layer thickness is approximately 40nm. This clear inflection point can be seen in Figure 22. The previously suggested 60nm thickness requirement was calculated using the average layer thickness across the entire cartridge, and the testing speed was 150mm/min. The tests in this project were done at 50mm/min reflecting the testing settings for in-process controls. This decrease in speed between projects can also account for some of the lower forces seen in the new data. Since layer thickness can vary greatly from bottom to top of a single cartridge, it is important to break down the analysis locally to get a more accurate measurement of minimum layer thickness. This 40nm minimum layer thickness appears to be a good minimum to use based on several samples comparing layer thickness and force at the some points along the cartridge as seen in Figure 23. In practice or production, 60nm might be a better target to ensure better coverage, but for the purposes of the following analyses, 40nm is used as the baseline for determining "good" coverage.

The rap.ID analysis was performed over 40mm starting from the front end of the rubber stopper in the cartridge (about 7mm from the flange edge). Starting thickness measurements at the front end of the rubber stopper allows comparison of force to layer thickness along the cartridge for a 40mm length.

Figure 23 shows that as the layer thickness nears or dips below 40nm, the gliding force rises compared to the minimum gliding force after the break loose force which happens within the first 3 millimeters of the cartridge. For comparison, in Figure 24, the layer thickness never approaches 40 nm and the forces stay low and even.

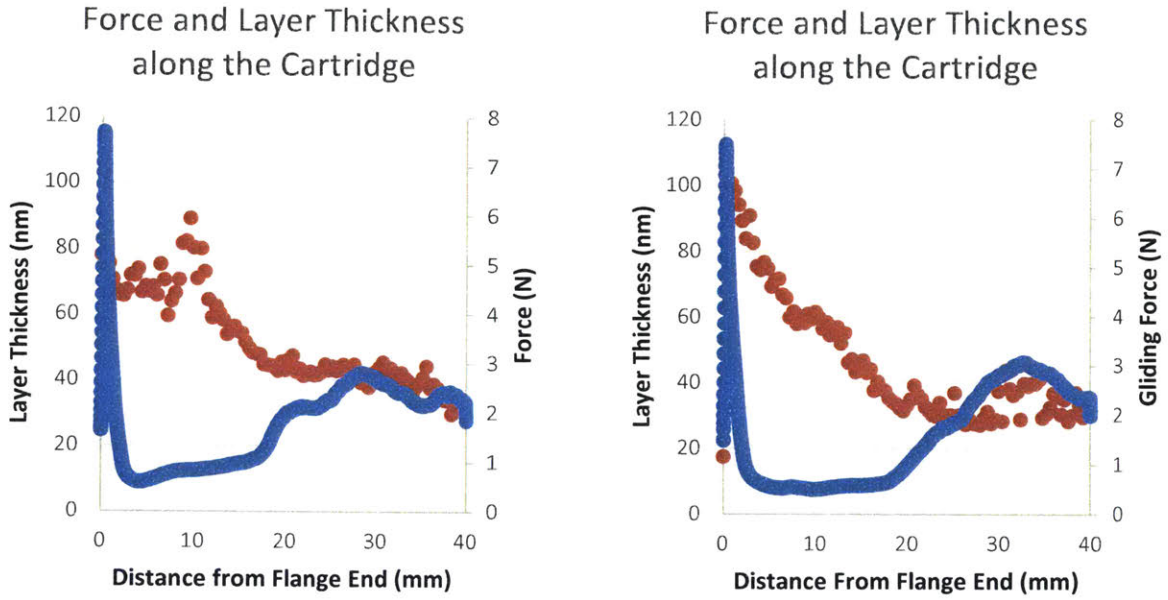

Figure 23: Force and Layer Thickness along a 40mm Cartridge – layer thickness below 40nm

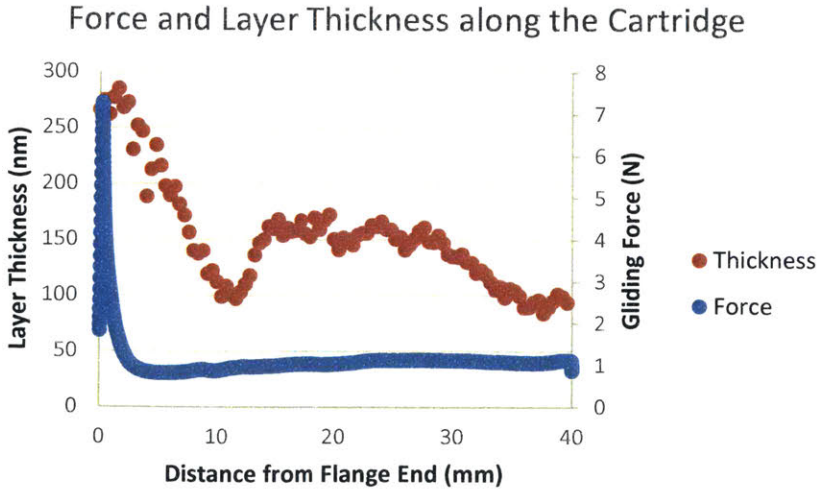

Figure 24: Force and Layer Thickness along a 40mm Cartridge- layer thickness above 40nm

6.2 Cleaning

Cleaning a surface before applying any type of coating is important to ensure good adhesion of the film. Contamination such as dust can block the silicone emulsion from properly coating the glass, and the film will not form properly, creating dry spots. The purpose of the cleaning experiment was to compare relative cleaning methods used across production areas.

6.2.1 Test Setup

Three different cleaning methods were used to prepare the samples. The first was a simple rinse with distilled water meant to mimic the cleaning method used in Production Area A. The second was cleaned in an ultrasonic bath to mimic the method in Production Areas B and C. The third was first cleaned with alcohol and then also cleaned in an ultrasonic bath to try to push the cleaning test further. The samples were siliconized using the flushing method with no air blow out at 1.5% concentration. Air was not used after flushing application to limit the effect of air pressure on the experiment and focus on the silicone adhesion. The lower concentration of 1.5% was intended to amplify the effects of the cleaning.

6.2.2 Results

There appears to be little difference in layer thickness, gliding force, and standard deviation of gliding force based on cleaning method. Since there were only five samples for each method created, a conclusion is difficult to make from the three sample sets. The limited analysis that was performed showed no statistical difference in layer thickness, gliding force, or standard deviation of gliding force due to cleaning method given a t value of 2.18 and 95% confidence interval. A .jmp report with results comparing gliding force, layer thickness, and standard deviation in the top, middle, and bottom of the cartridge is in Appendix D. In each area of the cartridge, there is no significant difference between layer thickness, gliding force or standard deviation.

Figure 25 shows the layer thickness by location based on cleaning method. In all three methods, the layer thickness is thicker at the bottom and thinner at the top, but there are no obvious differences between cleaning with alcohol, just rinsing, and the ultrasonic bath.

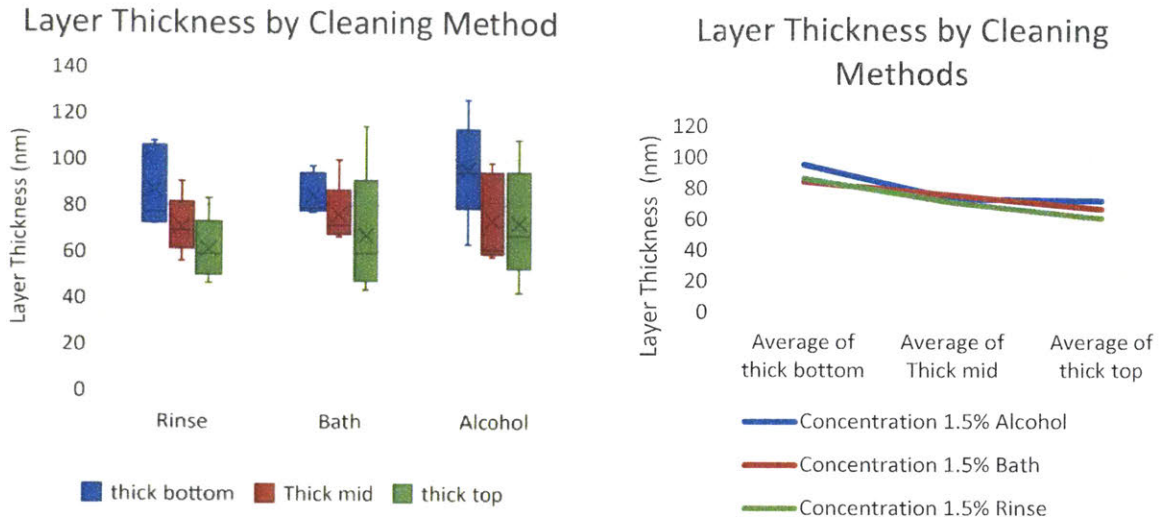

Figure 25: Layer Thickness by Cleaning Method- Box Plot (Left) and Line Chart (Right)

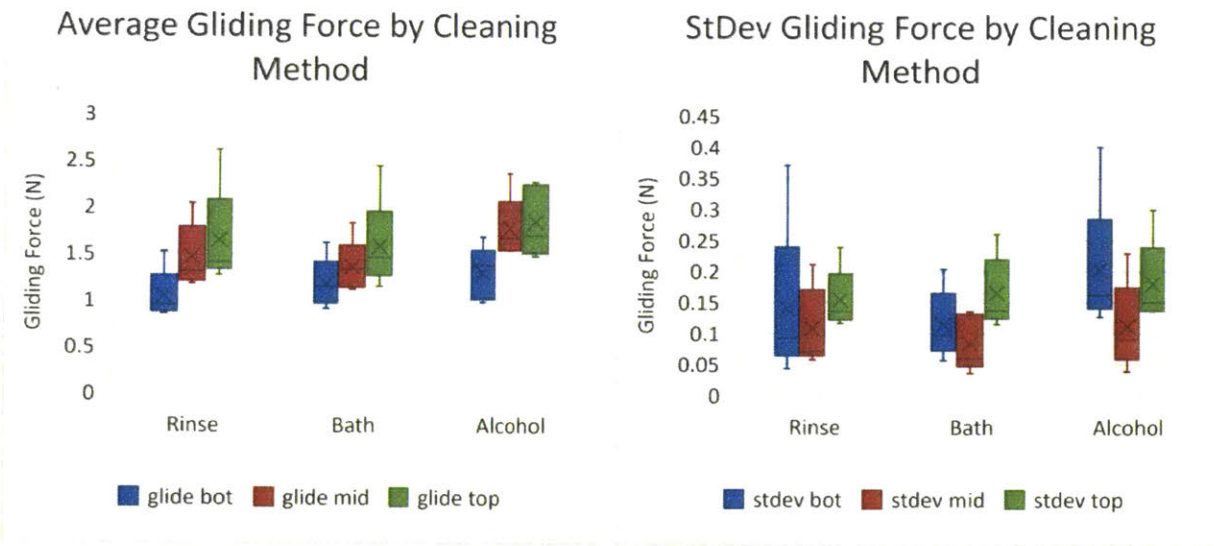

Figure 26: Box Plots of Average Gliding Force (Left) and Standard Deviation (Right) by Cleaning Method

Similar results are seen for gliding force and standard deviation in the samples, as shown in Figure 26. Gliding force rises on average as the rubber stopper moves toward the top of the cartridge for all samples, and there is no significant difference between cleaning method.

6.2.3 Conclusions

This test supports the conclusion that the differences in cleaning methods currently in the three different production areas are not a major contributor to differences in siliconization performance. Production area A does not do any pre-cleaning before the initial rinses prior to

siliconication, production area B has a bath, and production area C has an ultrasonic bath. Even taking the cleaning a step further by adding a solvent, alcohol, for cleaning does not significantly change how silicone adheres to the glass surface or the subsequent gliding forces.

It is possible that other more intensive cleaning methods not currently in use on the production lines could affect surface preparation significantly enough to make an impact on siliconization. In the past LGO project done by McArthur, atmospheric pressure plasma (APP) treatment was proposed as a method for better surface preparation [2].The results from those experiments did not show a large impact from APP treatment on siliconization, but there was a significant time delay between treatment and silicone application.

Though it is possible that cleaning may contribute to siliconization in more thorough surface preparation methods, the contribution of current cleaning differences between production areas compared to other variables is likely very small.

6.3 Heating Tunnel Tests

The maximum allowable standing time in the heating tunnel varies between production areas. In Production Areas A and B, which have flushing siliconization, the allowable standing time in the tunnel is a maximum of three hours and four hours, respectively. Production area C with the microdosing siliconization has an allowable standing time in the tunnel of 6 hours. All these times have been tested and approved in regards to maintaining current force specifications. However, this variation in heating time has the potential to affect the variation of forces between production areas. This experiment was designed to determine the effects of heating tunnel time on layer thickness, gliding force, and standard deviation.

6.3.1 Time in Tunnel

The silicone oil manufacturer's recommendations suggest shorter allowable heating times at high temperatures (approximately 300C), and other studies suggest heating times greater than one hour impact the friction force in the cartridges in a significant way [17], [20]. Despite this, product verification and qualification tests on the production lines at Sanofi have shown little impact to actual in process control test results for injection force, establishing these times as acceptable for production quality. However, differences in baking time may produce small differences in force performance, which would lead to variation in performance between production areas.

6.3.2 Test Setup and Rationale

Two sets of samples were created for the heating test on the flushing siliconization test setup, one at 2.1% concentration and one at 5% concentration of silicone solution. The 2.1% concentration is what is used on the production lines. The elevated 5% concentration was introduced to the experiment to evaluate if higher layer thickness is beneficial in reducing effects of extended time in the heating tunnel and evaluate if excess silicone remains after the baking process. Since this high concentration is not a realistic production scenario, only limited analysis

was done. For this test, none of the samples were blown out with air in order to isolate the effects of heating and not introduce further potential variability from the known effects of the air blow out step. Five samples of each combination were analyzed for a total of 40 samples (4 heating times * 2 concentrations * 5 samples).

These samples were baked at 300C for 30 minutes, 60 minutes, 180 minutes, and 360 minutes for each concentration. They were then analyzed on the Rap.ID at 12 Lines and 100 points over 40mm. Force readings were taken on the Zwick at the standard 50mm/min and 40mm distance.

6.3.3 Results

As shown in the box plots in Figure 27, a decrease in layer thickness is seen with increased baking times. As baking time increases, the layer thickness does tend to fall, though it is not conclusive that this is the only factor contributing to increased forces. In the 5% samples, the layer thickness never falls to the threshold of 40nm. The layer thickness is very thick in the 5% concentration samples, around an average of 120nm up to over 200nm after baking for only 30 minutes. It is very likely that there is still unbaked moisture and surfactants in the silicone emulsion.

The charts in Figure 28 show that although the gliding forces for the 5% concentration do rise over time, they are not as high as results in the 2% concentration samples. In the 2% concentration, after 30-60 minutes of baking, the average layer thickness is around 65nm, with only some points dipping below the 40nm point. After 60 minutes, the layer thickness drops another 10nm, but there are lower minimums indicating more dry spots in the longer-baked samples. Though there is a noticeable difference in the layer thickness at lower concentrations and longer baking times, the layer thickness may not be the sole reason for increased forces and variability. It is likely there are other chemical changes happening in the silicone properties that are also degrading the properties of the material and creating higher, more variable gliding forces.

There appears to be a jump in gliding force after 60 minutes of heating but before 180 minutes especially in the 2% concentration samples. This indicates that the overall impact of extended time in the heating tunnel is lessened by having a higher concentration of silicone emulsion. The maximum gliding force for baking times greater than 3 hours drastically increases in the 2% solution samples. This is an important finding because across all three production areas, the concentration is approximately 2% and the maximum allowable time in the heating tunnel is 3 hours for production area A. It is longer for areas B and C at 4 and 6 hours, respectively.

The charts in Figure 29 show there are similar increases seen in the gliding force standard deviation with increased baking time for both the 2% and the 5% concentration samples. The magnitude of the standard deviation is greater in the 2% concentration, but the increasing trend can be seen for each. This indicates that at 2% concentration, there is likely to be more variability in gliding forces along the cartridge, and this is exacerbated as baking times increase.

Again, the implications are that beyond at least 1 hour of baking time, the range of expected gliding forces increases, indicating there will be a design implication for the mechanical force of an insulin pen.

A .jmp report with results comparing gliding force, layer thickness, and standard deviation in the top, middle, and bottom of the cartridge is in Appendix E. This report only assesses the samples at the 2% concentration. Looking across the whole sample and using a t value of 2.12 for a 95% confidence interval, the overall average gliding force increases significantly beyond 60 minutes in the baking oven, but is not significantly different in the 30-60 minute range or in the 180-360 minute range. Similar results are seen for overall standard deviation across the whole sample and layer thickness, though in this test the greatest differences are seen at the 3-hour baking time. Overall, there is less difference in layer thickness at the bottom, middle, and top locations over time, but a very significant difference in gliding force in the bottom, middle, and top locations showing a clear statistical difference between gliding forces less than 60 minutes and more than 180 minutes. Standard deviation also increases over time in the baking tunnel at each location.

6.3.4 Conclusions

Statistical analysis of the results show that both heating time and concentration have a significant effect on the gliding forces of the samples. There is some lesser effect on layer thickness and standard deviation suggesting that though layer thickness is not getting lower with more baking time, there is some other effect due to heating causing increased gliding forces. This becomes more pronounced somewhere between one and three hours even though the layer thickness is not below the 40nm threshold in some cases. There is likely another chemical process impacting the qualities of the silicone at extended exposure to high temperatures, not just a thinning of the silicone layer. This relationship should be explored further to better understand the chemical properties of the silicone emulsion under prolonged extreme temperatures.

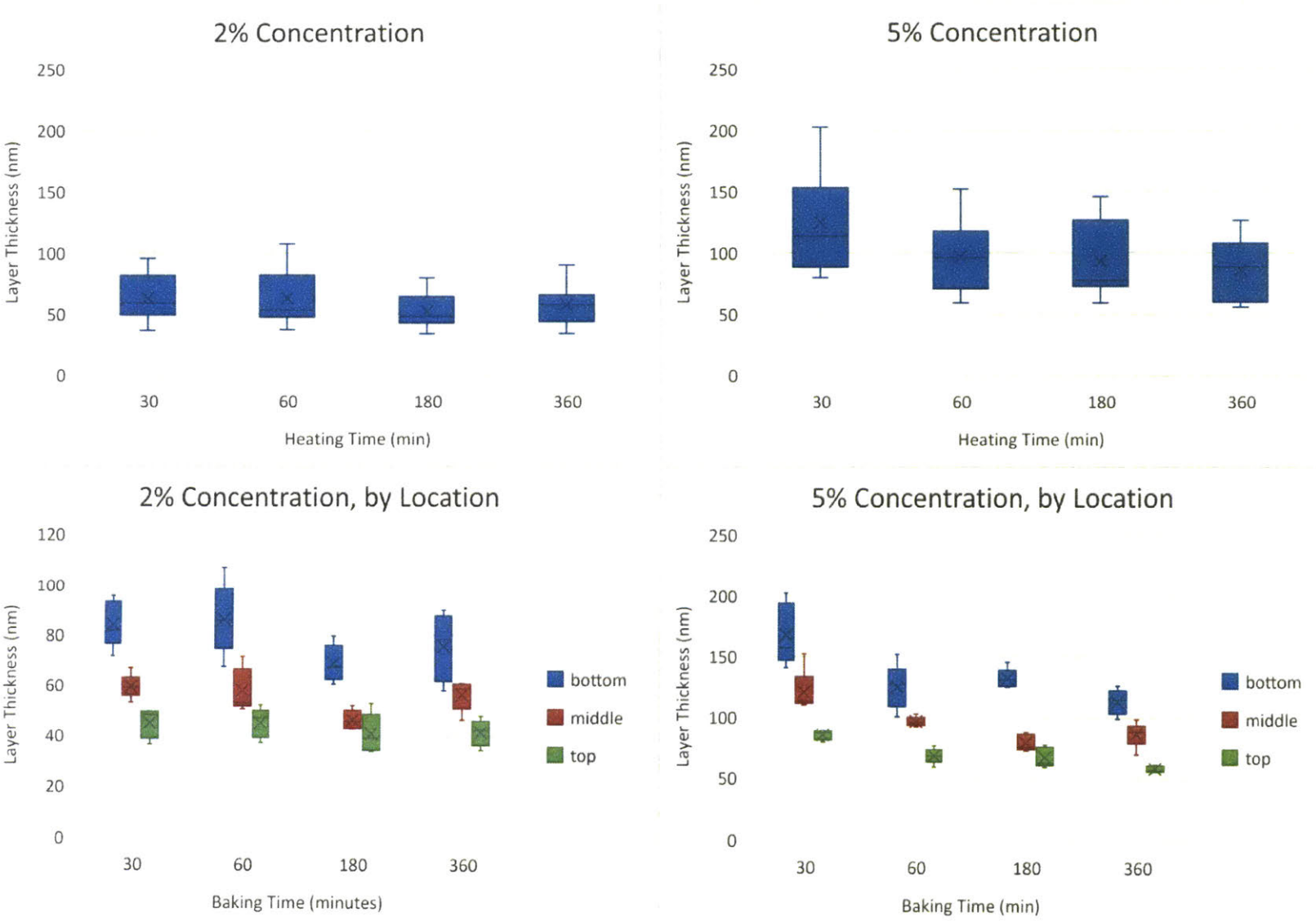

Figure 27: Layer Thickness by Heating Time Charts

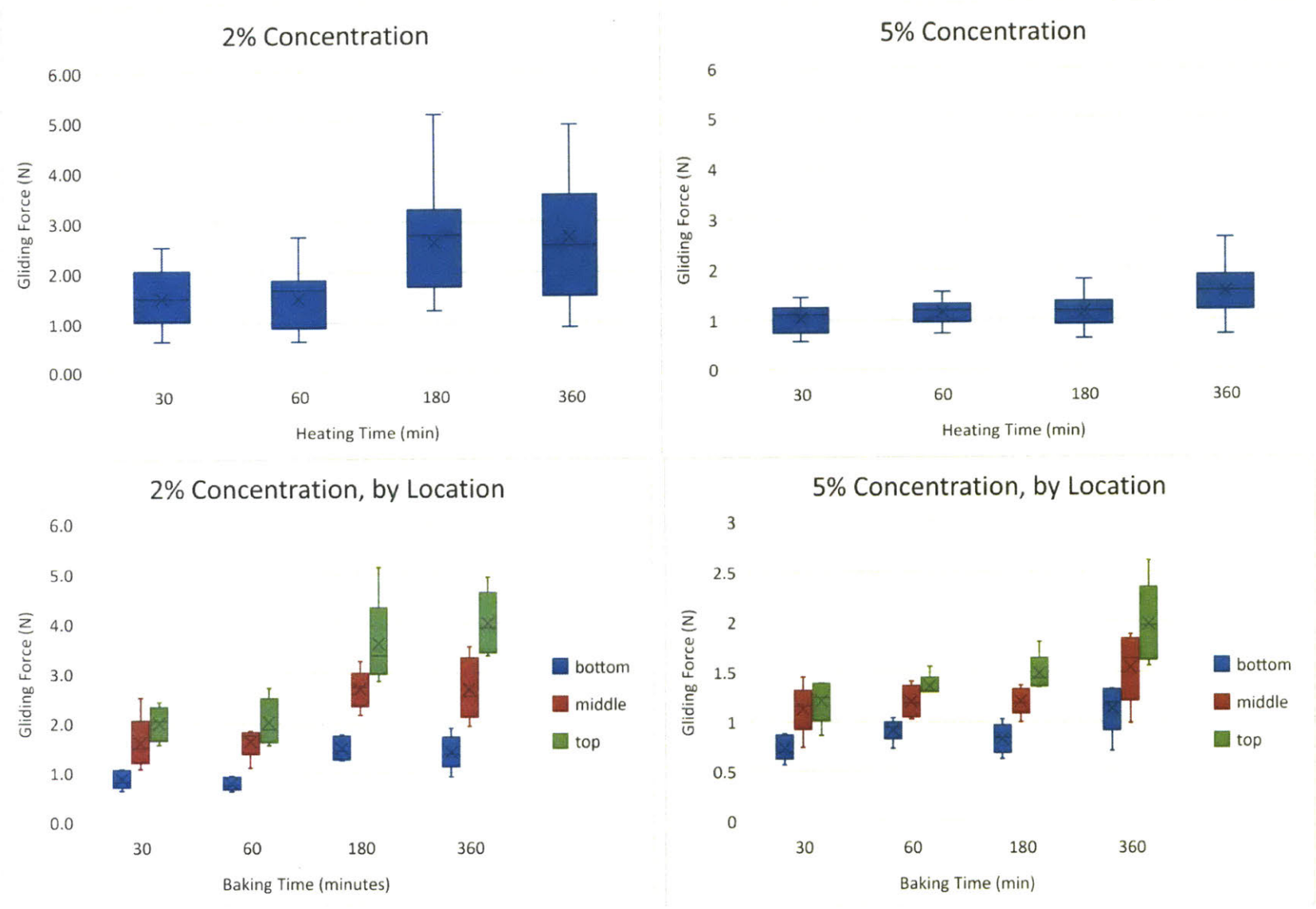

Figure 28: Gliding Force Heating Time Charts

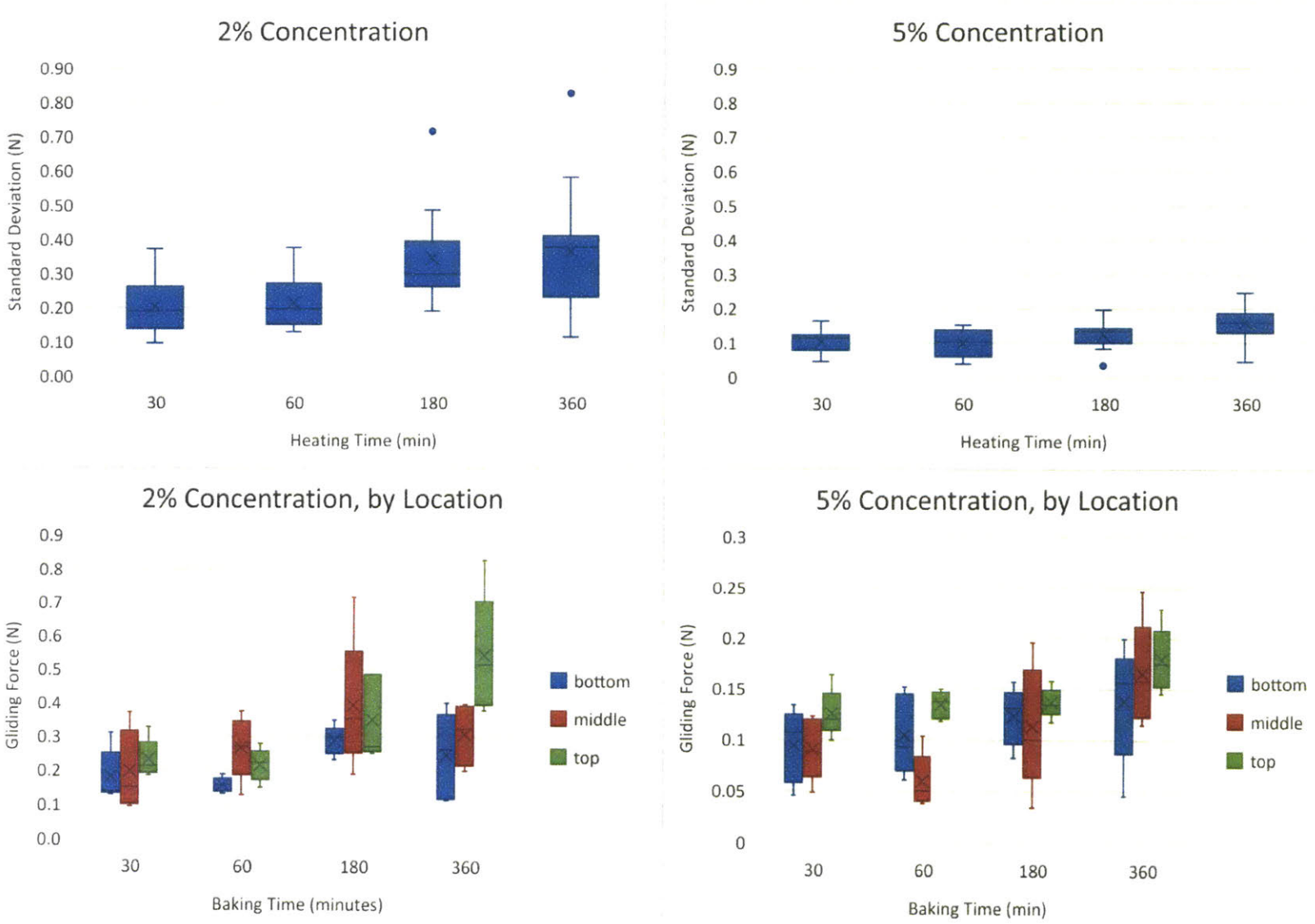

Figure 29: Standard Deviation Heating Time Chart

6.4 Standing Time

There is another effect that can occur with lengthy heating times. Since the silicone layer is liquid before it is baked on, it can move on the glass. Due to the process setup on all lines, there are always some cartridges that have been siliconized but not yet baked standing on the line between the siliconization station and the oven. Standing for any amount of time, the silicone runs down the sides of the glass, leaving a thinner layer at the top of the cartridge and a thicker layer at the bottom as depicted in Figure 30.

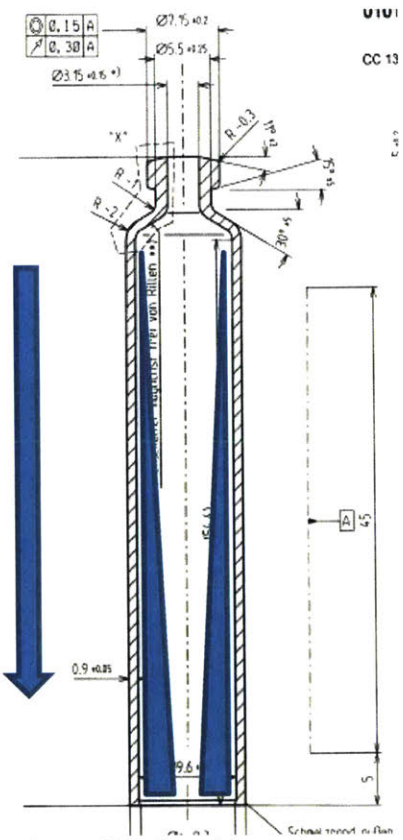

Figure 30: Cartridge with illustration of silicone flow down the barrel

Silicone flow due to standing time is a side effect from issues that may stop the production line. The most obvious issue associated with extended downtime is the extended heating time in the tunnel, but there are also implications for silicone migration before it is baked on to the cartridge. Until this silicone layer fully bakes on, it can migrate on the glass surface due to gravity. This is particularly obvious in the flushing process before the air nozzle blows out the excess emulsion, though the migration still occurs after air blow out as well. Observations of Rap.ID images show thinner layers at the top (needle) end of the cartridge, and thicker layers near the bottom (flange) end. It was not initially clear if this was due to thicker application at the bottom or if the silicone is running down from the top to the bottom of the cartridge due to gravity and standing time.

6.4.1 Standing Time Experiments

A lab experiment to test the effect of standing time was created with the variables of application thickness and standing time. The application thickness was thought to be important because a heavier application of silicone might run and move due to gravity easier than an application of fine, mist-like particles that would likely cling to the glass upon contact.

In this test, a 1.5% concentration and 2.1% concentration were held for approximately 10 minutes and 3 hours before baking. The ten-minute standing time was the time it took to make the samples and get them into the oven and is represented by 0 hours in the data analysis. Six samples of each set were made for a total of 24 samples. As with other tests, the samples were baked for 30 minutes at 300C.

6.4.2 Results

The results show a statistically significant difference between short and long standing time for layer thickness, gliding force, and standard deviation regardless of concentration. This is summarized in Figure 31, Figure 32, and Figure 33 respectively, and in the .jmp report in Appendix F. The statistical analysis does not analyze the effect of concentration but focuses only on the standing time, which shows statistical significance in both sample sets given a t value of 2.07 and a confidence interval of 95%. The samples that stood for three hours before being baked in the oven showed lower layer thicknesses in all areas, but the most drastic differences were in the tops of the cartridges. This then corresponded to higher gliding forces in the cartridges that stood for three hours, in particular in the tops of the cartridges. Finally, higher standard deviations occurred in cartridges that stood for 3 hours before baking in. This affect appears to be worse at lower concentrations.

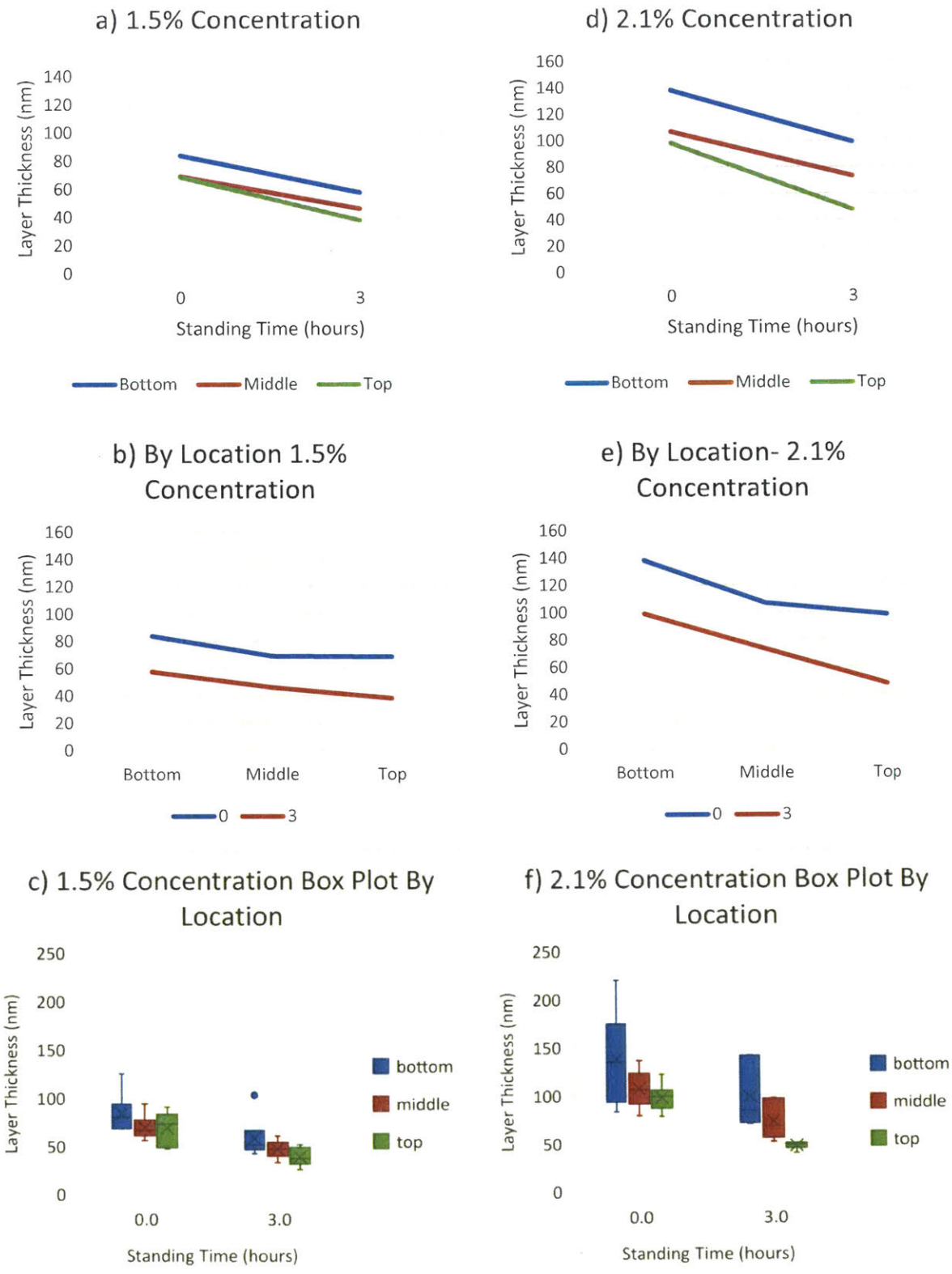

Figure 31: Layer Thickness by Standing Time and Concentration

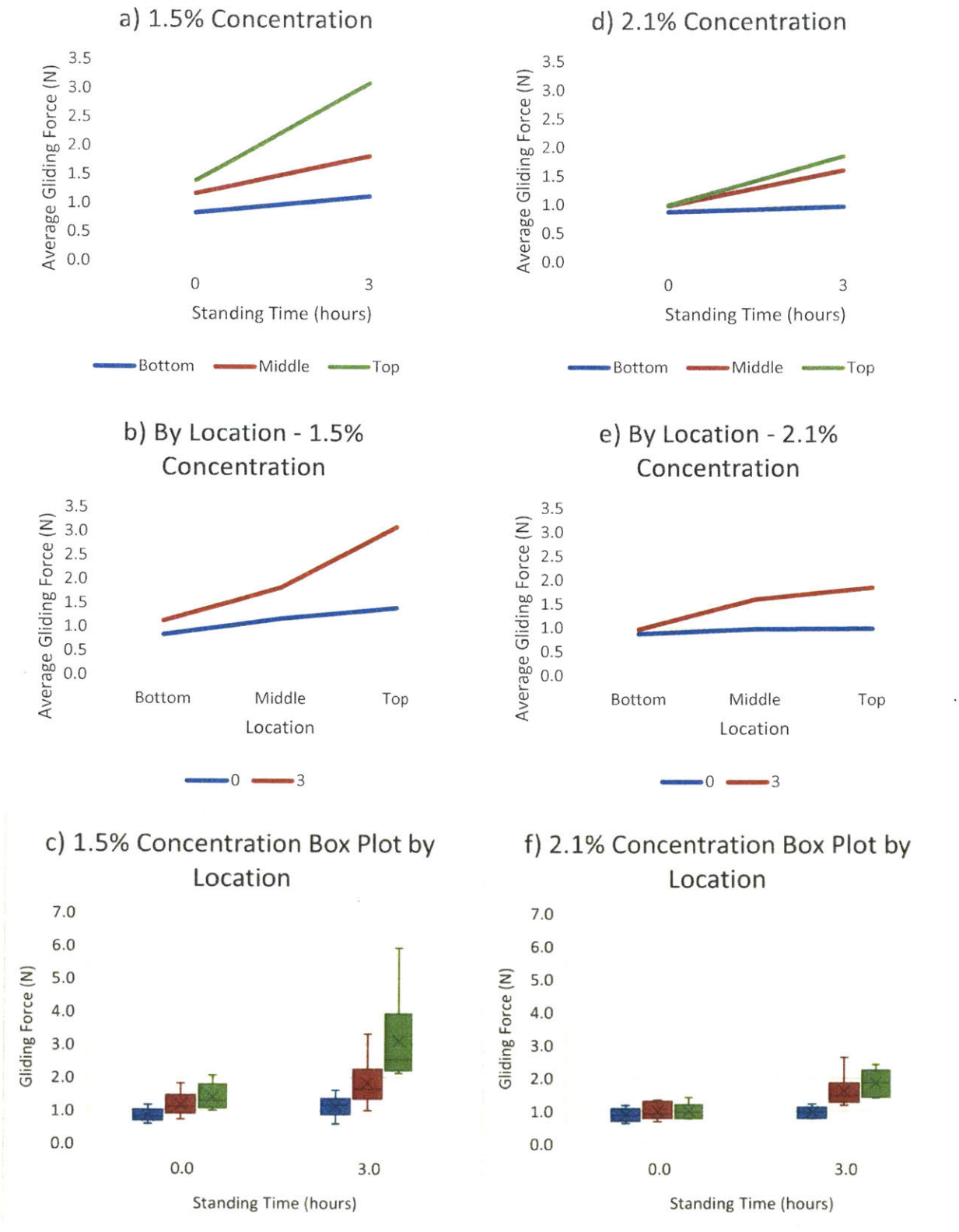

Figure 32: Gliding Force by Standing Time and Concentration

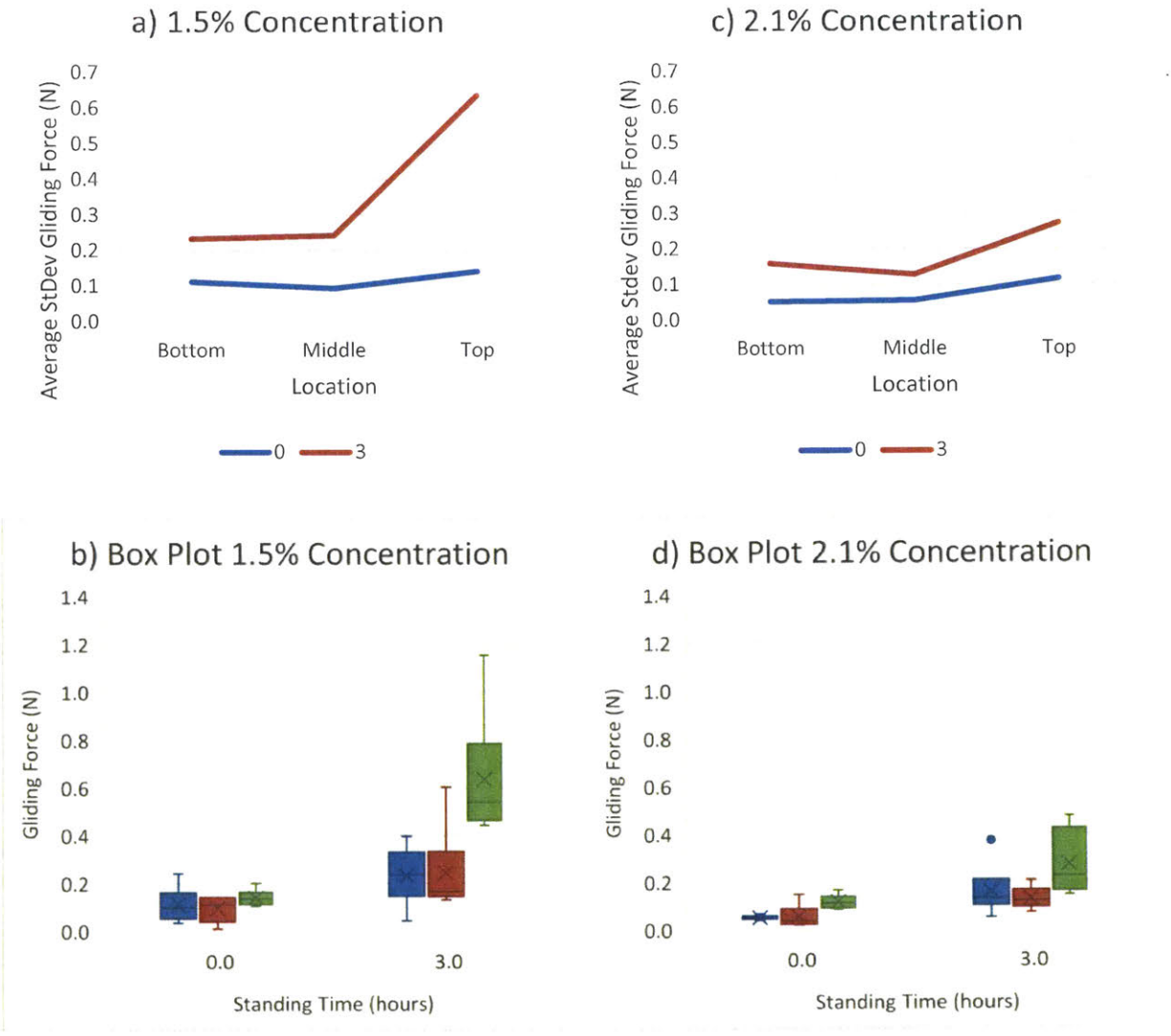

Figure 33: Standard Deviation of Gliding Force by Standing Time and Concentration

6.4.3 Conclusions

The most significant effects to the gliding force are in the top of the cartridge in both 1.5% and 2.1% concentrations. The most striking difference is with longer standing time and lower concentration. Though layer thickness over time decreases in all areas, at the top of the cartridge in particular it seems to pass below the ~40nm thickness threshold, which in turn causes higher and more erratic gliding forces. This is especially pronounced in lower concentration samples that start with a lower layer thickness in the first place. Longer standing effectively doubles the average gliding force and increases the standard deviation of gliding force in that area. Lower concentration silicone emulsion amplifies this effect. On average, each section lost about 25nm of thickness with prolonged standing time in the 1.5% concentration samples and about 40-60nm of thickness in the 2.1% concentration samples. The average gliding forces by location rose with

standing time in all areas, most notably in the low concentration silicone emulsion, high standing time scenario. On average, the standard deviation of gliding forces seen in the sample increased by about 0.1-0.5N depending on location.

6.5 Air Pressure Tests

Observations from powder coating and Rap.ID scans showed evidence of a streaking pattern in the silicone coverage. Powder coating is a destructive testing method used to evaluate silicone coverage in cartridges. It is destructive because after applying the talc powder, the sample cannot be further analyzed since it would disrupt Rap.ID analysis or force testing. The streaking pattern highlighted by the powder was particularly evident in samples from the flushing lines. Figure 34 shows a series of powder coated samples. Sample A is uncoated. The talc powder still adheres to the glass, but this sample serves as a control comparison for the others. Samples B and C are siliconized samples from a flushing production line, one unbaked and one baked (respectively). Sample C has a line near the bottom because it had a rubber stopper placed in it after the heating tunnel, but was removed from the production line before being filled with product. There is observable streaking in these samples. Samples D and E are siliconized unbaked and baked samples, respectively, from the microdosing production line. There is a more even coating applied over the entire area for both samples.

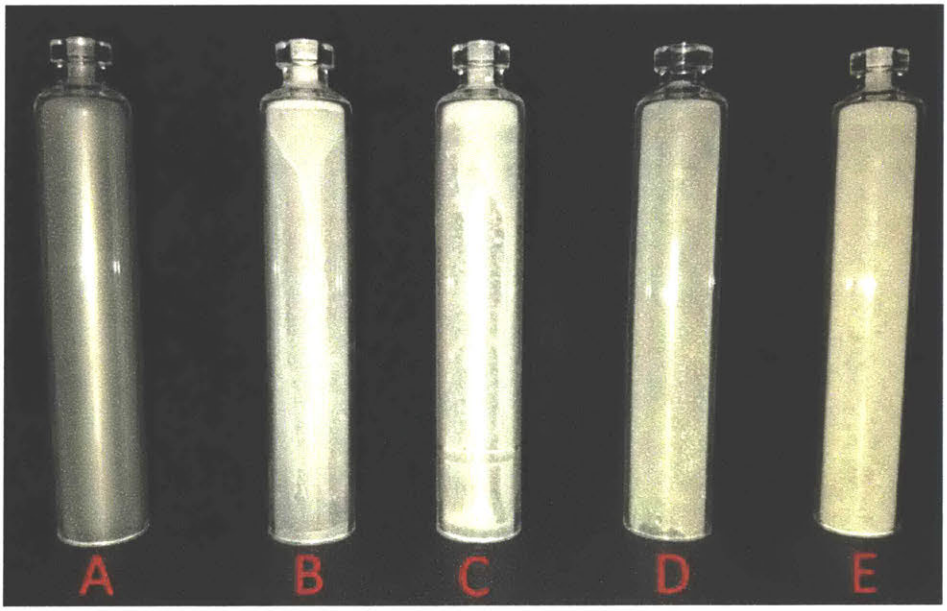

Figure 34: Powder Coated Samples. A: Unsiliconized sample with powder coating; B: Flushing sample unbaked; C: Flushing sample baked (note line where stopper was placed); D: Microdosing sample unbaked; E: Microdosing sample baked

Rap.ID imaging takes a long time per sample. The packaging development department at Sanofi Frankfurt specifies 12 Lines, 100 points per line in a 3mL 40mm cartridge as a standard. Each of these tests takes about 40-50 minutes. However, this resolution does not always detect the

streaking pattern since it only takes a snapshot of the layer thickness every 30° around the cartridge. Figure 35 shows a simplified diagram of how the measurement might miss some of the thin spots during measurement and report thick coating overall.

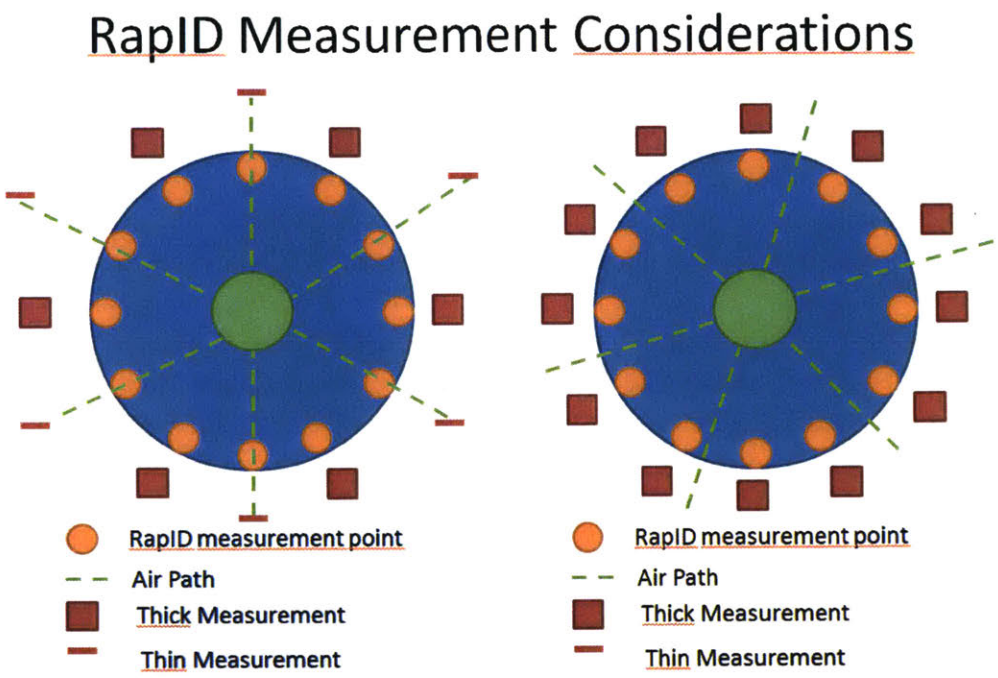

Figure 35: Rap.ID Measurement Considerations

After discovering this streaking in some cartridges, a higher resolution Rap.ID was performed using 36 lines, or 10° intervals, and the streaking problem became more obvious. This can be seen in Figure 36.

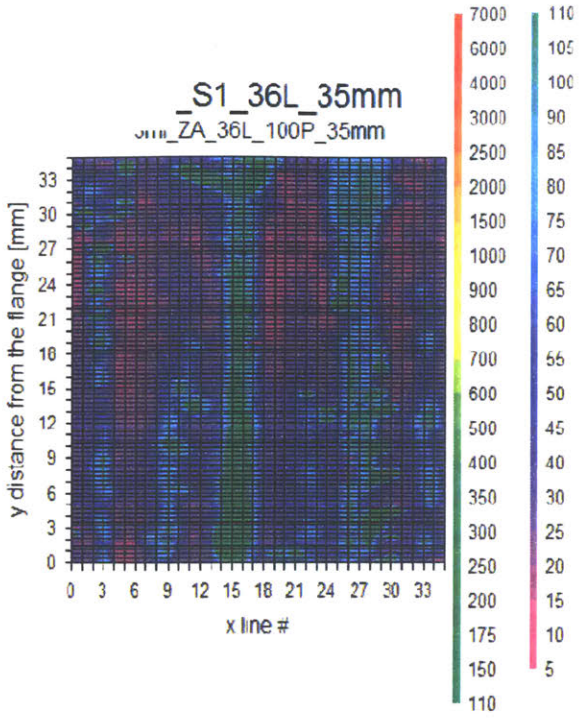

Figure 36: Rap.ID scan of streaking from Flushing Line A

The streaks appear to come from the six holes in the air nozzle that blows out the cartridge after siliconization. It appears that concentrated air streams may be blowing away too much silicone in some areas and leaving excess silicone in others. Figure 37 shows several pictures of the nozzle including the pattern of holes around the air nozzle and a diagram of air direction.

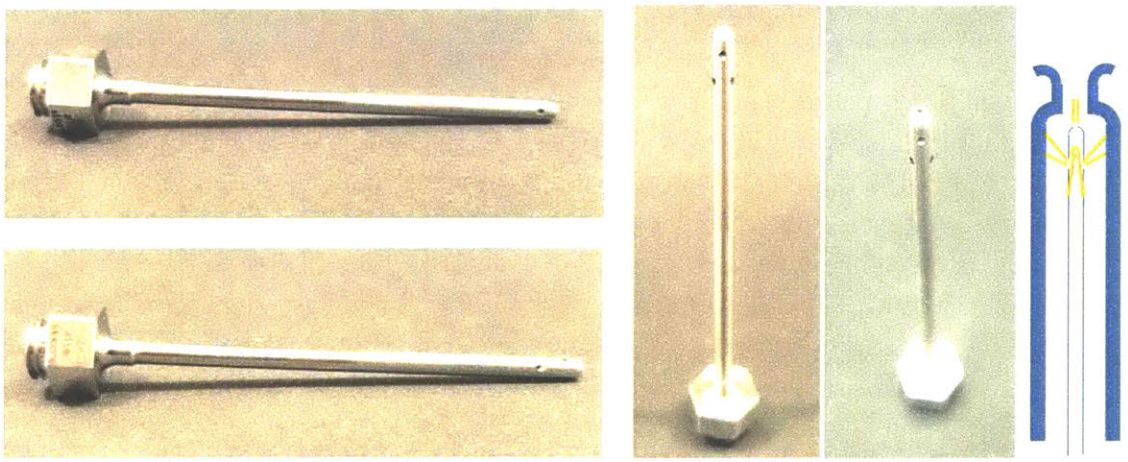

Figure 37: Air after silicone nozzle laying down (left), standing (center), and diagram (right)

6.5.1 Test Setup for Air Pressure and Speed

The purpose of this test was to investigate the effects of air pressure and nozzle speed on the final silicone layer inside of the 3mL glass cartridges. Visual observations have shown streaking

inside of some coated cartridges, while others have even coating. In particular, a set of 3mL samples had six low thickness streaks- the same number of air holes in the nozzle. For these samples, the production air pressure was about 1.5bar. Similar samples of 1.5mL cartridges were taken and observed as well, but lacked the same pattern and had a much more uniform coating. Although there is a difference in diameter of the cartridges, there is another stark difference between the air pressures used. The air pressure for the 1.5mL cartridges is approximately 0.8bar. The hypothesis is that the air pressure has a significant impact on the amount of silicone remaining in the glass cartridge. The duration of the spraying can also vary on the line so the effects of this were investigated as well. This test was used to investigate the interaction between air pressure and nozzle speed on silicone layer thickness and subsequent gliding forces.

6.5.2 Air Pressure and Nozzle Speed Experiments

Three air pressures were tested. The lowest air pressure was 0.8 bar, which is what the 1.5mL cartridges are produced at on the production line. These 1.5mL cartridges did not exhibit the streaking pattern in the production, so it was hypothesized that the low air pressure helps contribute to the uniform coating. This low air pressure threshold was also compared mathematically using the analysis described in Appendix A to ensure that an appropriate range of air pressures was being tested. The medium air pressure setting was 1.5 bar. This is close to the standard production setting for 3mL in the two flushing production areas, A and B. The highest setting was 3 bar. This is higher than the maximum allowable air pressure in the flushing production areas, but it exaggerates the effects of high air pressure to find the effects of over blowing out. Two speeds were tested: one fast at 0.8 second cycle time and one slow at 1.5 second cycle time. Six tests were performed: Low/Fast, Low/Slow, Medium/Fast, Medium/Slow, High/Fast, High/Slow. Each test was replicated six times to ensure an appropriate range of data was collected for statistical analysis. Due to the long analysis time, collecting more samples was not feasible as each sample took three hours to analyze in the rap.ID.

6.5.3 Experimental Setup and Procedure

The equipment for flushing-style siliconization was used. The 3mL glass cartridges were cleaned with deionized water. The flushing siliconization setup in the lab only allows for one sample at a time to be siliconized. The samples from a similar set were siliconized one by one and placed in the equipment starwheel for air blowout all together at the same time. The six different programs- Low/Fast, Low/Slow, Medium/Fast, Medium/Slow, High/Fast, High/Slow- were run for the six sets of data. Additionally, one set of samples with no air blow out was also made and analyzed in the same manner as the air blow out samples. All samples were baked as soon as possible after creation at 300 degrees C for 30 minutes.

6.5.4 Results

Rap.ID imaging was performed on the six samples from each set as well as the samples without the air blowout. Zwick force testing was also done on the samples. First, a visual comparison between the production line samples verified that the samples that were generated in the lab were an accurate representation of what was being produced by the flushing process in production.

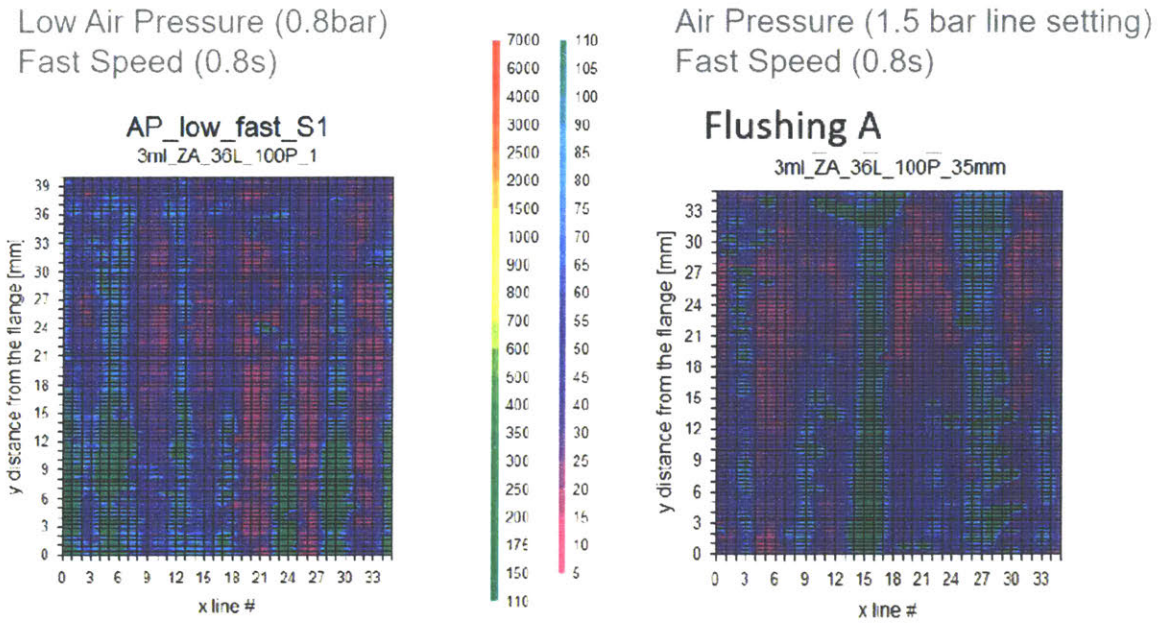

Figure 38: Comparison between Lab Produced Samples using Flushing method (left) and flushing line A production area sample

As seen in Figure 38, the samples are comparable visually in regards to the general streaking pattern. The major difference is that the lab sample that most closely represents the production sample had an air pressure of 0.8 bar, not 1.5 bar. The 1.5 bar sample from the lab also looks similar, but perhaps takes off more silicone than what is seen in production. A 1.5 bar sample is shown in Figure 39. The pink and purple colors indicate less silicone coverage. The average layer thickness for the line production sample was 54nm. The layer thickness for the medium (1.5 bar, fast) sample is 37nm. The average layer thickness for the low (0.8 bar, fast) sample is 58nm, which is more comparable to the actual production sample. This is likely because the lab equipment for air pressure is very different than the equipment and setup on the production line. Although the production line setting may be 1.5 bar on the air pressure pump, this may not actually be reflective of the pressure expressed at the nozzle. The air setup in the lab is less complex with fewer connections and shorter distances, so it is likely maintaining the pressure across the system better than in production. Additionally, the lab setup is only using one air nozzle, while production uses 12 simultaneously, so air pressures from the lab should be higher than what is seen in production. Any changes that are proposed for production in regards to air

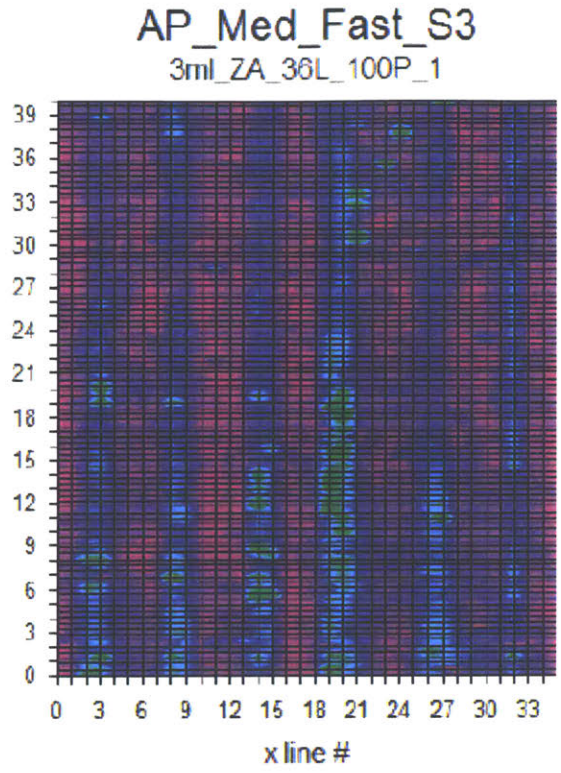

Figure 39: Rap.ID layer thickness profile - 1.5 bar sample

pressure may need to be experimented with on the production line given the individual and unique air pressure setups. Finally, the time between siliconization and air blow out in the lab is much greater than in production since all samples from a set are siliconized and then blown out together in production. In the lab there is more time for the silicone to run down the sample before blow out, which leads to lower average layer thicknesses, especially at the top of the samples. Though not a perfect replication of production settings, findings from air pressure lab testing are still valuable in quantifying the amount of silicone lost due to increasing air pressures.

6.5.5 Analysis of Results and Recommendations

A visual comparison of the samples can be seen in Figure 40. As pressure increases, layer thickness decreases as shown by more pink and purple in the imaging results. The effect of speed is less clear. The top row of samples had a fast speed (0.8 second cycle time), and the lower row had a slow speed (1.5 second cycle time). There is more silicone left at the bottom of the slow speed samples, and it is suspected that the test equipment does not hold constant air pressure as the air nozzle moves down the sample, so more silicone is blown out of the top, but the lower air pressure at the bottom allows more silicone to stay there. This effect is exaggerated in the samples with the slow speed since the air pressure has more time to decrease by the time the air holes in the air nozzle reach the bottom of the cartridge. These are limitations to the test equipment, so the results were interpreted with this in mind.

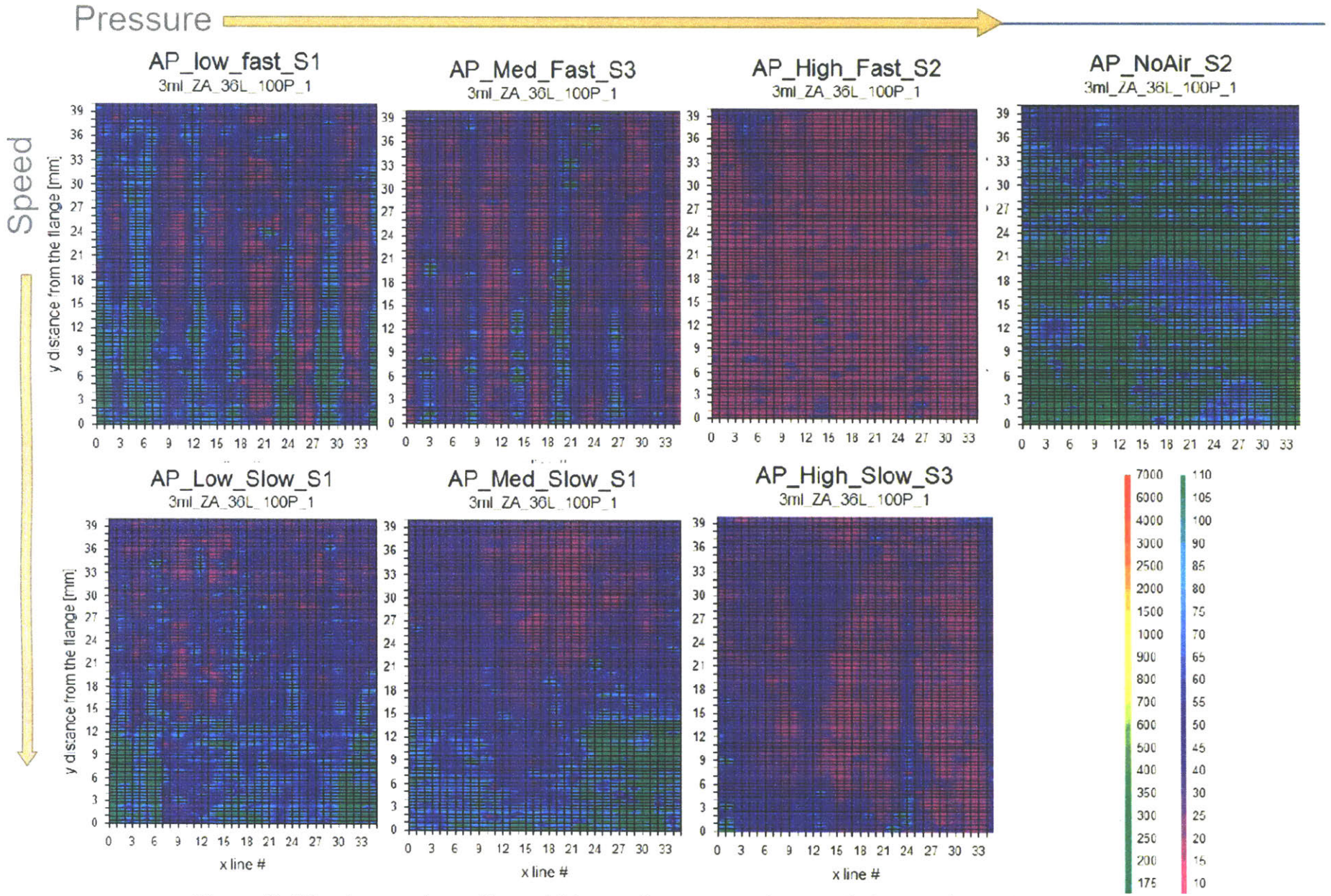

Figure 40: Visual comparison of layer thickness of a representative sample from each sample set

The effect of speed appears less clear mainly due to the effect of falling air pressure as the nozzle reaches the bottom of the cartridge. This variation in pressure obscures a potential effect of speed. Essentially, in the fast samples, more silicone gets blown off throughout the cartridge because the overall pressure is higher throughout. The slow cycle samples see more of a pressure drop, and less silicone is blown out resulting in better coverage. Intuitively, if the pressure remained the same throughout the cycle and did not drop at all, more silicone should be blown out in the slower cycle. However, due to the setup that allows a pressure drop, this effect is not seen. Figure 41 shows a lack of correlation between air nozzle speed and the gliding forces realized. Given this finding, the samples were evaluated with only air pressure as a factor.

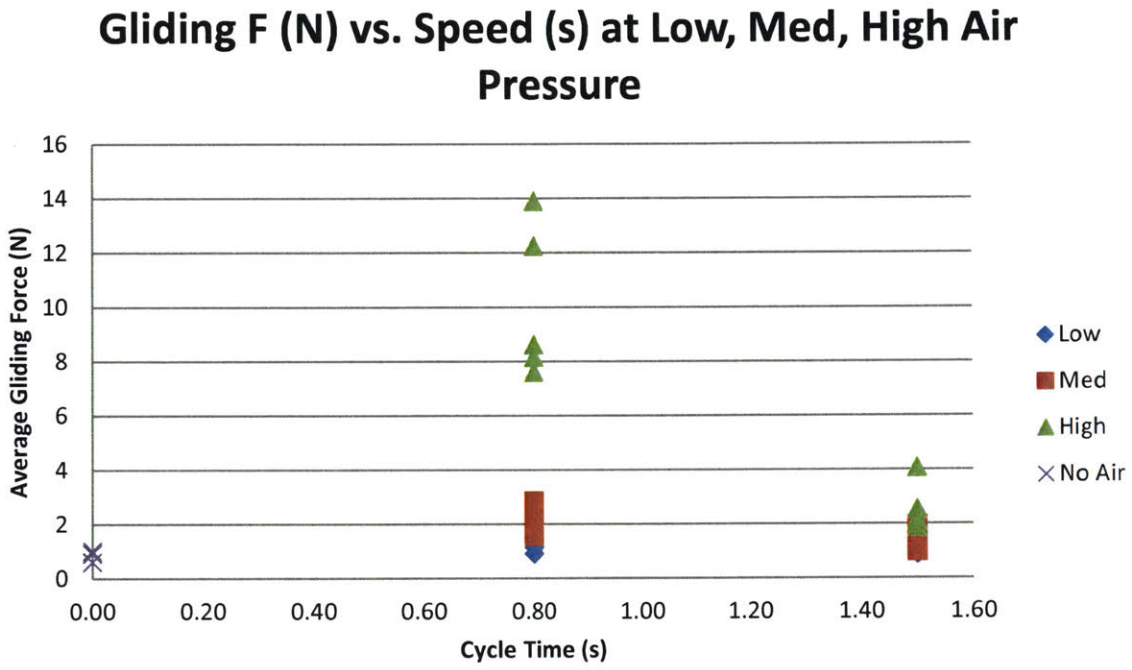

Figure 41: Gliding force and Speed- lack of correlation

All the samples from the air pressure tests regardless of testing speed were compared against the samples that did not receive air blow out treatment to determine how much silicone was lost in the air blow out process. Figure 42 shows the average layer thickness as air pressure increases. The most significant force increases seen at 3 bar are not realistic in actual production settings, the figure on the right removes the pressures at 3 bar to see more clearly the difference between more realistic line setting pressures.

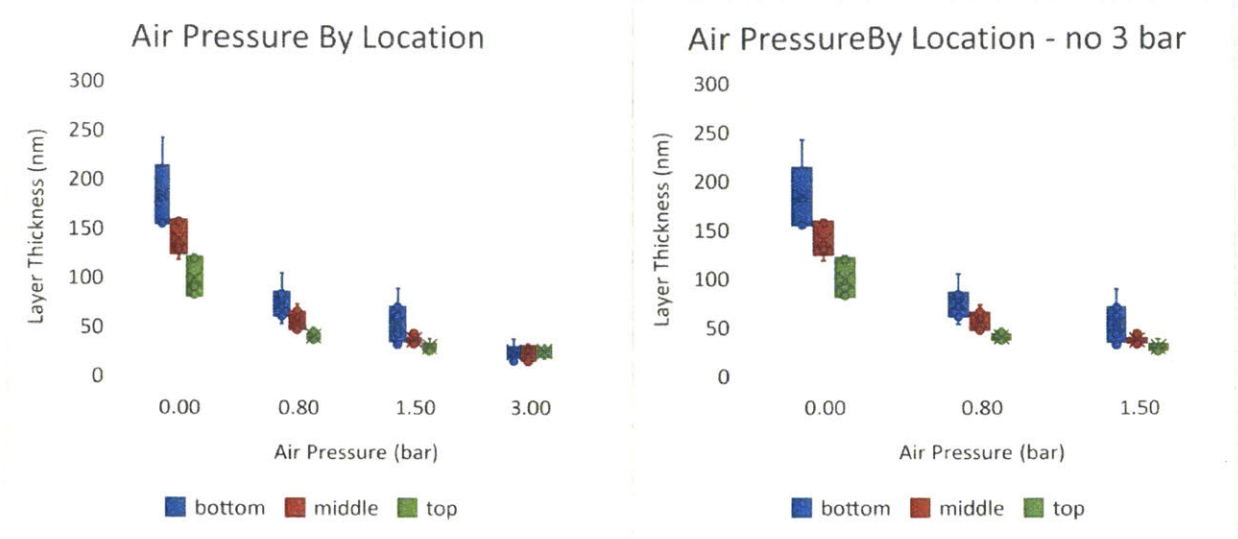

Figure 42: Layer Thickness versus Air Pressure by Location

Figure 43 shows a clearer visual relationship between the air pressure and average layer thickness in each location without error bars.

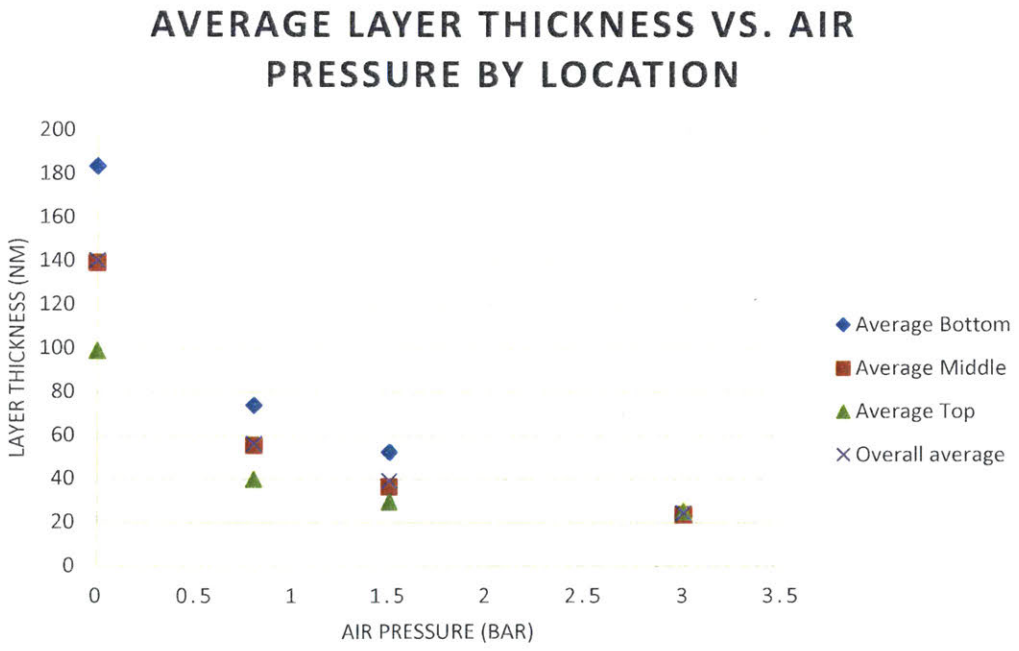

Figure 43: Average Layer Thickness vs. Air Pressure

The samples lost an average of about 75nm under 0.8 bar pressure with a range of ~45-100nm. At the standard 1.5bar the samples lost 60-120nm, averaging about 88nm, and at the highest pressure on average 100nm ranging from 60-140nm.

Air pressure has a significant effect on the amount of silicone remaining in the glass cartridge. As expected, the average gliding force increased with higher air pressures over the cartridge as well. Figure 44 shows the average gliding force versus air pressure for the top, middle, and bottom of the cartridges. The most significant force increases seen at 3 bar are not realistic in actual production settings, so the chart to the right in Figure 44 removes the pressures at 3 bar to see more clearly the difference between more realistic line setting pressures.

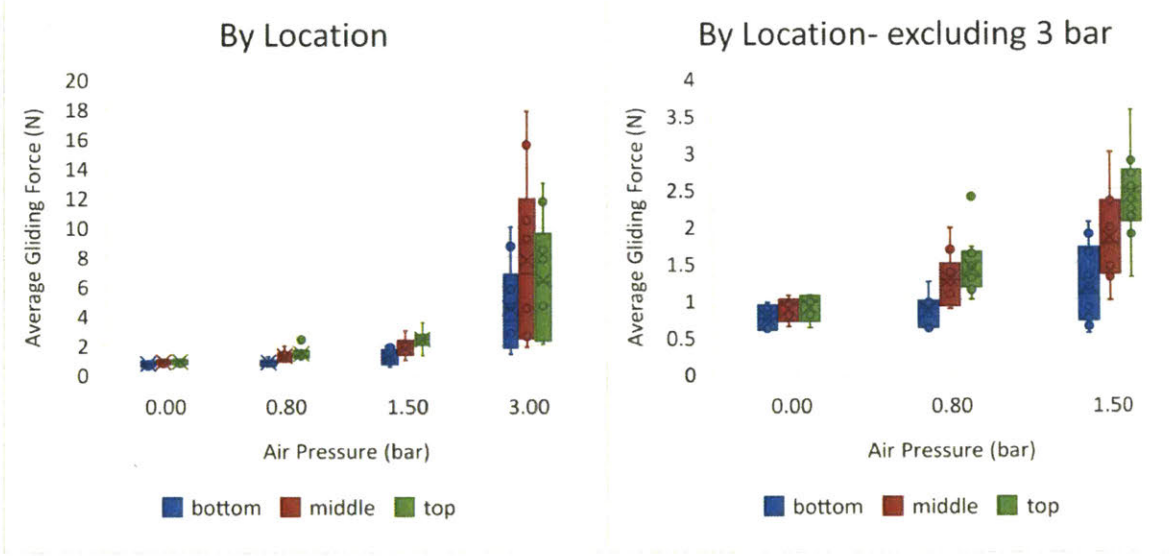

Figure 44: Gliding Force vs Air Pressure by Location Full Results (Left) and Excluding 3 bar (Right)

As expected with lower layer thickness seen in higher air pressure samples, the corresponding gliding force rises with increased air pressure. Additionally, the difference between average forces in the bottom and the top of the cartridge increases as the air pressure increases. This presents a difficult challenge in designing for a set force in dispensing product from the syringe if the forces vary greatly from the bottom of the cartridge where the rubber stopper starts to the top of the cartridge where the rubber stopper ends.

Though the forces are not as high as seen in the 3 bar air pressure samples, the average gliding force can still double from forces seen when there is no blow out to the 1.5 bar situation for the top of the cartridge. Figure 45 shows the average gliding force data without the box plot format for easier visual representation of the relationship between air pressure and gliding force.

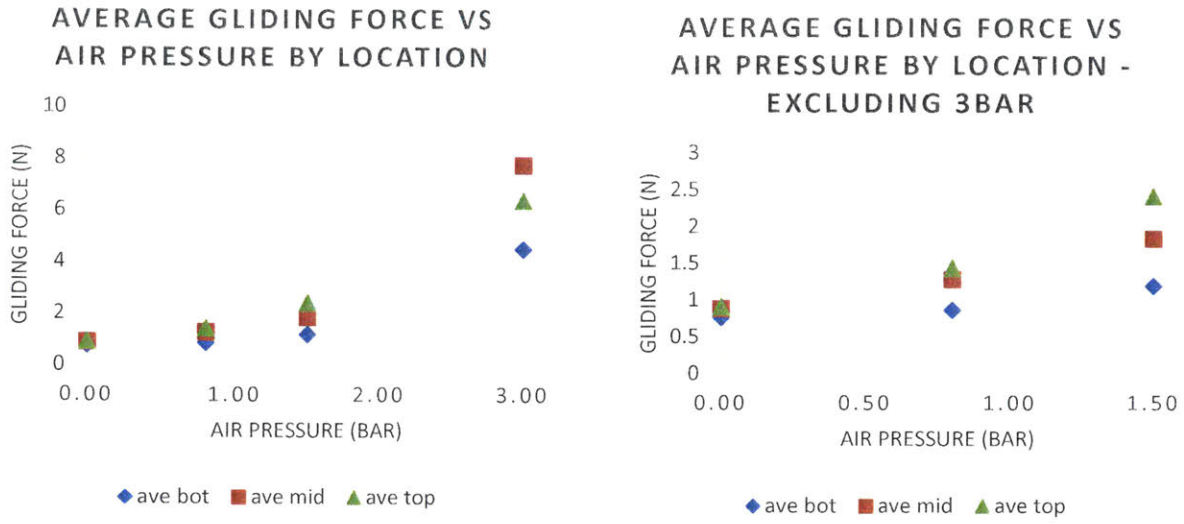

Figure 45: Gliding Force vs. Air Pressure including 3 bar (left) and excluding 3 bar (right)

Standard deviation of gliding force also increases with air pressure. This is exaggerated in the 3 bar air pressure samples as seen in Figure 46. The overall standard deviation for the samples is included in these plots since the differences in forces over the cartridge are important to note for design of the insulin pen. Figure 46 also shows the data with the 3 bar samples removed.

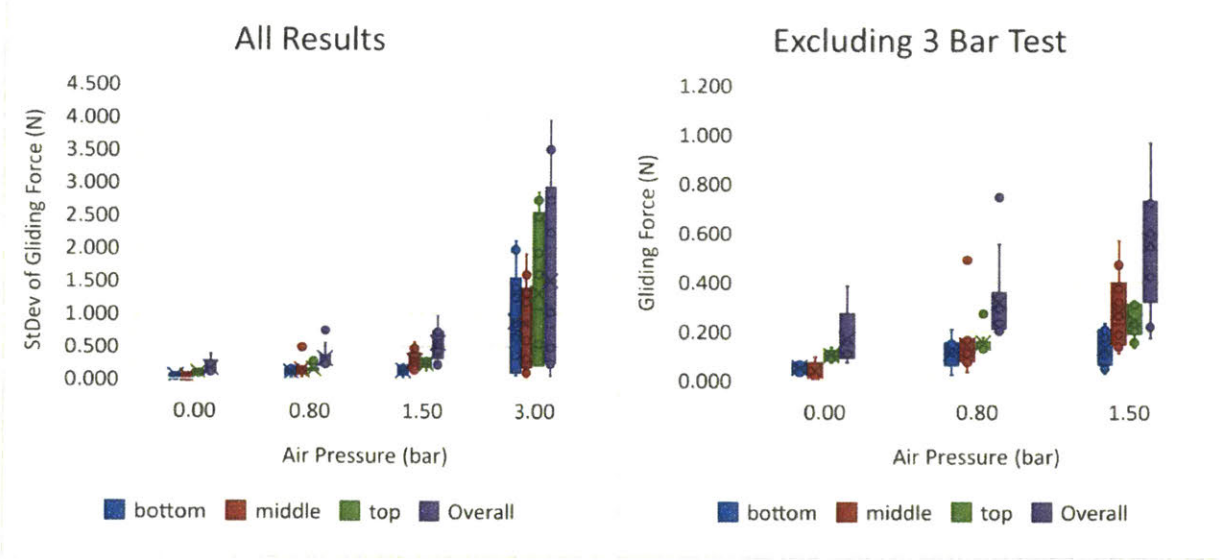

Figure 46: Standard Deviation of gliding force versus air pressure all results (Left) excluding 3 bar (Right)

Even at lower air pressures, the standard deviation of the gliding force in an area increases with increased air pressure. This is less pronounced in the bottom of the cartridge where there is more silicone left in place.

6.5.5 Conclusions

On average, a cartridge blown out at 0.8-1.5 bar will lose 80-100nm in layer thickness versus not getting blown out at all. The average increase in gliding force is approximately up to 1N with an increase in standard deviation of 0.15-0.25N. With starting layer thicknesses of over 200nm before blowout, this can be a manageable process step, and indeed that is what is observed in daily production on the lines. The effect of the speed of the needle is not statistically significant for impact on layer thickness, gliding force, and standard deviation. The effect of air pressure is statistically significant on layer thickness, gliding force, and standard deviation especially at the top of the cartridge given a t-value of 2.07 and a confidence interval of 95%. The .jmp report in Appendix G evaluating air pressure backs up this summary of the statistical significance of air pressure effect on different areas of the cartridge.

6.6 Concentration

The removal of excess silicone in the flushing process with pressurized air removes a lot of silicone, so the following test was conducted to determine if lower concentrations of silicone can be used without blowout. This maintains an acceptable layer thickness coating on the cartridge but lessens the risk of over-siliconization. There are concerns surrounding free or excess silicone in medication delivery and its effects on health and interactions with medications [16]. Since even baked on silicone can migrate from the surface of the cartridge, minimizing the amount of silicone applied is a way to mitigate this risk [26].

6.6.1 Test Setup

Three sets of samples were made using three different concentrations of silicone emulsion: 1.0%, 1.5%, and 2.1%. The silicone emulsion was applied using the flushing method but the samples were not blown out with air afterward to isolate the effects of concentration from air pressure usually seen in the flushing method.

6.6.2 Results

Figure 47 shows that layer thickness increases as concentration of silicone emulsion increases. This is particularly pronounced in the bottom of the cartridge, presumably because any excess emulsion at the top will run down the side. Though less silicone clings to the top of the cartridge in all three concentration tests, the layer thickness at the top is thickest at 2.1% concentration. At 1.5% and 2.1% the average layer thickness stays above 40nm in the top of the cartridge. At 1.0% the average layer thickness at the top can dip below 40nm regularly. This causes increased gliding forces in the top of the cartridge.

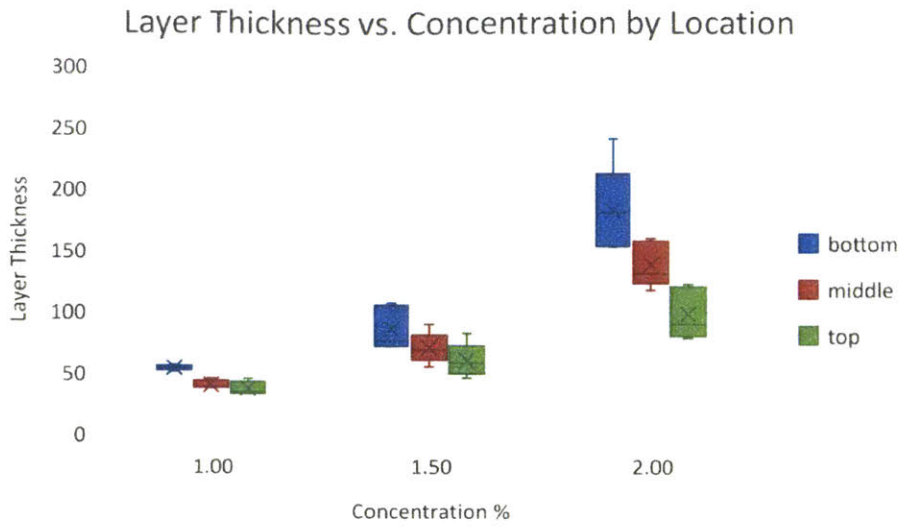

Figure 47: Layer thickness versus concentration by location

The average gliding force decreases as concentration increases in line with the layer thickness as demonstrated above. Figure 48 shows a box plot of the average gliding force as concentration increases. This chart displays not only that the average gliding force falls with increased concentration but also that the range of gliding force values tightens.

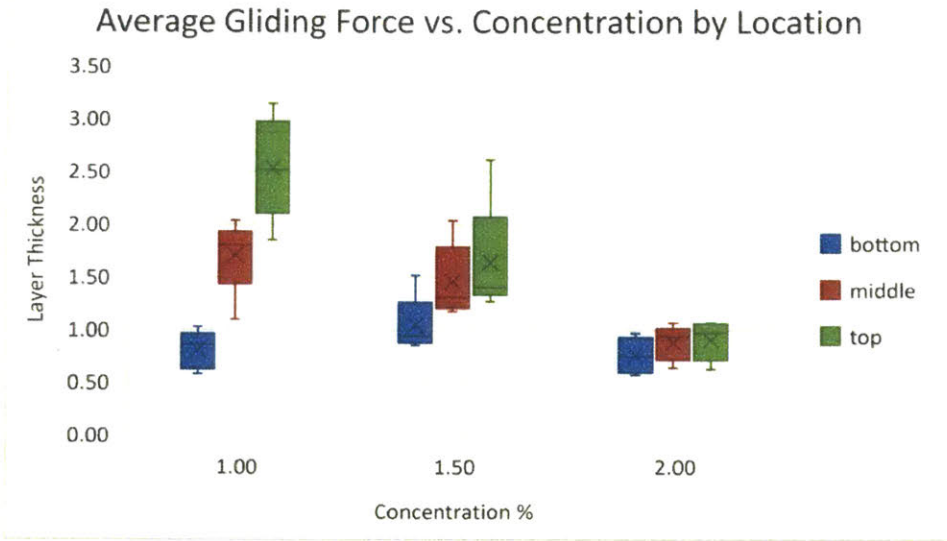

Figure 48: Average Gliding Force by Concentration

The force test profiles can be seen in Figure 49. Using 2N as a baseline for repeatable production results based on the microdosing production line, the 2.1% concentration is the only set that reliably remains below this 2N line. The 1.5% concentration mostly stays below 2N but has a

couple samples that run above the line at the top of the cartridge. Finally in the 1.0% concentration, every sample goes above the 2N limit.

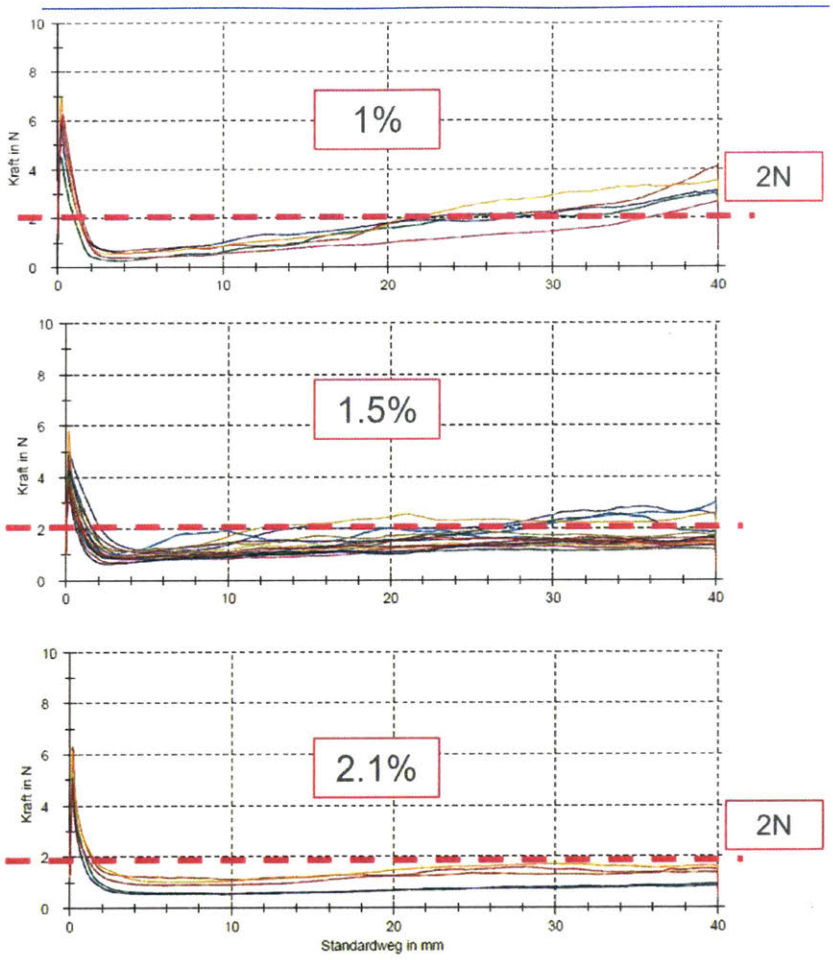

Figure 49: Gliding force Profiles for 1%, 1.5%, and 2.1% concentrations

Figure 50 shows the average standard deviation of the gliding force decreases in the 1.5% and 2.1% samples as compared to the 1.0% samples. When taken across the entire sample as seen in Figure 53 right, the standard deviations in both higher concentrations are on average below the 0.5N standard deviation often seen on the microdosing line production in process control tests.

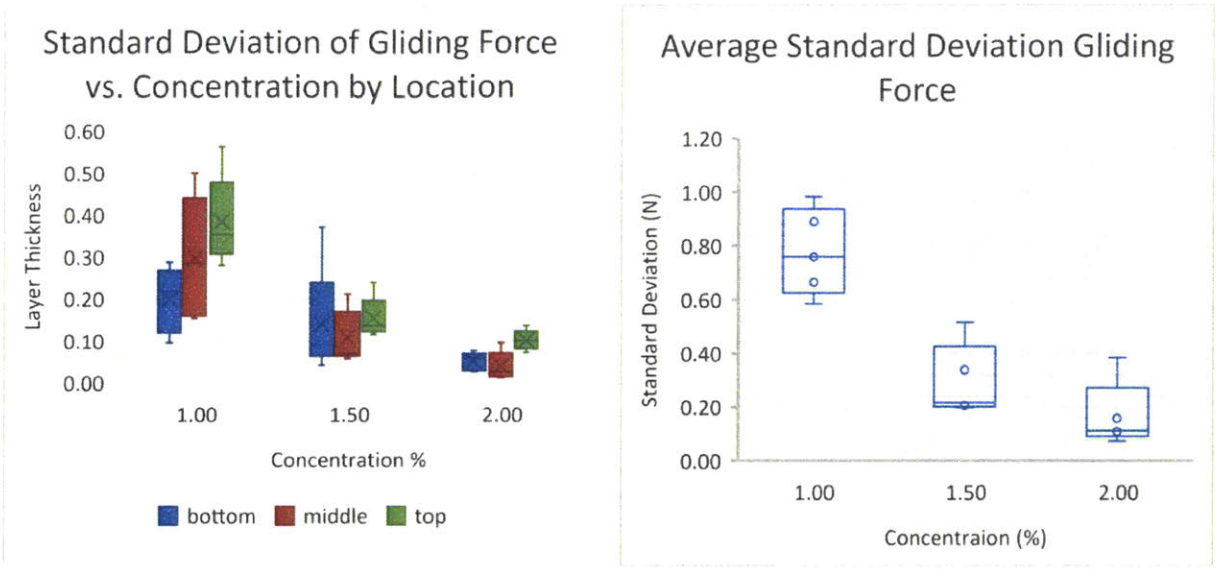

Figure 50: Average Standard Deviation by Concentration – Box Plot By Location (Left) and Average Standard Deviation Over Entire Cartridge (Right)

Visually in Figure 51, Rap.ID imaging shows the increasing silicone layer thickness as concentration of silicone emulsion increases. The average layer thickness over the entire sample goes from 44nm in the 1.0% sample to 73nm in the 1.5% sample and finally to 140nm in the 2.1% sample.

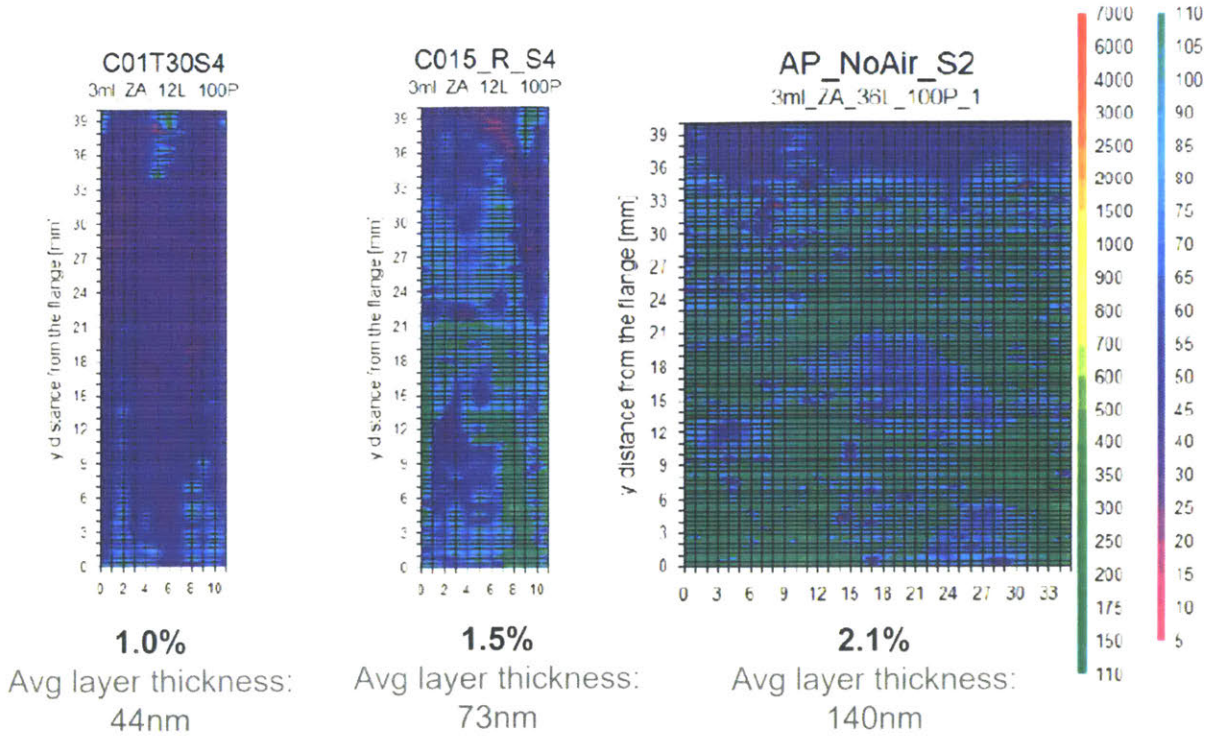

Figure 51: Rap.ID comparison of silicone emulsion concentration

6.6.3 Conclusions

Based on these results, acceptable force results can be produced with 1.5% and 2.0% concentrations with no air blow out. The 1.5% concentration is not quite as low in gliding force or standard deviation as the 2.1% concentration, but may pass tighter process control standards without out air blow out versus with blow out at 2% concentration. There is a statistically significant difference between the 1% concentration and the other two higher concentrations in evaluating layer thickness, gliding force, and standard deviation especially in the middle and top of the cartridge given a t value of 2.07 and a 95% confidence interval. A .jmp report analysis can be found in Appendix G. There is a bigger difference between the 1% and the others than the 1.5% and 2.1% concentrations. This suggests that it may be acceptable to lower the concentration to 1.5% without causing significant changes to gliding force in the cartridges if the air blow out step is removed. There is also little difference seen in the bottoms of the cartridges across all concentrations, which makes sense considering that the silicone emulsion is likely running down the cartridge due to gravity as discussed in the standing time section.

7 Conclusions

In order to create a 40nm layer thickness in cartridges, several process areas were investigated. The process for selecting testing parameters was based off of differences in current production methods and settings with the hypothesis that differences in these areas would help describe

differences in siliconization results. Cleaning, heating time, standing time, air pressure, and concentration were explored as potential factors that could affect siliconization.

The current cleaning procedures in the three production areas are different, but tests show that the differences are not significant. More advanced cleaning methods could be evaluated as methods to improve siliconization, but current differences between the production areas are not driving differences in siliconization performance.

There are different maximum heating times allowed between production areas. This not only affects the amount of time a cartridge is exposed to very high temperatures, but also increases the maximum standing time a siliconized cartridge could face before baking in. Heating times greater than one hour and less than three hours show a step jump in gliding force. This should be investigated further to determine the exact amount of time that leads to the step jump. Additionally, since maximum heating time directly affects potential standing time, lower limits to heating time should be investigated. Shortening the allowable heating time in the tunnel will have impacts on line loss since the line will need to be cleared with shorter production interruptions.

Air pressure of the air blow out step in the flushing process is an important contributor to layer thickness and gliding force. Higher air pressures blow out more silicone and lead to higher gliding forces. Potential solutions could include lowering the air pressure, modifying the nozzle to reduce air pressure and even out air coverage, and removing the air blow out step altogether. Removal of the air blow out step would likely require a reduction in the concentration of silicone to prevent excess silicone in the cartridge. The interaction between silicone and drug product is not the focus of this project, but it should be considered first before implementing any change that would increase free silicone in the cartridge.

Tests conducted in the lab show sensitivity of layer thickness and gliding force to concentration. If the air blow out step were removed, a reduction in concentration would likely be implemented, but would need to be carefully controlled to eliminate the possibility of applying too little silicone. It also highlights the importance of standardizing current procedures to ensure the correct silicone concentration is being used in production.

Each of the effects explored above could happen in isolation or in combination with multiple effects. For instance, a every cartridge on the flushing line gets blown out, but some could also stand for a while on the line before entering the heating tunnel if the production line were to go down. Alternatively, they could stand in the heating tunnel for an extended period of time in a similar situation. The concentration is set at 2.1% but if mixed incorrectly, a significant change to the silicone layer could occur. A summary of these effects can be seen in Table 4.

Table 4: Summary of Parameter Setting Effects

Effect	Layer Thickness	Force	Standard Deviation
Heating	-10 to -20 nm	+0.5 to +1 N	+0.05 to +0.15 N
Standing	-25 to -60 nm	+1 to +1.5 N	+0.1 to +0.5 N
Air Pressure	-80 to -100 nm	+1 to +1.5 N	+0.15 to +0.25 N
Concentration	-50 to -125 nm	+0.5 to +1.5 N	+0.15 to +0.3 N
Cleaning	No significant change	No significant change	No significant change
Potential Cumulative Effect	**-165 to -305 nm**	**+3 to +5.5 N**	**+0.05 to +0.5N**

The effects above were studied in isolation from each other, but there is reason to believe that separate effects could be additive if they were to occur to the same cartridge. This is an opportunity for future research to investigate how these effects interact with one another.

Any one issue in one of these process steps is likely not enough to upset the entire process and create out of specification cartridges, but each occurrence lends itself to more variability in the drug delivery forces. This makes it more difficult to design an effective auto-inject pen that is comfortable and efficient. A combination of these factors could add up to excessively high forces in rare occurrences, but these potential effects could be offset by some modifications to the production processes. These recommendations are explored in Section 8.

8 Recommendations

8.1 Modified Nozzle

A modified air nozzle test displayed significant increases in layer thickness at the top and middle of the cartridge. The air nozzle was modified to open up the existing air holes into slots that extended almost the whole circumference of the nozzle. The test setup and findings are in Appendix B. Though there are only statistically significant differences seen in the top and middle layer thickness of the cartridges using the new nozzle, further modifications to the design may result in a greater improvement in results.

The widened air holes reduce air pressure at the nozzle tip, which reduces air pressure seen in the cartridge. There are other ways to reduce this air pressure. A simple air pressure reduction could be effective even with the existing six-hole air nozzle. Given the different setup between lab equipment and production equipment, which includes longer air piping distances and a different compression pump setup, the best method to approach this change would be through production line experimentation. Reducing air pressure too far should not be a concern except if leaving too much silicone in the cartridge proves to interfere with the insulin.

Another option for nozzle modification could be a nozzle tip with more of a meshed pattern. Figure 52 shows an illustration of what such a nozzle might look like. This modification would allow for completely even air pressure around the entire circumference of the cartridge. There should be no streaking with a uniform mesh-like design. This would also require a significant reduction in air pressure to ensure that too much silicone is not removed.

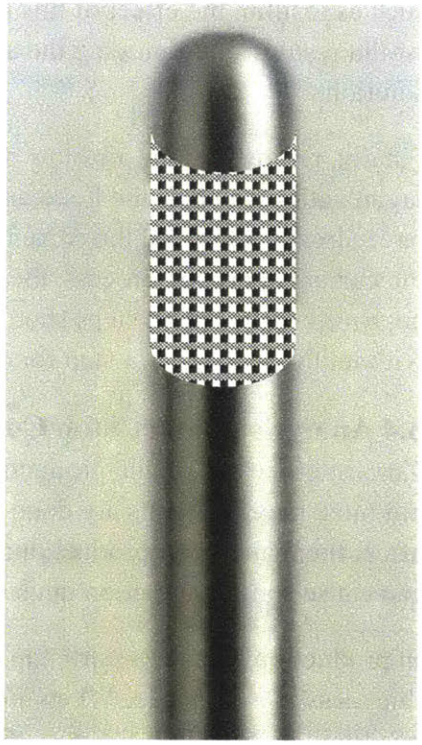

Figure 52: Illustration of a modified mesh-top air nozzle

8.2 Concentration Mixing Procedure

The next recommendation is to ensure that the silicone mixing procedure is evaluated for accuracy and repeatability. Even slight changes in silicone concentration appear to have significant effects on layer thickness, gliding force, and standard deviation.

The current procedure is outlined in Section 4.2.4 Silicone Solution. The process for measuring both silicone and water is currently manual and somewhat subjective based on operator interpretation. Additionally, the release valves from the mixing tank are controlled manually. These steps of the process could be more automated to avoid mixing variability. A small change in the concentration of silicone emulsion can have large impacts on forces in the cartridge. If the valve between the mixing tank and holding tank is left open, too much water could be added to the solution causing extremely thin layer thicknesses. Additionally, if an operator adds too much or too little silicone into the measurement container, this could cause variability in performance even if the difference is small enough that the layer thickness is technically within specification. A difference of less than 1% concentration shows drastically different results as shown in Section 6.6 Concentration.

8.3 Removal of Air Blow out Process Step

Part of the motivation behind the air pressure and concentration studies was to test the hypothesis that the flushing process for siliconization can be done without the air blow out process step. Removing this step would increase layer thickness, reduce gliding force, and reduce standard deviation on flushing lines. This would increase repeatability and consistency across flushing production areas and bring the flushing process more in line with the microdosing process.

There are obstacles to implementing this change immediately. First, further research should investigate the interaction between silicone and molecular properties of insulin or other medications that might benefit from changes in this process step. Additionally, though the silicone is in theory baked on to the surface, research shows that the silicone can still come off in the medical solution after filling [26]. For a medication that is frequently injected into the skin

such as insulin, the effect of this should be studied further. An increase in layer thickness that would result from removing the air blowout step could lead to more silicone in the insulin solution.

Finally, removal of the air blow out step would likely need approval from various regulatory organizations such as the Food and Drug Administration. The FDA and similar organizations have already approved the current air blowout process within a certain range of air pressures. For the current approved process, the air pressures should be brought down to the low end of this approved range. Next, steps should be taken to prove the safety and reliability of the process without the air blow out step for official approval.

8.4 Analysis of Start/Stop Conditions

Current processes on the production lines operate well within specification in the current process, but most measurements are done during steady-state operation. Most of the time, this will not affect the majority of production; however, start/stop states can cause unforeseen conditions that can cause some production deviations that are not considered normal.

In production area A, a start/stop condition was observed that could cause excessively low layer thickness in a cartridge. When the production line stops, the configuration of the machine stop position lends itself to the possibility of creating a slug of 24 cartridges with very low layer thickness through a combination of standing time and air blow out. The siliconization and air blow out nozzles stop with the top of the nozzles in the top of the cartridges during a machine cycle stop. Each station, air blow out and siliconization, has 12 cartridges on it at any given time. When the machine stops in this position with the nozzles up, the cartridges over the siliconization station get siliconized. The cartridges over the air blow out station have been siliconized already and are awaiting blow out. At this point there are 24 cartridges sitting with silicone applied but not blown out yet.

The line can be down for up to three hours. After three hours, the heating tunnel damage is considered too great and the line is cleared back to before the siliconization station. In the worst case scenario though, these 24 cartridges can theoretically sit for two hours and fifty-nine minutes with silicone running down the side and leaving very thin layers at the top and eventually the middle of the cartridge.

The first thing that happens when the line starts up again is that the air blows out the 12 cartridges over the air station and then when the cartridges over the siliconization station move to the air station, they get blown out as well. This means that cartridges that have been standing for anywhere up to three hours get blasted at full air pressure at the top of the cartridge where there is now very little silicone left. This could create a very small slug of product that would have higher than average gliding forces especially at the top of the cartridge. The odds of catching these samples in an in-process control check are relatively small given that the line can hold thousands of cartridges at a time.

The process should be modified to not blow out the set of samples over the air blow out station immediately after startup, and the samples over the silicone station should be re-siliconized before moving to the air blowout station.

This is just one example of how start/stop conditions could have affect multiple key aspects of siliconization, but the process as a whole should be evaluated for start/stop situations that could cause similar problems.

8.5 Conclusions

There are many processes and parameters in production that affect siliconization. The resulting layer thickness has great effects on gliding force and standard deviation of gliding force, especially once that layer thickness gets below 40nm on average in any segment of the cartridge. The current surface preparations or cleaning methods on the three production lines are different, but this appears to have a negligible effect on the overall performance of the silicone layer and forces in the cartridge. The application methods of flushing and microdosing lead to obvious difference in silicone layer thickness and gliding forces, but this seems to be driven mostly by the air blow out process step associated with the flushing method. Reduction of this air pressure, modification of the nozzle, or removal of this process step are all potential ways to solve this issue. The amount of time a siliconized cartridge stands before baking in is also an important factor that can greatly reduce the layer thickness at the top of the cartridge especially when the concentration is lower than the standard 2.1% and/or when standing times are extremely long. The concentration of the solution is important with differences of 0.5% showing significant differences in layer thickness, gliding force, and standard deviation. Finally, the time in the heating tunnel, or "baking-in" has an impact on layer thickness and gliding force as well. This is a smaller impact than what is seen through other processes and can be mitigated by shortening the maximum allowable time in the tunnel.

The final recommendations are to modify the air blow out nozzle for the flushing process or remove the air blow out process step entirely if possible. The procedures around silicone emulsion dilution and mixing should be evaluated for consistency and automated where possible. Finally, start/stop conditions should be evaluated to ensure they are not creating stacking issues that can impact siliconization layer thickness and through that gliding force and deviation to ensure the most reliable and repeatable product.

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Appendices

Appendix A: Using Reynolds Number to Scale Air Pressure for Different Diameter Cartridges

Assume Re, Reynolds number, can be used as a scaling factor with fluid density ρ, velocity V, diameter D, area, A and viscosity, μ. D_1, P_1, D_2, P_2 refer to pressures and diameters of flow through a pipe, which is used to represent the cartridge. See Section 3.1.4 and Figure 53 for schematics showing the nomenclatures and definitions in regards to the cartridge calculations.

$$Re = \frac{\rho V D}{\mu}$$

$$V \sim \sqrt{\Delta P} * \frac{d^2}{D^2}$$

Therefore:

$$Re \sim \frac{\rho * \sqrt{\Delta P} * d^2}{\mu D}$$

For D_1 and D_2:

$$Re_1 \sim \frac{\rho * \sqrt{\Delta P_1} * d^2}{\mu D_1}$$

$$Re_2 \sim \frac{\rho * \sqrt{\Delta P_2} * d^2}{\mu D_2}$$

Solving $Re_1 = Re_2$ yields

$$\Delta P_2 = \Delta P_1 * \left(\frac{D_2}{D_1}\right)^2$$

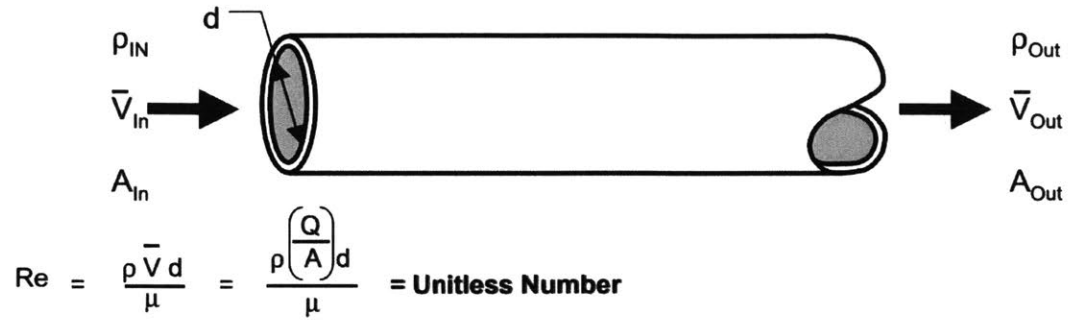


Figure 53: Depiction of variables used in Reynolds number in pipe flow applications [29]

Appendix B: Modified Nozzle Test

New Nozzle Design

An existing air nozzle was modified to widen the air holes. This was intended to combat the effect of high air pressure on the removal of silicone from the cartridge in the flushing siliconization method. The standard production nozzle was milled to widen the air holes into two layers of slots around the diameter of the nozzle. A comparison between the old nozzle and new nozzle is in Figure 54.

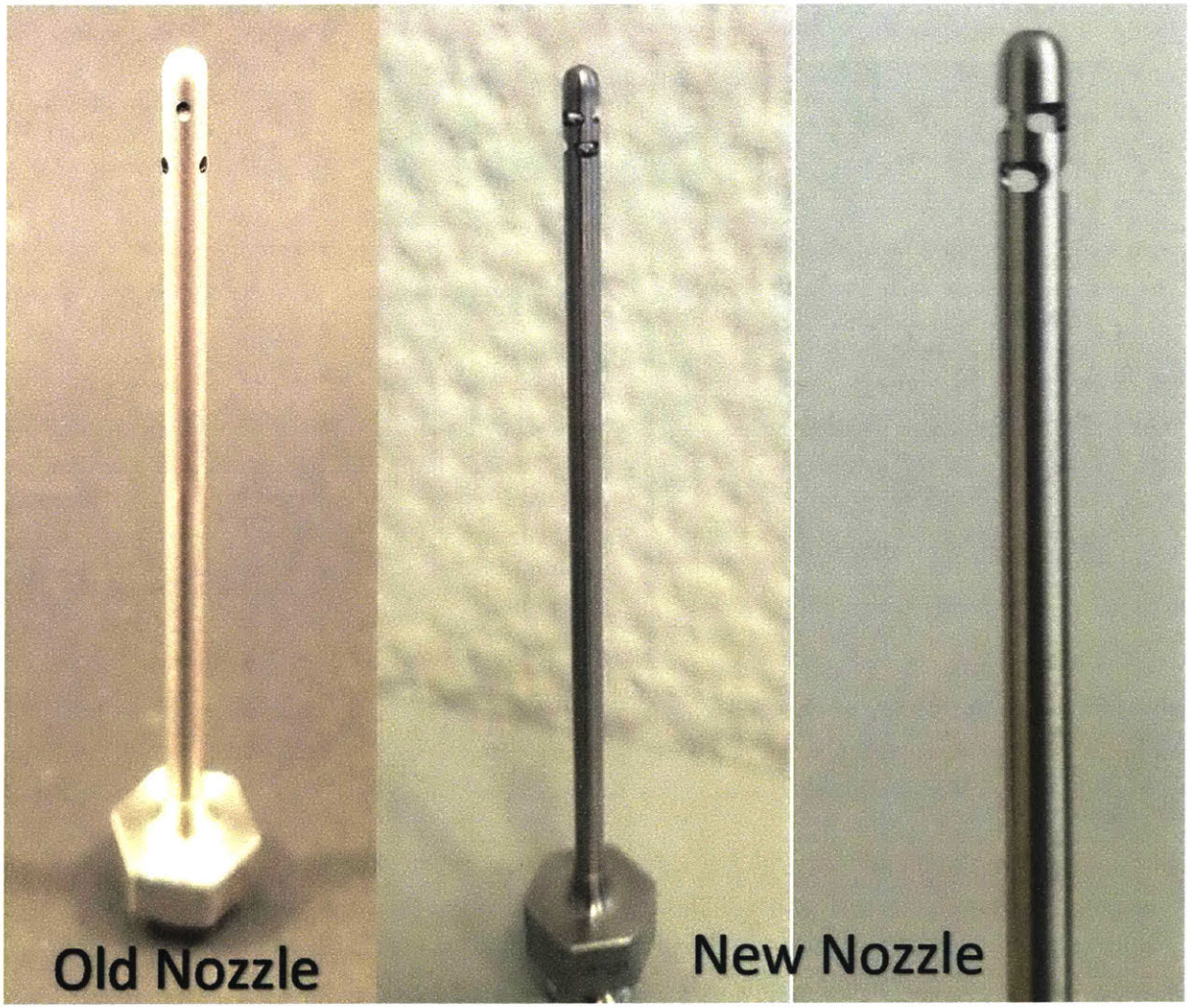


Figure 54: Comparison of Old and New Nozzles

The idea behind the design was to lower the air velocity at the nozzle tip by widening the nozzle holes. This concept was explored through application of fluid dynamic principles in Section 3.1.4 and Appendix A. The new nozzle experiment was done with the same experimental setup as described in Section 6.5 except there were no samples created at 3 bar pressure.

Results

Use of the new nozzle left more silicone in place in all locations along the cartridge when tested at 0.8 bar. As discussed in Section 6.5, this 0.8 bar air pressure was the most representative of actual production settings to produce similar layer thicknesses and streaking patterns. The new layer profile can be seen in Figure 55 below.

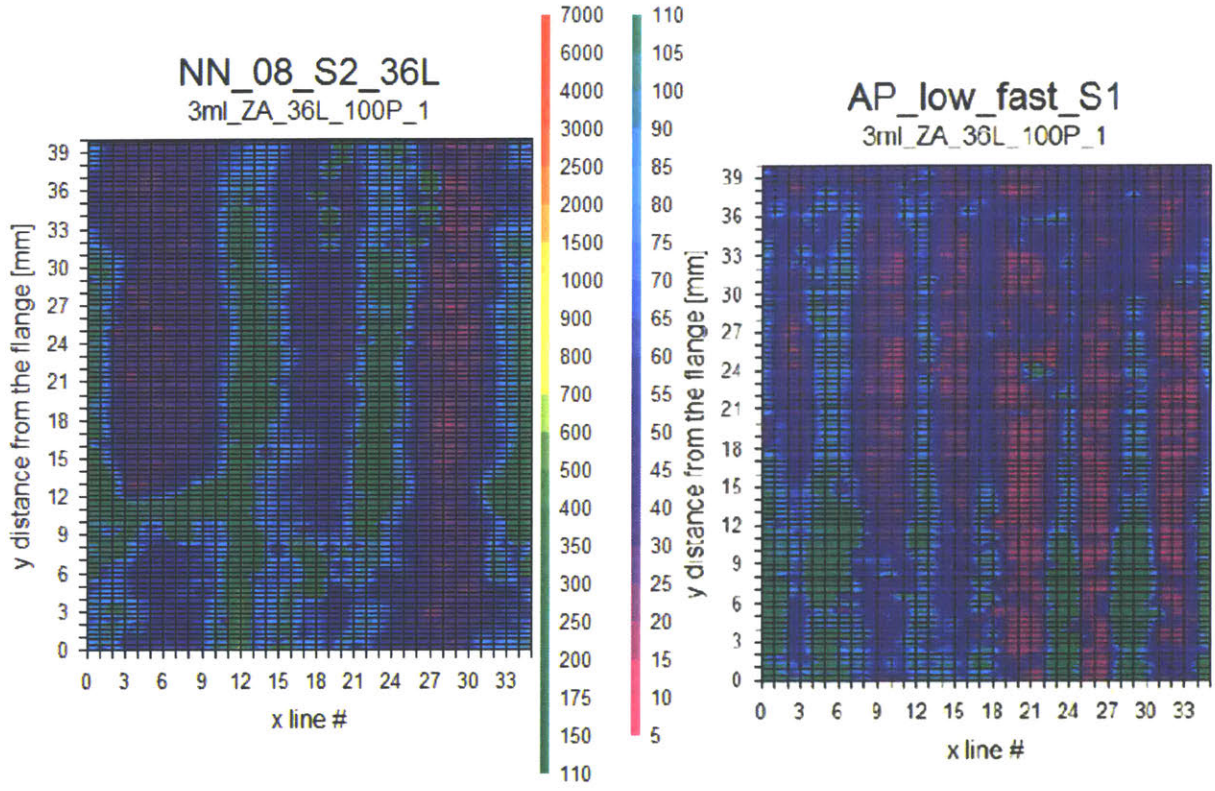


Figure 55: New Nozzle Layer Thickness Profile, Rap.ID Image. New Profile (left), Old Profile (right)

Similar streaking to the old nozzle can be seen in the new nozzle Rap.ID layer thickness profile. The new nozzle, as expected, only has three streaks instead of the six seen with the old nozzle. Table 5 summarizes a comparison of the old and new nozzles in regards to layer thickness, gliding force, and standard deviation at 0.8 and 1.5 bar.

Table 5: Comparison of Old and New Nozzles

Nozzle →	**Old – 6 pinholes**	**New – 3 slots**
Layer Thickness		
0.8 bar	56 nm	70 nm
1.5 bar	39 nm	45 nm
Gliding Force		
0.8 bar	1.23 N	1.14 N
1.5 bar	1.81 N	2.23 N
Standard Deviation		
0.8 bar	0.32 N	0.17 N
1.5 bar	0.56 N	0.39 N

The average layer thickness also increases in the new nozzle samples compared to the old nozzle samples at 0.8 bar. Though the average layer thickness is slightly thicker than the old nozzle layer thickness and above the 40nm threshold, Figure 56 shows that the new nozzle at 1.5 bar clears out silicone much more evenly as compared to the old nozzle. There is more silicone at the bottom and less at the top in the old cartridge. The rubber stopper likely carries up some of that excess silicone from the bottom to lubricate the cartridge as it moves up.

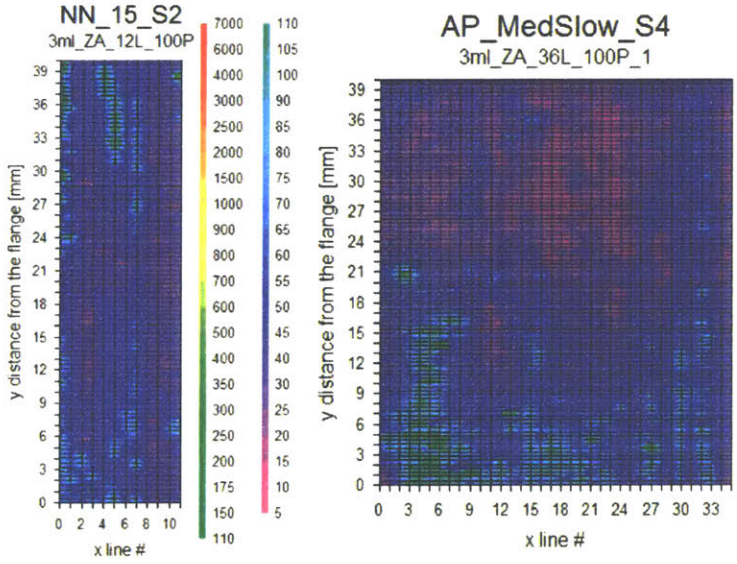


Figure 56: New Nozzle at 1.5 bar 12 Lines (Left) Old Nozzle at 1.5 bar 36 Lines (Right)

Since the 0.8 bar air pressure setting in the lab setup is most similar to reality in the production area, those results can be taken as the closest proxy to how a modified nozzle would contribute to silicone layer thickness in production. A numerical comparison of these results is shown below. Figure 57 compares average layer thickness by location or bottom, middle, top and compares the

new and old nozzle configurations. In all locations at 0.8 bar the average layer thickness increases with use of the new nozzle. Due to the small sample sizes of only 5 samples each, it is difficult to draw a strong conclusion through statistical data analysis, but a t-test with t value of 2.31 and confidence interval of 95% showed that the only significant difference between the two nozzles was seen in the layer thickness at the top and middle of the cartridge. The top of the cartridge is the most critical for seeing increased forces, so increasing layer thickness in this portion of the cartridge is important.

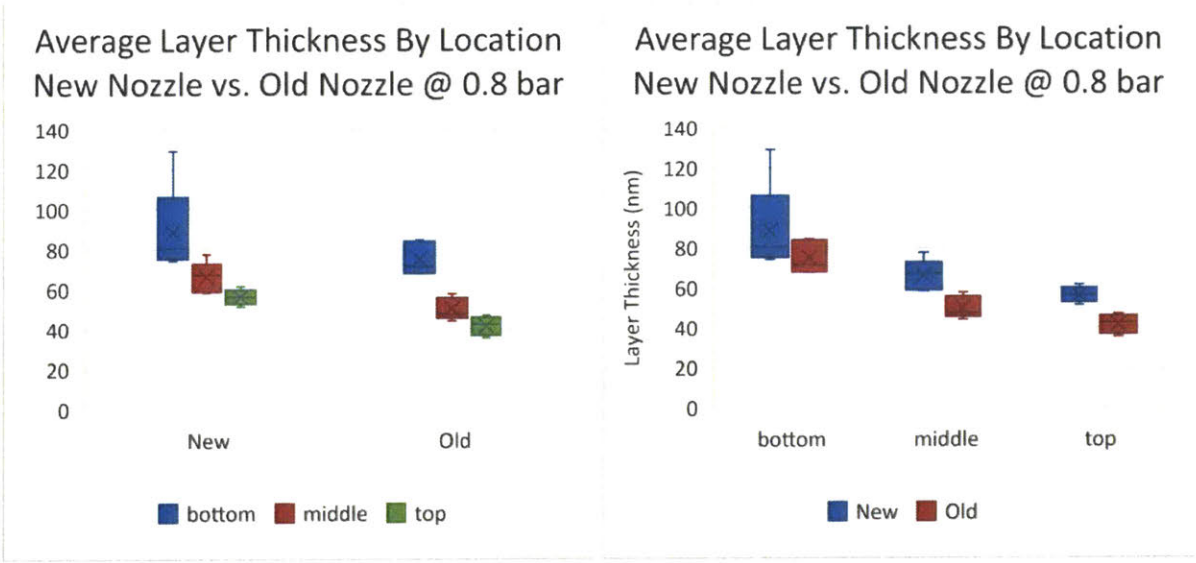


Figure 57: Average Layer Thickness by Location Comparison New vs. Old Nozzles

More samples need to be evaluated to draw better conclusions about the effect on gliding forces and standard deviation. It appears that a small increase in layer thickness leads to a reduction in gliding force and standard deviation as seen in Figure 58. The results of a limited statistical analysis report included at the end of this appendix do not show statistical significance of this gliding force change. Beyond the layer thickness in the top and the bottom, there does not appear to be much difference between the old and new nozzle.

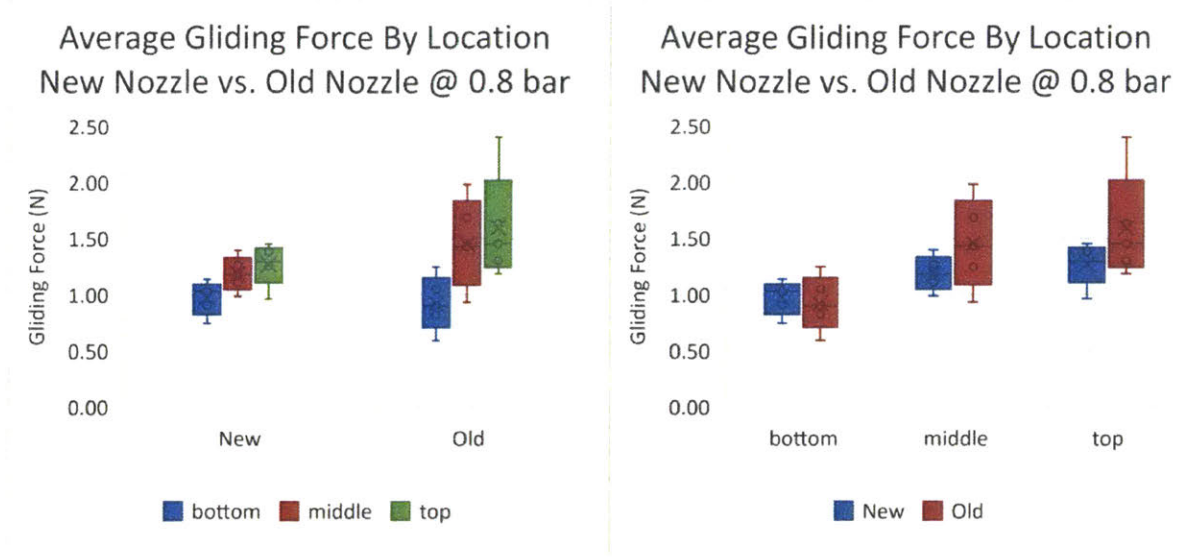


Figure 58: Average Gliding Force Comparison by Location for New and Old Nozzles

Similar patterns are seen for the standard deviation, as seen in Figure 59, which decreases with use of the new nozzle. Though the range of observed standard deviations tightens drastically with the new nozzle, there is technically no statistical difference between the old and new nozzle in all locations.

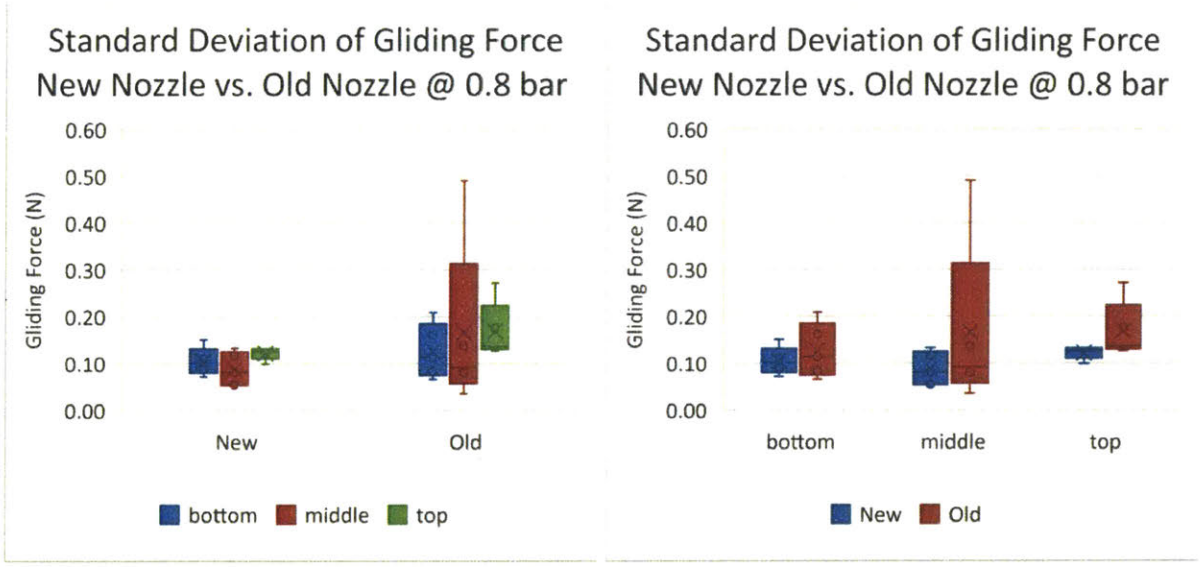


Figure 59: Standard Deviation of Gliding Force Comparison of New and Old Nozzles

Conclusions

There is some improvement in layer thickness and gliding force seen with use of the new, wider-hole air nozzle, but the effect is small. The slight improvement in layer thickness that the top and middle of the cartridge indicates that modifications that reduce air pressure in the cartridge are

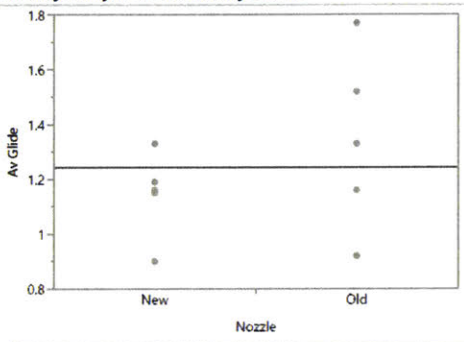
effective in increasing layer thickness. Further investigation into designs that would be even more uniform and allow for ever lower air pressure should be done.

Statistical Analysis

New Nozzle 0.8 bar Final

Fit Group

Oneway Analysis of Av Glide By Nozzle

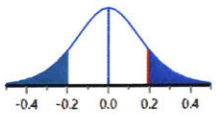


t Test

Old-New

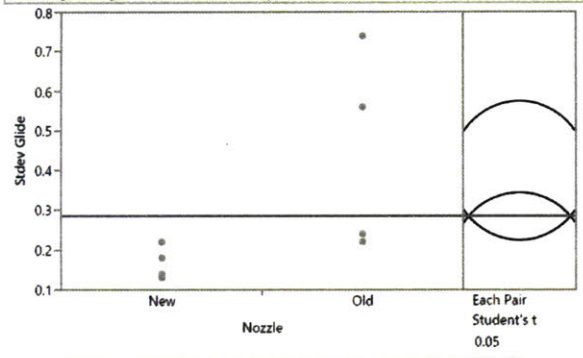
Assuming unequal variances

Difference	0.19400	t Ratio	1.200003
Std Err Dif	0.16167	DF	5.723346
Upper CL Dif	0.59426	Prob > |t|	0.2774
Lower CL Dif	-0.20626	Prob > t	0.1387
Confidence	0.95	Prob < t	0.8613



Fit Group

Oneway Analysis of Stdev Glide By Nozzle

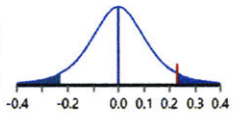


t Test

Old-New

Assuming unequal variances

Difference	0.23000	t Ratio	2.144761
Std Err Dif	0.10724	DF	4.184954
Upper CL Dif	0.52262	Prob > |t|	0.0955
Lower CL Dif	-0.06262	Prob > t	0.0478*
Confidence	0.95	Prob < t	0.9522



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.30600	0.05

LSD Threshold Matrix

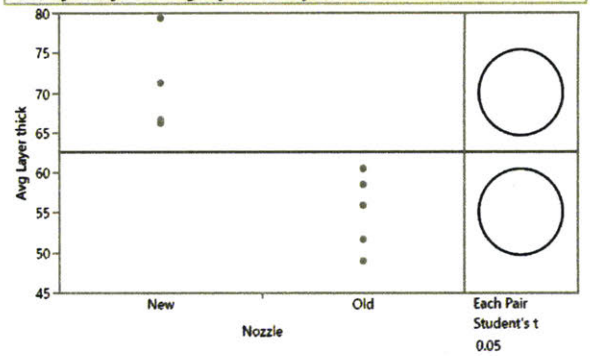
Abs(Dif)-LSD

	Old	New
Old	-0.24729	-0.01729
New	-0.01729	-0.24729

Positive values show pairs of means that are significantly different.

Fit Group

Oneway Analysis of Avg Layer thick By Nozzle

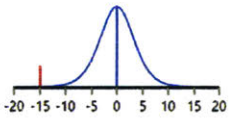


t Test

Old-New

Assuming unequal variances

Difference	-14.920	t Ratio	-4.52958
Std Err Dif	3.294	DF	7.795249
Upper CL Dif	-7.289	Prob > |t|	0.0021*
Lower CL Dif	-22.551	Prob > t	0.9990
Confidence	0.95	Prob < t	0.0010*



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.30600	0.05

LSD Threshold Matrix

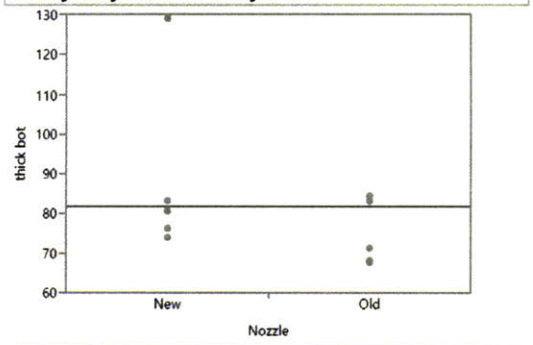
Abs(Dif)-LSD

	New	Old
New	-7.5957	7.3242
Old	7.3242	-7.5957

Positive values show pairs of means that are significantly different.

Fit Group

Oneway Analysis of thick bot By Nozzle

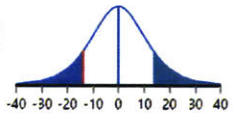


t Test

Old-New

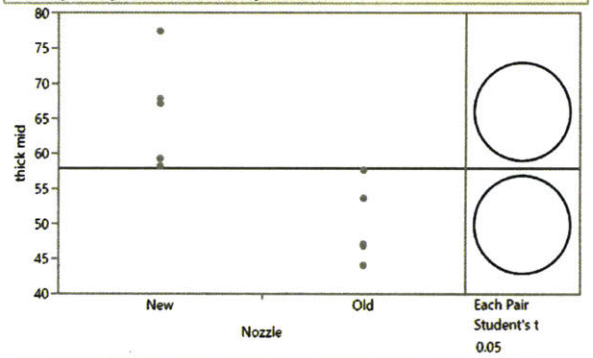
Assuming unequal variances

Difference	-13.666	t Ratio	-1.25763
Std Err Dif	10.866	DF	5.013405
Upper CL Dif	14.244	Prob > |t|	0.2639
Lower CL Dif	-41.575	Prob > t	0.8680
Confidence	0.95	Prob < t	0.1320



Fit Group

Oneway Analysis of thick mid By Nozzle

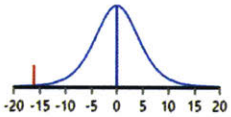


t Test

Old-New

Assuming unequal variances

Difference	-16.111	t Ratio	-3.76469
Std Err Dif	4.279	DF	7.277367
Upper CL Dif	-6.069	Prob > |t|	0.0065*
Lower CL Dif	-26.152	Prob > t	0.9967
Confidence	0.95	Prob < t	0.0033*



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.30600	0.05

LSD Threshold Matrix

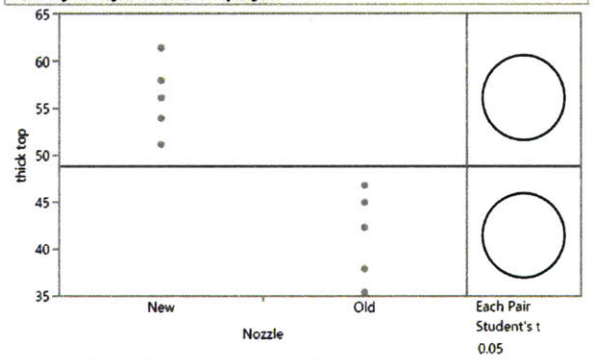
Abs(Dif)-LSD

	New	Old
New	-9.8684	6.2424
Old	6.2424	-9.8684

Positive values show pairs of means that are significantly different.

Fit Group

Oneway Analysis of thick top By Nozzle

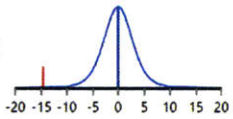


t Test

Old-New

Assuming unequal variances

Difference	-14.660	t Ratio	-5.3211
Std Err Dif	2.755	DF	7.692168
Upper CL Dif	-8.262	Prob > |t|	0.0008*
Lower CL Dif	-21.057	Prob > t	0.9996
Confidence	0.95	Prob < t	0.0004*



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.30600	0.05

LSD Threshold Matrix

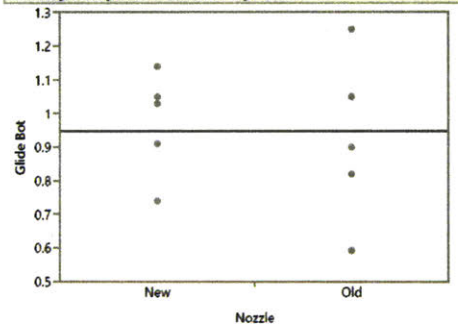
Abs(Dif)-LSD

	New	Old
New	-6.3531	8.3066
Old	8.3066	-6.3531

Positive values show pairs of means that are significantly different.

Fit Group

Oneway Analysis of Glide Bot By Nozzle

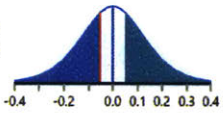


t Test

Old-New

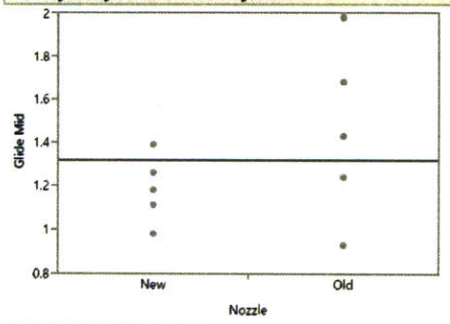
Assuming unequal variances

Difference	-0.05156	t Ratio	-0.39607
Std Err Dif	0.13018	DF	6.714495
Upper CL Dif	0.25894	Prob > |t|	0.7043
Lower CL Dif	-0.36207	Prob > t	0.6478
Confidence	0.95	Prob < t	0.3522



Fit Group

Oneway Analysis of Glide Mid By Nozzle

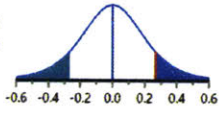


t Test

Old-New

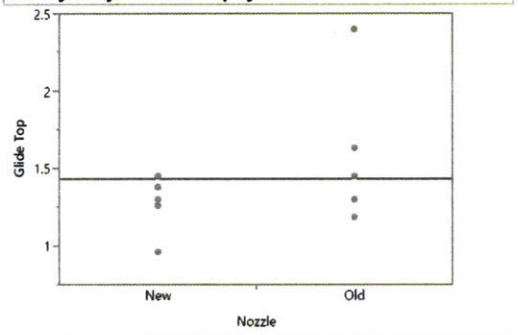
Assuming unequal variances

Difference	0.26784	t Ratio	1.387857
Std Err Dif	0.19298	DF	5.149248
Upper CL Dif	0.75962	Prob > |t|	0.2222
Lower CL Dif	-0.22395	Prob > t	0.1111
Confidence	0.95	Prob < t	0.8889



Fit Group

Oneway Analysis of Glide Top By Nozzle

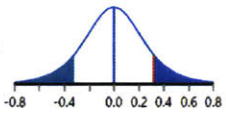


t Test

Old-New

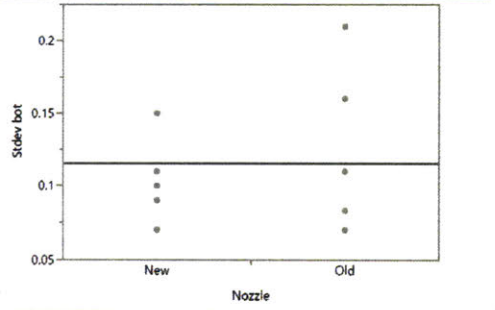
Assuming unequal variances

Difference	0.32302	t Ratio	1.398571
Std Err Dif	0.23096	DF	5.196243
Upper CL Dif	0.91005	Prob > |t|	0.2187
Lower CL Dif	-0.26401	Prob > t	0.1094
Confidence	0.95	Prob < t	0.8906



Fit Group

Oneway Analysis of Stdev bot By Nozzle

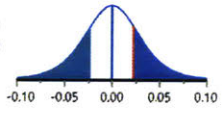


t Test

Old-New

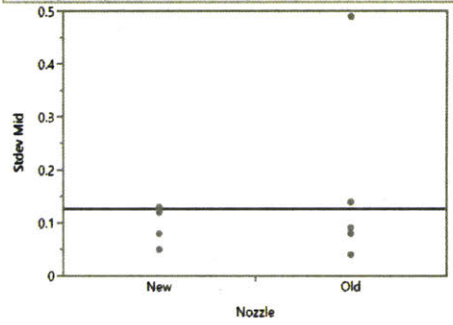
Assuming unequal variances

Difference	0.02260	t Ratio	0.775831
Std Err Dif	0.02913	DF	5.959319
Upper CL Dif	0.09400	Prob > |t|	0.4675
Lower CL Dif	-0.04880	Prob > t	0.2338
Confidence	0.95	Prob < t	0.7662



Fit Group

Oneway Analysis of Stdev Mid By Nozzle

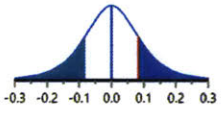


t Test

Old-New

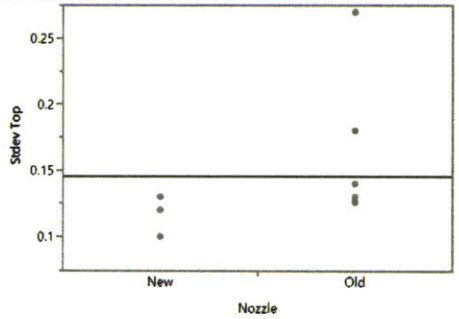
Assuming unequal variances

Difference	0.08220	t Ratio	0.98162
Std Err Dif	0.08374	DF	4.339546
Upper CL Dif	0.30770	Prob > |t|	0.3778
Lower CL Dif	-0.14330	Prob > t	0.1889
Confidence	0.95	Prob < t	0.8111



Fit Group

Oneway Analysis of Stdev Top By Nozzle

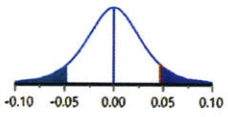


t Test

Old-New

Assuming unequal variances

Difference	0.04720	t Ratio	1.711404
Std Err Dif	0.02758	DF	4.373508
Upper CL Dif	0.12126	Prob > |t|	0.1560
Lower CL Dif	-0.02686	Prob > t	0.0780
Confidence	0.95	Prob < t	0.9220



Appendix C: Break Loose Force Over Time

Test Setup

In investigation of why break loose force may appear lower than gliding force in some cases, the following study was proposed. Cartridges were siliconized using the flushing method and stoppers were placed in the cartridges. The cartridges were then held for various amounts of time from essentially 0 seconds, where the stopper was placed in the cartridge and then immediately put in the Zwick testing machine, up to a month. The following timescales were used (all times in hours):

0.0001
0.5
1
2
4
6
8
16
24
48
168
360
696

Results

The maximum break loose force rises significantly over the first 48 hours and then levels off around 1 week of standing time with a gradual increase out to a month as shown by Figure 60. Further tests beyond a month were not conducted.

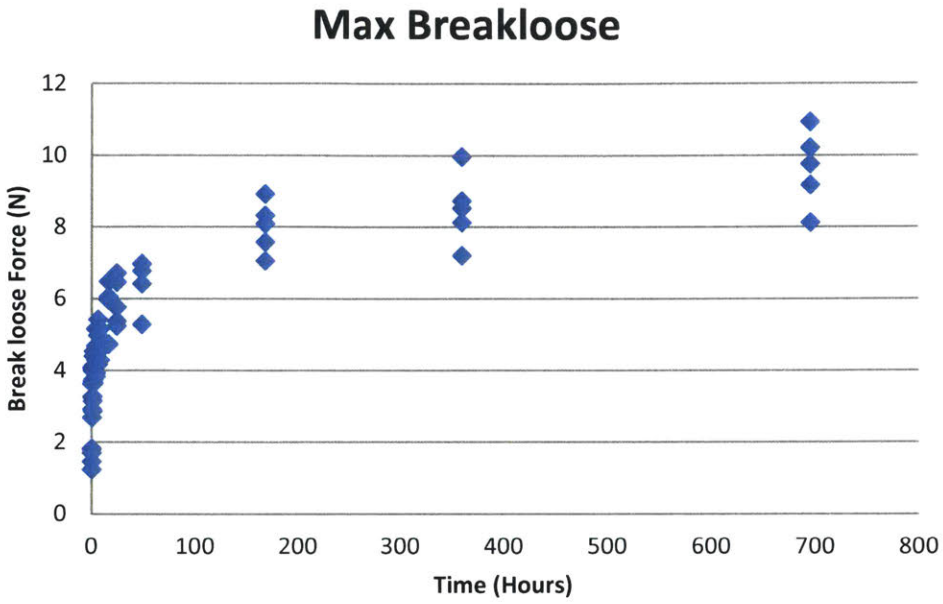


Figure 60: Max Break loose Force over Time

This suggests that in-process control testing done immediately after samples are pulled from the line might show lower break loose force than samples that have been sitting for a few hours. Though interesting, in the larger picture of the end-use consumer, the variation in break loose force immediately after production is not important. A consumer would not receive an insulin pen within a few hours of production, so engineers can design a pen to accommodate asymptotic force behavior.

The gliding force is not affected by time as strikingly as break loose force. There may be a slight increase over time, but given the short time frame and limited samples, this does not appear to be a significant increase as shown in Figure 61.

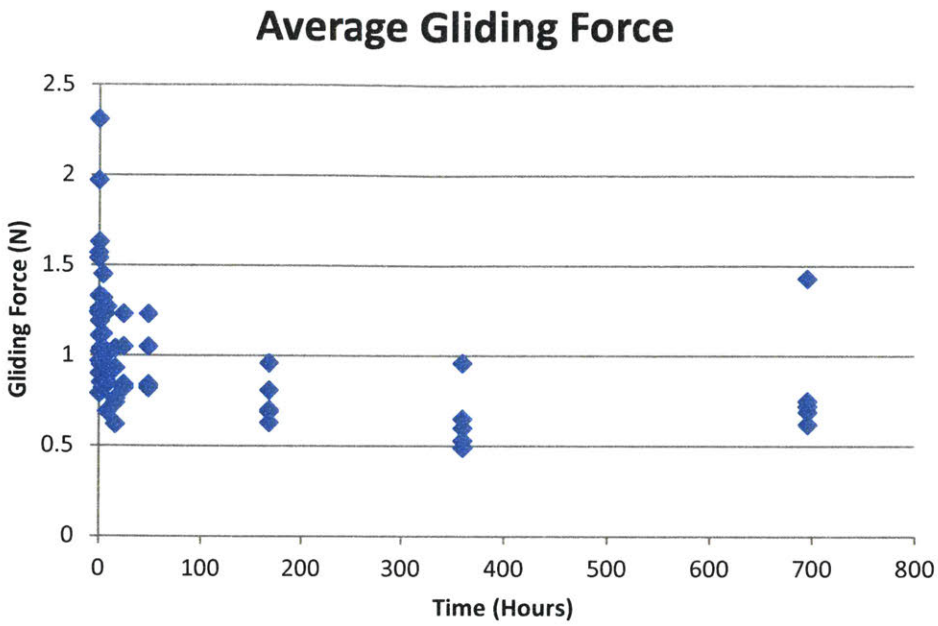
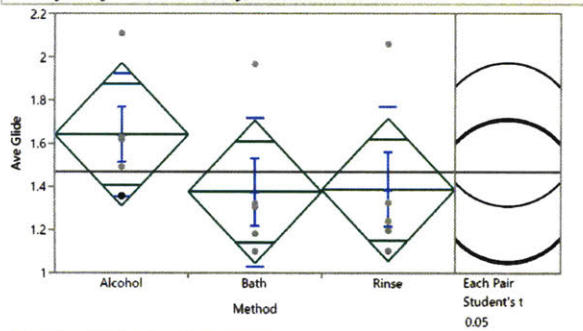


Figure 61: Average Gliding Force over Time

Appendix D: Cleaning Processes Statistical Analysis

Fit Group

Oneway Analysis of Ave Glide By Method



Oneway Anova

Summary of Fit

Rsquare	0.14051
Adj Rsquare	-0.00274
Root Mean Square Error	0.340559
Mean of Response	1.46755
Observations (or Sum Wgts)	15

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio	Prob > F
Method	2	0.2275259	0.113763	0.9809	0.4031
Error	12	1.3917634	0.115980		
C. Total	14	1.6192894			

Means for Oneway Anova

Level	Number	Mean	Std Error	Lower 95%	Upper 95%
Alcohol	5	1.64164	0.15230	1.3098	1.9735
Bath	5	1.37573	0.15230	1.0439	1.7076
Rinse	5	1.38528	0.15230	1.0534	1.7171

Std Error uses a pooled estimate of error variance

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
Alcohol	5	1.64164	0.284205	0.12710	1.2887	1.9945
Bath	5	1.37573	0.343487	0.15361	0.9492	1.8022
Rinse	5	1.38528	0.386245	0.17273	0.9057	1.8649

Means Comparisons

Fit Group

Oneway Analysis of Ave Glide By Method

Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.17881	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	Alcohol	Rinse	Bath
Alcohol	-0.46929	-0.21293	-0.20339
Rinse	-0.21293	-0.46929	-0.45975
Bath	-0.20339	-0.45975	-0.46929

Positive values show pairs of means that are significantly different.

Connecting Letters Report

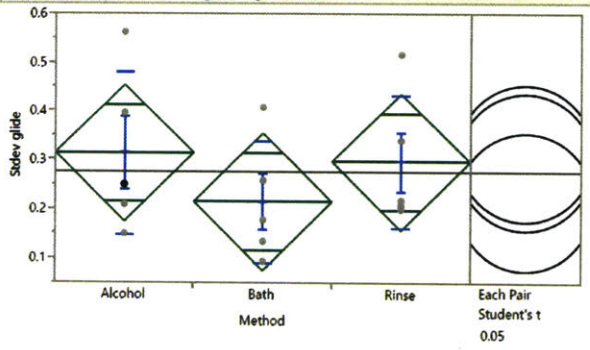
Level		Mean
Alcohol	A	1.6416371
Rinse	A	1.3852781
Bath	A	1.3757338

Levels not connected by same letter are significantly different.

Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
Alcohol	Bath	0.2659033	0.2153883	-0.203387	0.7351940	0.2406
Alcohol	Rinse	0.2563590	0.2153883	-0.212932	0.7256497	0.2570
Rinse	Bath	0.0095443	0.2153883	-0.459746	0.4788351	0.9654

Oneway Analysis of Stdev glide By Method



Fit Group

Oneway Analysis of Stdev glide By Method

Oneway Anova

Summary of Fit

Rsquare	0.102174
Adj Rsquare	-0.04746
Root Mean Square Error	0.143158
Mean of Response	0.273839
Observations (or Sum Wgts)	15

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio	Prob > F
Method	2	0.02798749	0.013994	0.6828	0.5238
Error	12	0.24593136	0.020494		
C. Total	14	0.27391885			

Means for Oneway Anova

Level	Number	Mean	Std Error	Lower 95%	Upper 95%
Alcohol	5	0.312843	0.06402	0.17335	0.45234
Bath	5	0.213622	0.06402	0.07413	0.35311
Rinse	5	0.295053	0.06402	0.15556	0.43455

Std Error uses a pooled estimate of error variance

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
Alcohol	5	0.312843	0.166304	0.07437	0.10635	0.51934
Bath	5	0.213622	0.123822	0.05537	0.05988	0.36737
Rinse	5	0.295053	0.135992	0.06082	0.12620	0.46391

Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.17881	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	Alcohol	Rinse	Bath
Alcohol	-0.19727	-0.17948	-0.09805
Rinse	-0.17948	-0.19727	-0.11584
Bath	-0.09805	-0.11584	-0.19727

Positive values show pairs of means that are significantly different.

Fit Group

Oneway Analysis of Stdev glide By Method

Means Comparisons

Comparisons for each pair using Student's t

Connecting Letters Report

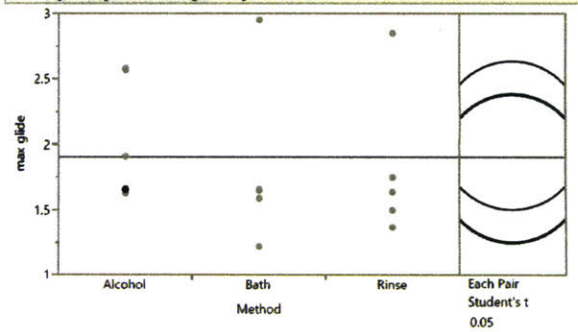
Level		Mean
Alcohol	A	0.31284347
Rinse	A	0.29505271
Bath	A	0.21362166

Levels not connected by same letter are significantly different.

Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
Alcohol	Bath	0.0992218	0.0905412	-0.098051	0.2964942	0.2946
Rinse	Bath	0.0814310	0.0905412	-0.115841	0.2787034	0.3861
Alcohol	Rinse	0.0177908	0.0905412	-0.179482	0.2150631	0.8475

Oneway Analysis of max glide By Method



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.17881	0.05

Fit Group

Oneway Analysis of max glide By Method

Means Comparisons

Comparisons for each pair using Student's t

LSD Threshold Matrix

Abs(Dif)-LSD

	Alcohol	Rinse	Bath
Alcohol	-0.80001	-0.55201	-0.54401
Rinse	-0.55201	-0.80001	-0.79201
Bath	-0.54401	-0.79201	-0.80001

Positive values show pairs of means that are significantly different.

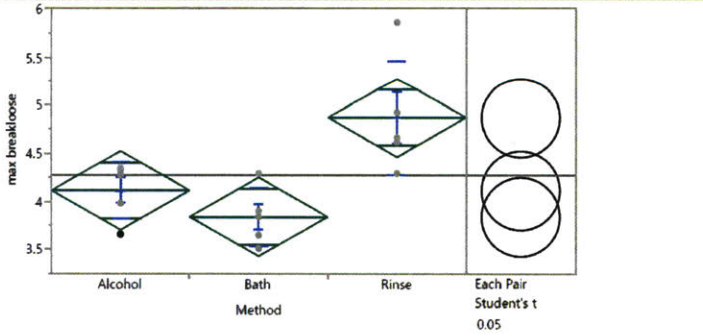
Connecting Letters Report

Level		Mean
Alcohol	A	2.0700000
Rinse	A	1.8220000
Bath	A	1.8140000

Levels not connected by same letter are significantly different.

Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
Alcohol	Bath	0.2560000	0.3671784	-0.544013	1.056013	0.4990
Alcohol	Rinse	0.2480000	0.3671784	-0.552013	1.048013	0.5122
Rinse	Bath	0.0080000	0.3671784	-0.792013	0.808013	0.9830



Fit Group

Oneway Analysis of max breakloose By Method

Oneway Anova

Summary of Fit

Rsquare	0.573126
Adj Rsquare	0.50198
Root Mean Square Error	0.420282
Mean of Response	4.272667
Observations (or Sum Wgts)	15

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio	Prob > F
Method	2	2.8458533	1.42293	8.0557	0.0061*
Error	12	2.1196400	0.17664		
C. Total	14	4.9654933			

Means for Oneway Anova

Level	Number	Mean	Std Error	Lower 95%	Upper 95%
Alcohol	5	4.11200	0.18796	3.7025	4.5215
Bath	5	3.83800	0.18796	3.4285	4.2475
Rinse	5	4.86800	0.18796	4.4585	5.2775

Std Error uses a pooled estimate of error variance

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
Alcohol	5	4.11200	0.290637	0.12998	3.7511	4.4729
Bath	5	3.83800	0.296260	0.13249	3.4701	4.2059
Rinse	5	4.86800	0.598055	0.26746	4.1254	5.6106

Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.17881	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	Rinse	Alcohol	Bath
Rinse	-0.57915	0.17685	0.45085
Alcohol	0.17685	-0.57915	-0.30515
Bath	0.45085	-0.30515	-0.57915

Positive values show pairs of means that are significantly different.

Fit Group

Oneway Analysis of max breakloose By Method

Means Comparisons

Comparisons for each pair using Student's t

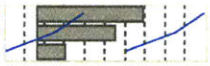
Connecting Letters Report

Level		Mean
Rinse	A	4.8680000
Alcohol	B	4.1120000
Bath	B	3.8380000

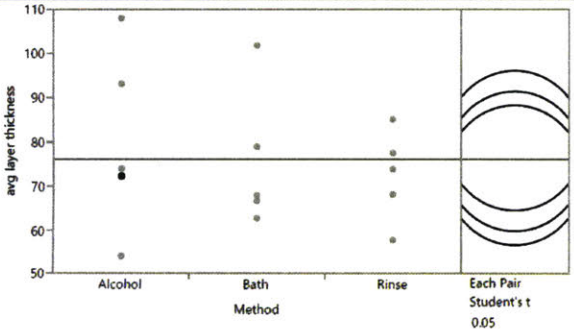
Levels not connected by same letter are significantly different.

Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
Rinse	Bath	1.030000	0.2658095	0.450851	1.609149	0.0022*
Rinse	Alcohol	0.756000	0.2658095	0.176851	1.335149	0.0148*
Alcohol	Bath	0.274000	0.2658095	-0.305149	0.853149	0.3230



Oneway Analysis of avg layer thickness By Method



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.17881	0.05

Fit Group

Oneway Analysis of avg layer thickness By Method

Means Comparisons

Comparisons for each pair using Student's t

LSD Threshold Matrix

Abs(Dif)-LSD

	Alcohol	Bath	Rinse
Alcohol	-22.243	-17.562	-14.451
Bath	-17.562	-22.243	-19.132
Rinse	-14.451	-19.132	-22.243

Positive values show pairs of means that are significantly different.

Connecting Letters Report

Level		Mean
Alcohol	A	80.337382
Bath	A	75.656566
Rinse	A	72.545791

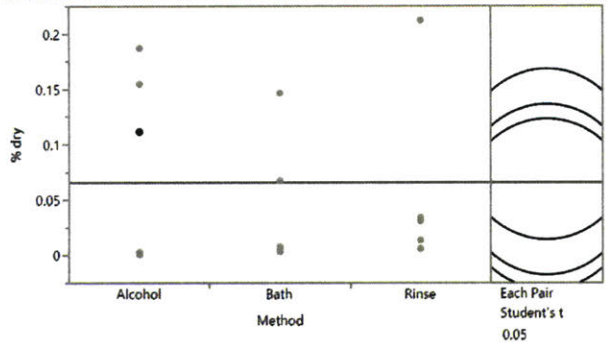
Levels not connected by same letter are significantly different.

Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
Alcohol	Rinse	7.791590	10.20863	-14.4511	30.03427	0.4601
Alcohol	Bath	4.680815	10.20863	-17.5619	26.92350	0.6548
Bath	Rinse	3.110775	10.20863	-19.1319	25.35346	0.7658

Fit Group

Oneway Analysis of % dry By Method



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.17881	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	Alcohol	Rinse	Bath
Alcohol	-0.10896	-0.07694	-0.06364
Rinse	-0.07694	-0.10896	-0.09566
Bath	-0.06364	-0.09566	-0.10896

Positive values show pairs of means that are significantly different.

Connecting Letters Report

Level		Mean
Alcohol	A	0.09158000
Rinse	A	0.05956000
Bath	A	0.04626000

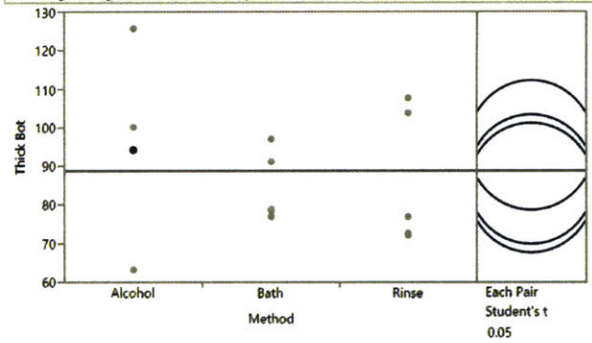
Levels not connected by same letter are significantly different.

Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
Alcohol	Bath	0.0453200	0.0500105	-0.063643	0.1542835	0.3827
Alcohol	Rinse	0.0320200	0.0500105	-0.076943	0.1409835	0.5340
Rinse	Bath	0.0133000	0.0500105	-0.095663	0.1222635	0.7948

Fit Group

Oneway Analysis of Thick Bot By Method



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.17881	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	Alcohol	Rinse	Bath
Alcohol	-23.693	-14.836	-12.631
Rinse	-14.836	-23.693	-21.487
Bath	-12.631	-21.487	-23.693

Positive values show pairs of means that are significantly different.

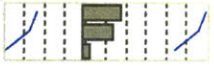
Connecting Letters Report

Level		Mean
Alcohol	A	95.549016
Rinse	A	86.692842
Bath	A	84.487463

Levels not connected by same letter are significantly different.

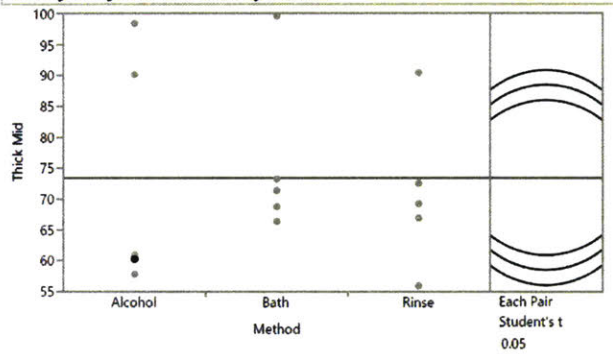
Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
Alcohol	Bath	11.06155	10.87406	-12.6310	34.75409	0.3291
Alcohol	Rinse	8.85617	10.87406	-14.8364	32.54871	0.4313
Rinse	Bath	2.20538	10.87406	-21.4872	25.89792	0.8427



Fit Group

Oneway Analysis of Thick Mid By Method



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.17881	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	Bath	Alcohol	Rinse
Bath	-21.197	-18.815	-16.318
Alcohol	-18.815	-21.197	-18.699
Rinse	-16.318	-18.699	-21.197

Positive values show pairs of means that are significantly different.

Connecting Letters Report

Level		Mean
Bath	A	75.895973
Alcohol	A	73.514124
Rinse	A	71.016617

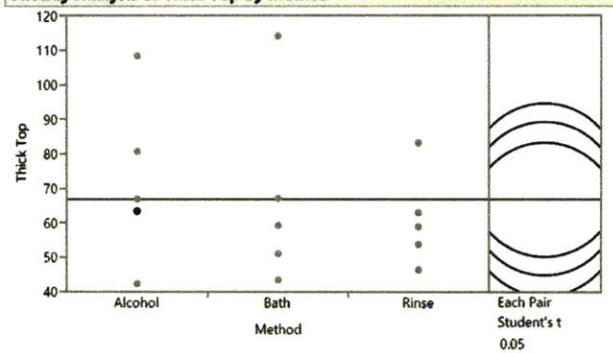
Levels not connected by same letter are significantly different.

Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
Bath	Rinse	4.879356	9.728629	-16.3175	26.07622	0.6251
Alcohol	Rinse	2.497507	9.728629	-18.6994	23.69437	0.8017
Bath	Alcohol	2.381849	9.728629	-18.8150	23.57871	0.8107

Fit Group

Oneway Analysis of Thick Top By Method



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.17881	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	Alcohol	Bath	Rinse
Alcohol	-31.422	-26.058	-20.089
Bath	-26.058	-31.422	-25.453
Rinse	-20.089	-25.453	-31.422

Positive values show pairs of means that are significantly different.

Connecting Letters Report

Level		Mean
Alcohol	A	72.388600
Bath	A	67.024444
Rinse	A	61.055375

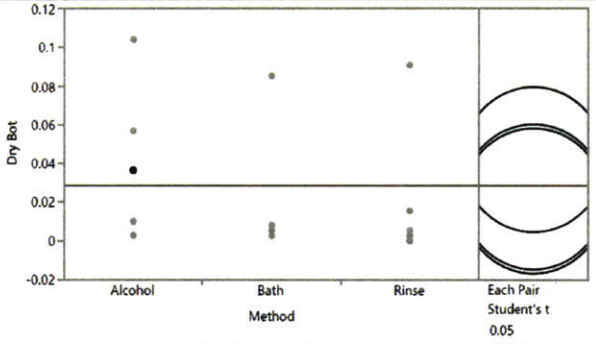
Levels not connected by same letter are significantly different.

Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
Alcohol	Rinse	11.33323	14.42177	-20.0891	42.75557	0.4472
Bath	Rinse	5.96907	14.42177	-25.4533	37.39142	0.6863
Alcohol	Bath	5.36416	14.42177	-26.0582	36.78650	0.7164

Fit Group

Oneway Analysis of Dry Bot By Method



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.17881	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	Alcohol	Rinse	Bath
Alcohol	-0.05314	-0.03390	-0.03180
Rinse	-0.03390	-0.05314	-0.05104
Bath	-0.03180	-0.05104	-0.05314

Positive values show pairs of means that are significantly different.

Connecting Letters Report

Level		Mean
Alcohol	A	0.04210000
Rinse	A	0.02286000
Bath	A	0.02076000

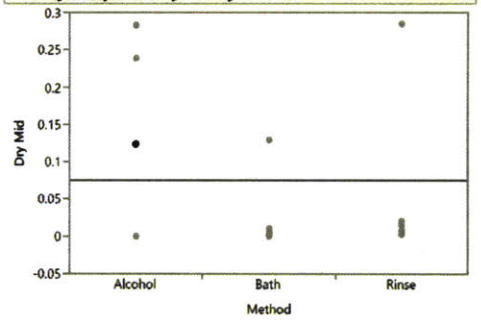
Levels not connected by same letter are significantly different.

Ordered Differences Report

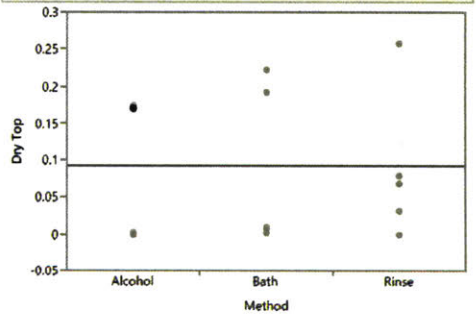
Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
Alcohol	Bath	0.0213400	0.0243880	-0.031797	0.0744769	0.3987
Alcohol	Rinse	0.0192400	0.0243880	-0.033897	0.0723769	0.4455
Rinse	Bath	0.0021000	0.0243880	-0.051037	0.0552369	0.9328

Fit Group

Oneway Analysis of Dry Mid By Method

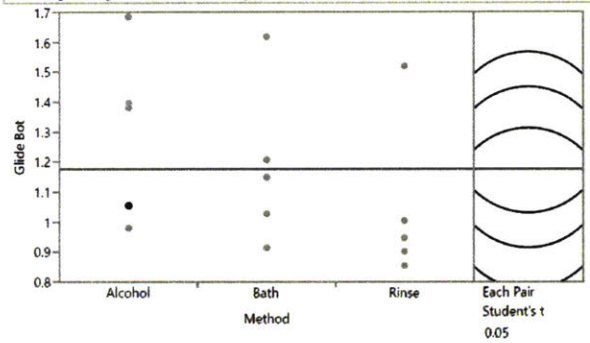


Oneway Analysis of Dry Top By Method



Fit Group

Oneway Analysis of Glide Bot By Method



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.17881	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	Alcohol	Bath	Rinse
Alcohol	-0.37939	-0.26277	-0.12476
Bath	-0.26277	-0.37939	-0.24139
Rinse	-0.12476	-0.24139	-0.37939

Positive values show pairs of means that are significantly different.

Connecting Letters Report

Level		Mean
Alcohol	A	1.2999502
Bath	A	1.1833275
Rinse	A	1.0453216

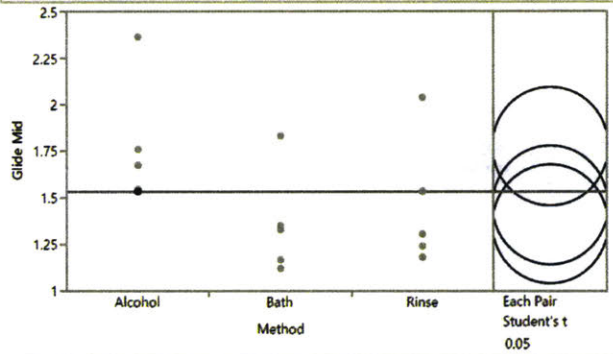
Levels not connected by same letter are significantly different.

Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
Alcohol	Rinse	0.2546286	0.1741283	-0.124764	0.6340216	0.1693
Bath	Rinse	0.1380059	0.1741283	-0.241387	0.5173989	0.4434
Alcohol	Bath	0.1166227	0.1741283	-0.262770	0.4960157	0.5157

Fit Group

Oneway Analysis of Glide Mid By Method



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.17881	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	Alcohol	Rinse	Bath
Alcohol	-0.44998	-0.13356	-0.03292
Rinse	-0.13356	-0.44998	-0.34934
Bath	-0.03292	-0.34934	-0.44998

Positive values show pairs of means that are significantly different.

Connecting Letters Report

Level		Mean
Alcohol	A	1.7763932
Rinse	A	1.4599713
Bath	A	1.3593355

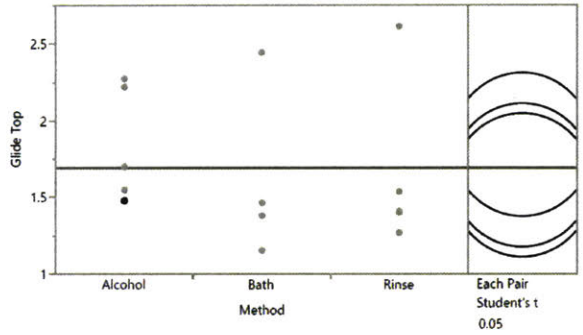
Levels not connected by same letter are significantly different.

Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
Alcohol	Bath	0.4170578	0.2065255	-0.032923	0.8670382	0.0664
Alcohol	Rinse	0.3164219	0.2065255	-0.133559	0.7664023	0.1514
Rinse	Bath	0.1006359	0.2065255	-0.349345	0.5506163	0.6348

Fit Group

Oneway Analysis of Glide Top By Method



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.17881	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	Alcohol	Rinse	Bath
Alcohol	-0.66302	-0.46399	-0.39896
Rinse	-0.46399	-0.66302	-0.59798
Bath	-0.39896	-0.59798	-0.66302

Positive values show pairs of means that are significantly different.

Connecting Letters Report

Level		Mean
Alcohol	A	1.8450365
Rinse	A	1.6460146
Bath	A	1.5809752

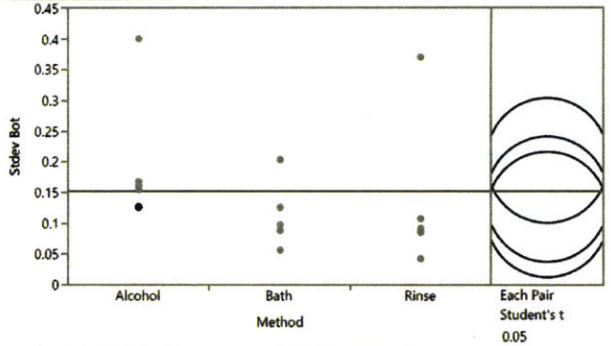
Levels not connected by same letter are significantly different.

Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
Alcohol	Bath	0.2640613	0.3043018	-0.398955	0.9270780	0.4025
Alcohol	Rinse	0.1990219	0.3043018	-0.463995	0.8620386	0.5254
Rinse	Bath	0.0650394	0.3043018	-0.597977	0.7280562	0.8343

Fit Group

Oneway Analysis of Stdev Bot By Method



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.17881	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	Alcohol	Rinse	Bath
Alcohol	-0.14422	-0.08131	-0.05621
Rinse	-0.08131	-0.14422	-0.11912
Bath	-0.05621	-0.11912	-0.14422

Positive values show pairs of means that are significantly different.

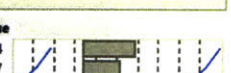
Connecting Letters Report

Level		Mean
Alcohol	A	0.20244633
Rinse	A	0.13953907
Bath	A	0.11443827

Levels not connected by same letter are significantly different.

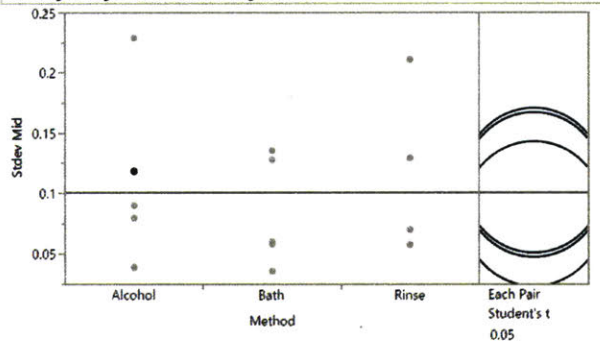
Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
Alcohol	Bath	0.0880081	0.0661907	-0.056209	0.2322252	0.2084
Alcohol	Rinse	0.0629073	0.0661907	-0.081310	0.2071244	0.3607
Rinse	Bath	0.0251008	0.0661907	-0.119116	0.1693179	0.7111



Fit Group

Oneway Analysis of Stdev Mid By Method



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.17881	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	Alcohol	Rinse	Bath
Alcohol	-0.08465	-0.08105	-0.05690
Rinse	-0.08105	-0.08465	-0.06050
Bath	-0.05690	-0.06050	-0.08465

Positive values show pairs of means that are significantly different.

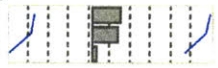
Connecting Letters Report

Level		Mean
Alcohol	A	0.11126526
Rinse	A	0.10766561
Bath	A	0.08351877

Levels not connected by same letter are significantly different.

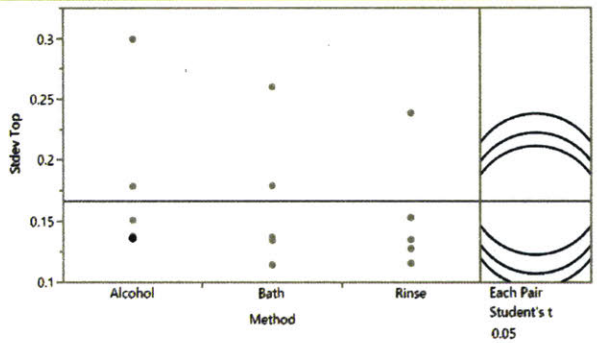
Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
Alcohol	Bath	0.0277465	0.0388498	-0.056900	0.1123929	0.4888
Rinse	Bath	0.0241468	0.0388498	-0.060500	0.1087933	0.5459
Alcohol	Rinse	0.0035997	0.0388498	-0.081047	0.0882461	0.9277



Fit Group

Oneway Analysis of Stdev Top By Method



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.17881	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	Alcohol	Bath	Rinse
Alcohol	-0.08166	-0.06602	-0.05506
Bath	-0.06602	-0.08166	-0.07070
Rinse	-0.05506	-0.07070	-0.08166

Positive values show pairs of means that are significantly different.

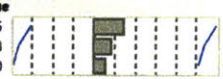
Connecting Letters Report

Level		Mean
Alcohol	A	0.18060456
Bath	A	0.16496367
Rinse	A	0.15400677

Levels not connected by same letter are significantly different.

Ordered Differences Report

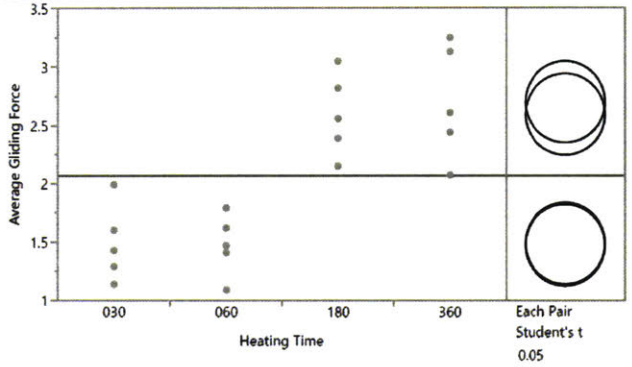
Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
Alcohol	Rinse	0.0265978	0.0374793	-0.055063	0.1082583	0.4915
Alcohol	Bath	0.0156409	0.0374793	-0.066020	0.0973014	0.6838
Bath	Rinse	0.0109569	0.0374793	-0.070704	0.0926174	0.7750



Appendix E: Heating Time Statistical Analysis

Fit Group

Oneway Analysis of Average Gliding Force By Heating Time



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.11991	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	360	180	030	060
360	-0.49260	-0.38660	0.71740	0.73140
180	-0.38660	-0.49260	0.61140	0.62540
030	0.71740	0.61140	-0.49260	-0.47860
060	0.73140	0.62540	-0.47860	-0.49260

Positive values show pairs of means that are significantly different.

Connecting Letters Report

Level		Mean
360	A	2.7000000
180	A	2.5940000
030	B	1.4900000
060	B	1.4760000

Levels not connected by same letter are significantly different.

Fit Group

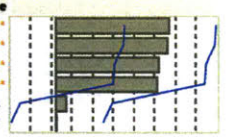
Oneway Analysis of Average Gliding Force By Heating Time

Means Comparisons

Comparisons for each pair using Student's t

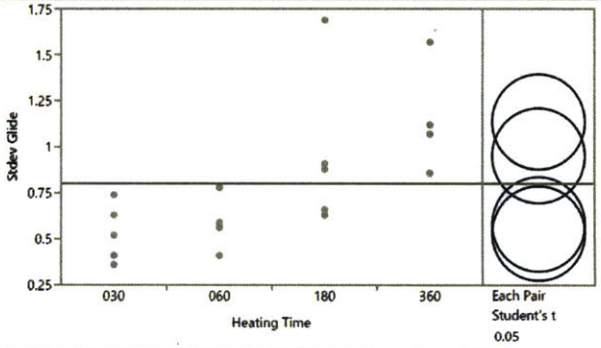
Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
360	060	1.224000	0.2323704	0.731397	1.716603	<.0001*
360	030	1.210000	0.2323704	0.717397	1.702603	<.0001*
180	060	1.118000	0.2323704	0.625397	1.610603	0.0002*
180	030	1.104000	0.2323704	0.611397	1.596603	0.0002*
360	180	0.106000	0.2323704	-0.386603	0.598603	0.6544
030	060	0.014000	0.2323704	-0.478603	0.506603	0.9527



Missing Rows 20

Oneway Analysis of Stdev Glide By Heating Time



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.11991	0.05

Fit Group

Oneway Analysis of Stdev Glide By Heating Time

Means Comparisons

Comparisons for each pair using Student's t

LSD Threshold Matrix

Abs(Dif)-LSD

	360	180	060	030
360	-0.36425	-0.18025	0.19175	0.24175
180	-0.18025	-0.36425	0.00775	0.05775
060	0.19175	0.00775	-0.36425	-0.31425
030	0.24175	0.05775	-0.31425	-0.36425

Positive values show pairs of means that are significantly different.

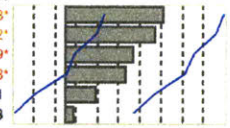
Connecting Letters Report

Level		Mean
360	A	1.1380000
180	A	0.9540000
060	B	0.5820000
030	B	0.5320000

Levels not connected by same letter are significantly different.

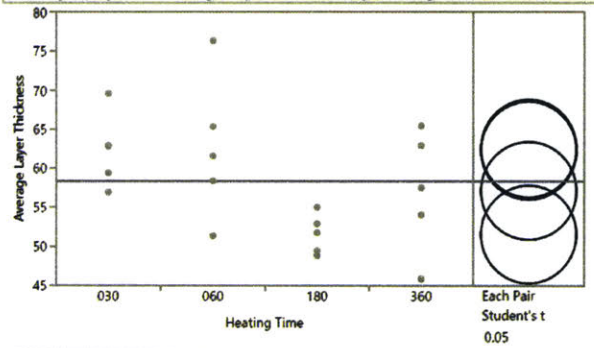
Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
360	030	0.6060000	0.1718255	0.241746	0.9702538	0.0028*
360	060	0.5560000	0.1718255	0.191746	0.9202538	0.0052*
180	030	0.4220000	0.1718255	0.057746	0.7862538	0.0259*
180	060	0.3720000	0.1718255	0.007746	0.7362538	0.0458*
360	180	0.1840000	0.1718255	-0.180254	0.5482538	0.3001
060	030	0.0500000	0.1718255	-0.314254	0.4142538	0.7748



Fit Group

Oneway Analysis of Average Layer Thickness By Heating Time



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.11991	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	060	030	360	180
060	-8.8670	-8.6016	-3.4240	2.1583
030	-8.6016	-8.8670	-3.6894	1.8929
360	-3.4240	-3.6894	-8.8670	-3.2847
180	2.1583	1.8929	-3.2847	-8.8670

Positive values show pairs of means that are significantly different.

Connecting Letters Report

Level		Mean
060	A	62.607458
030	A	62.342059
360	A B	57.164486
180	B	51.582187

Levels not connected by same letter are significantly different.

Fit Group

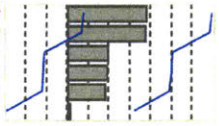
Oneway Analysis of Average Layer Thickness By Heating Time

Means Comparisons

Comparisons for each pair using Student's t

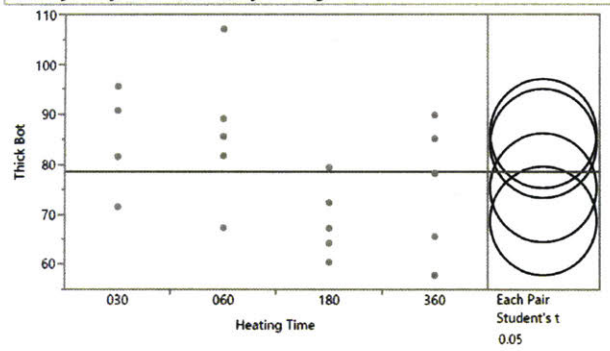
Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
060	180	11.02527	4.182742	2.15825	19.89229	0.0180*
030	180	10.75987	4.182742	1.89286	19.62689	0.0205*
360	180	5.58230	4.182742	-3.28472	14.44931	0.2007
060	360	5.44297	4.182742	-3.42404	14.30999	0.2116
030	360	5.17757	4.182742	-3.68944	14.04459	0.2336
060	030	0.26540	4.182742	-8.60162	9.13242	0.9502



Missing Rows 20

Oneway Analysis of Thick Bot By Heating Time



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.11991	0.05

Fit Group

Oneway Analysis of Thick Bot By Heating Time

Means Comparisons

Comparisons for each pair using Student's t

LSD Threshold Matrix

Abs(Dif)-LSD

	060	030	360	180
060	-15.422	-13.432	-4.550	2.063
030	-13.432	-15.422	-6.540	0.073
360	-4.550	-6.540	-15.422	-8.809
180	2.063	0.073	-8.809	-15.422

Positive values show pairs of means that are significantly different.

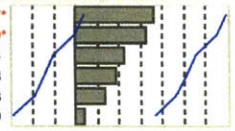
Connecting Letters Report

Level		Mean
060	A	86.206642
030	A	84.216552
360	A B	75.334366
180	B	68.721631

Levels not connected by same letter are significantly different.

Ordered Differences Report

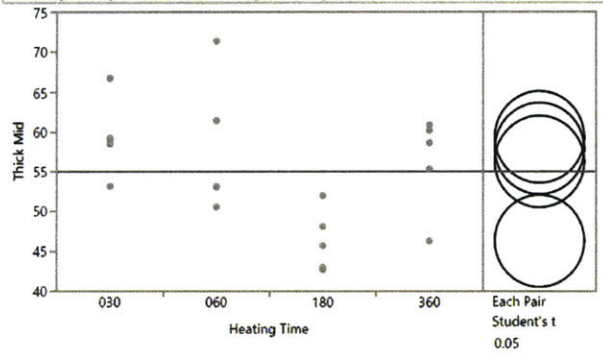
Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
060	180	17.48501	7.274798	2.0631	32.90689	0.0287*
030	180	15.49492	7.274798	0.0730	30.91680	0.0490*
060	360	10.87228	7.274798	-4.5496	26.29416	0.1545
030	360	8.88219	7.274798	-6.5397	24.30407	0.2398
360	180	6.61274	7.274798	-8.8091	22.03462	0.3768
060	030	1.99009	7.274798	-13.4318	17.41197	0.7879



Missing Rows 20

Fit Group

Oneway Analysis of Thick Mid By Heating Time



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.11991	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	030	060	360	180
030	-8.1619	-6.7155	-5.0758	4.9162
060	-6.7155	-8.1619	-6.5222	3.4698
360	-5.0758	-6.5222	-8.1619	1.8302
180	4.9162	3.4698	1.8302	-8.1619

Positive values show pairs of means that are significantly different.

Connecting Letters Report

Level		Mean
030	A	59.376688
060	A	57.930278
360	A	56.290609
180	B	46.298528

Levels not connected by same letter are significantly different.

Fit Group

Oneway Analysis of Thick Mid By Heating Time

Means Comparisons

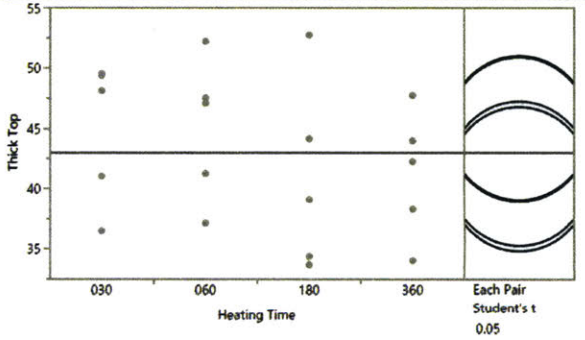
Comparisons for each pair using Student's t

Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
030	180	13.07816	3.850131	4.91625	21.24007	0.0037*
060	180	11.63175	3.850131	3.46984	19.79366	0.0081*
360	180	9.99208	3.850131	1.83017	18.15399	0.0195*
030	360	3.08608	3.850131	-5.07583	11.24799	0.4346
060	360	1.63967	3.850131	-6.52224	9.80158	0.6759
030	060	1.44641	3.850131	-6.71550	9.60832	0.7121

Missing Rows 20

Oneway Analysis of Thick Top By Heating Time



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.11991	0.05

Fit Group

Oneway Analysis of Thick Top By Heating Time

Means Comparisons

Comparisons for each pair using Student's t

LSD Threshold Matrix

Abs(Dif)-LSD

	060	030	360	180
060	-8.4703	-8.3508	-4.6889	-4.2315
030	-8.3508	-8.4703	-4.8084	-4.3510
360	-4.6889	-4.8084	-8.4703	-8.0129
180	-4.2315	-4.3510	-8.0129	-8.4703

Positive values show pairs of means that are significantly different.

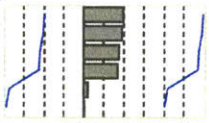
Connecting Letters Report

Level		Mean
060	A	45.048209
030	A	44.928688
360	A	41.266803
180	A	40.809408

Levels not connected by same letter are significantly different.

Ordered Differences Report

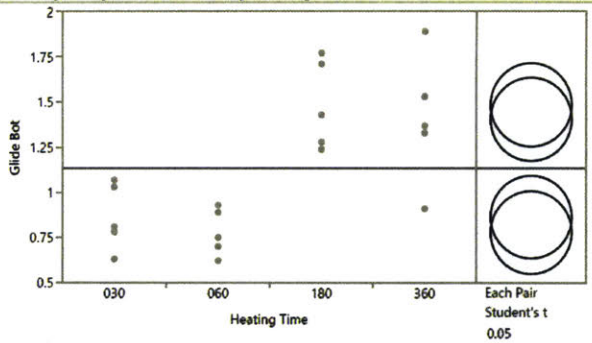
Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
060	180	4.238801	3.995603	-4.23150	12.70910	0.3045
030	180	4.119279	3.995603	-4.35102	12.58958	0.3179
060	360	3.781406	3.995603	-4.68889	12.25171	0.3580
030	360	3.661885	3.995603	-4.80841	12.13218	0.3730
360	180	0.457395	3.995603	-8.01290	8.92769	0.9103
060	030	0.119521	3.995603	-8.35078	8.58982	0.9765



Missing Rows 20

Fit Group

Oneway Analysis of Glide Bot By Heating Time



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.11991	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	180	360	030	060
180	-0.32529	-0.24529	0.29671	0.38271
360	-0.24529	-0.32529	0.21671	0.30271
030	0.29671	0.21671	-0.32529	-0.23929
060	0.38271	0.30271	-0.23929	-0.32529

Positive values show pairs of means that are significantly different.

Connecting Letters Report

Level		Mean
180	A	1.4860000
360	A	1.4060000
030	B	0.8640000
060	B	0.7780000

Levels not connected by same letter are significantly different.

Fit Group

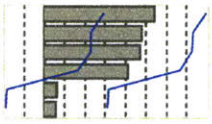
Oneway Analysis of Glide Bot By Heating Time

Means Comparisons

Comparisons for each pair using Student's t

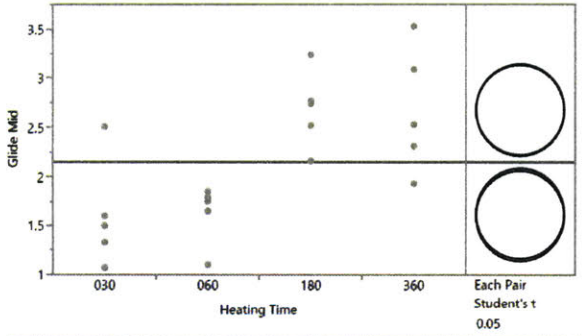
Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
180	060	0.7080000	0.1534471	0.382707	1.033293	0.0003*
360	060	0.6280000	0.1534471	0.302707	0.953293	0.0008*
180	030	0.6220000	0.1534471	0.296707	0.947293	0.0009*
360	030	0.5420000	0.1534471	0.216707	0.867293	0.0028*
030	060	0.0860000	0.1534471	-0.239293	0.411293	0.5829
180	360	0.0800000	0.1534471	-0.245293	0.405293	0.6093



Missing Rows 20

Oneway Analysis of Glide Mid By Heating Time



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.11991	0.05

Fit Group

Oneway Analysis of Glide Mid By Heating Time

Means Comparisons

Comparisons for each pair using Student's t

LSD Threshold Matrix

Abs(Dif)-LSD

	180	360	060	030
180	-0.65298	-0.64498	0.40502	0.43102
360	-0.64498	-0.65298	0.39702	0.42302
060	0.40502	0.39702	-0.65298	-0.62698
030	0.43102	0.42302	-0.62698	-0.65298

Positive values show pairs of means that are significantly different.

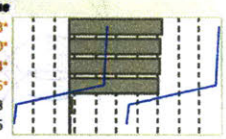
Connecting Letters Report

Level		Mean
180	A	2.6860000
360	A	2.6780000
060	B	1.6280000
030	B	1.6020000

Levels not connected by same letter are significantly different.

Ordered Differences Report

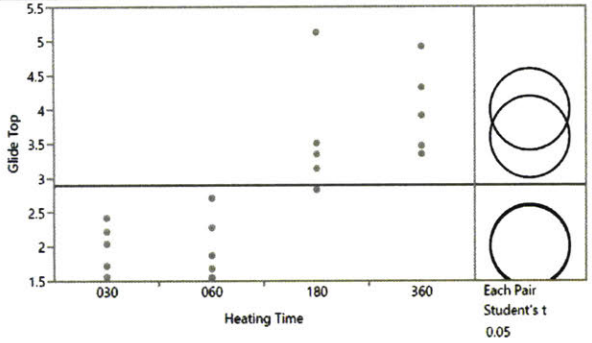
Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
180	030	1.084000	0.3080243	0.431018	1.736982	0.0028*
360	030	1.076000	0.3080243	0.423018	1.728982	0.0030*
180	060	1.058000	0.3080243	0.405018	1.710982	0.0034*
360	060	1.050000	0.3080243	0.397018	1.702982	0.0036*
060	030	0.026000	0.3080243	-0.626982	0.678982	0.9338
180	360	0.008000	0.3080243	-0.644982	0.660982	0.9796



Missing Rows 20

Fit Group

Oneway Analysis of Glide Top By Heating Time



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.11991	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	360	180	060	030
360	-0.8397	-0.4377	1.1363	1.1623
180	-0.4377	-0.8397	0.7343	0.7603
060	1.1363	0.7343	-0.8397	-0.8137
030	1.1623	0.7603	-0.8137	-0.8397

Positive values show pairs of means that are significantly different.

Connecting Letters Report

Level		Mean
360	A	3.9940000
180	A	3.5920000
060	B	2.0180000
030	B	1.9920000

Levels not connected by same letter are significantly different.

Fit Group

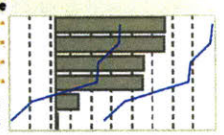
Oneway Analysis of Glide Top By Heating Time

Means Comparisons

Comparisons for each pair using Student's t

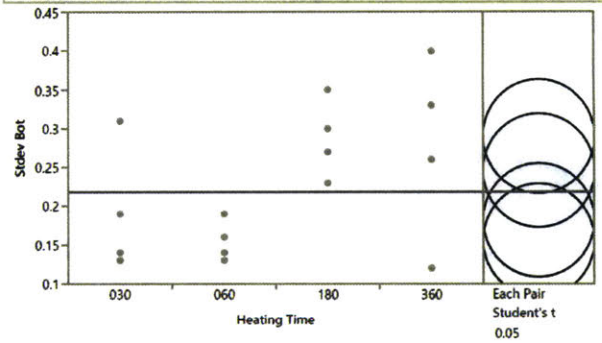
Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
360	030	2.002000	0.3961237	1.16226	2.841745	0.0001*
360	060	1.976000	0.3961237	1.13626	2.815745	0.0001*
180	030	1.600000	0.3961237	0.76026	2.439745	0.0010*
180	060	1.574000	0.3961237	0.73426	2.413745	0.0011*
360	180	0.402000	0.3961237	-0.43774	1.241745	0.3253
060	030	0.026000	0.3961237	-0.81374	0.865745	0.9485



Missing Rows 20

Oneway Analysis of Stdev Bot By Heating Time



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.11991	0.05

Fit Group

Oneway Analysis of Stdev Bot By Heating Time

Means Comparisons

Comparisons for each pair using Student's t

LSD Threshold Matrix

Abs(Dif)-LSD

	180	360	030	060
180	-0.10349	-0.05949	0.00451	0.03051
360	-0.05949	-0.10349	-0.03949	-0.01349
030	0.00451	-0.03949	-0.10349	-0.07749
060	0.03051	-0.01349	-0.07749	-0.10349

Positive values show pairs of means that are significantly different.

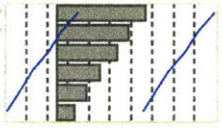
Connecting Letters Report

Level		Mean
180	A	0.29000000
360	A B	0.24600000
030	B	0.18200000
060	B	0.15600000

Levels not connected by same letter are significantly different.

Ordered Differences Report

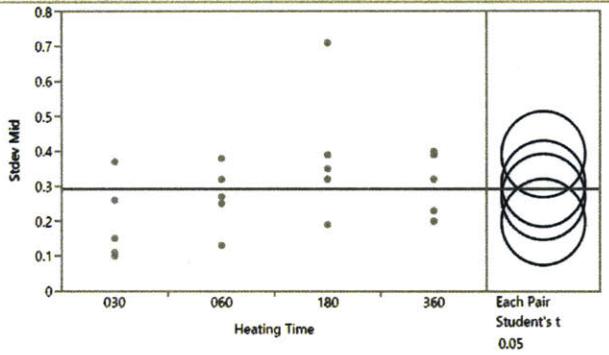
Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
180	060	0.1340000	0.0488160	0.030515	0.2374853	0.0144*
180	030	0.1080000	0.0488160	0.004515	0.2114853	0.0418*
360	060	0.0900000	0.0488160	-0.013485	0.1934853	0.0838
360	030	0.0640000	0.0488160	-0.039485	0.1674853	0.2083
180	360	0.0440000	0.0488160	-0.059485	0.1474853	0.3808
030	060	0.0260000	0.0488160	-0.077485	0.1294853	0.6016



Missing Rows 20

Fit Group

Oneway Analysis of Stdev Mid By Heating Time



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.11991	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	180	360	060	030
180	-0.17405	-0.09005	-0.05205	0.01995
360	-0.09005	-0.17405	-0.13605	-0.06405
060	-0.05205	-0.13605	-0.17405	-0.10205
030	0.01995	-0.06405	-0.10205	-0.17405

Positive values show pairs of means that are significantly different.

Connecting Letters Report

Level		Mean
180	A	0.39200000
360	A B	0.30800000
060	A B	0.27000000
030	B	0.19800000

Levels not connected by same letter are significantly different.

Fit Group

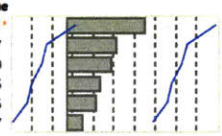
Oneway Analysis of Stdev Mid By Heating Time

Means Comparisons

Comparisons for each pair using Student's t

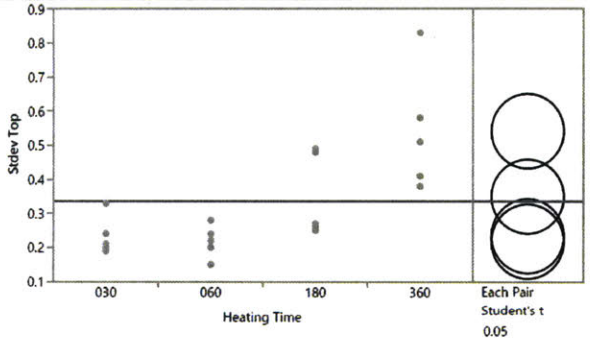
Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
180	030	0.1940000	0.0821036	0.019948	0.3680518	0.0311*
180	060	0.1220000	0.0821036	-0.052052	0.2960518	0.1567
360	030	0.1100000	0.0821036	-0.064052	0.2840518	0.1990
180	360	0.0840000	0.0821036	-0.090052	0.2580518	0.3215
060	030	0.0720000	0.0821036	-0.102052	0.2460518	0.3935
360	060	0.0380000	0.0821036	-0.136052	0.2120518	0.6497



Missing Rows 20

Oneway Analysis of Stdev Top By Heating Time



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.11991	0.05

Fit Group

Oneway Analysis of Stdev Top By Heating Time

Means Comparisons

Comparisons for each pair using Student's t

LSD Threshold Matrix

Abs(Dif)-LSD

	360	180	030	060
360	-0.15443	0.03757	0.15357	0.16957
180	0.03757	-0.15443	-0.03843	-0.02243
030	0.15357	-0.03843	-0.15443	-0.13843
060	0.16957	-0.02243	-0.13843	-0.15443

Positive values show pairs of means that are significantly different.

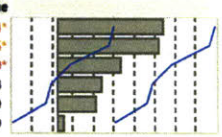
Connecting Letters Report

Level		Mean
360	A	0.54200000
180	B	0.35000000
030	B	0.23400000
060	B	0.21800000

Levels not connected by same letter are significantly different.

Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
360	060	0.3240000	0.0728492	0.169567	0.4784333	0.0004*
360	030	0.3080000	0.0728492	0.153567	0.4624333	0.0006*
360	180	0.1920000	0.0728492	0.037567	0.3464333	0.0180*
180	060	0.1320000	0.0728492	-0.022433	0.2864333	0.0888
180	030	0.1160000	0.0728492	-0.038433	0.2704333	0.1309
030	060	0.0160000	0.0728492	-0.138433	0.1704333	0.8289

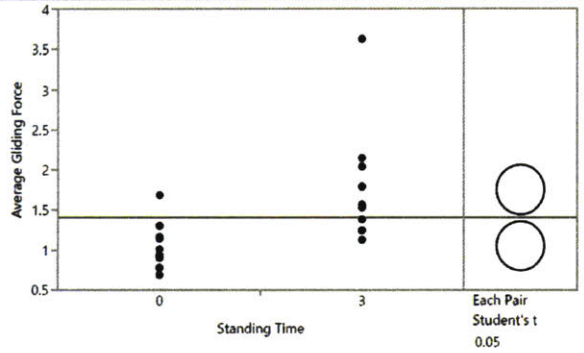


Missing Rows 20

Appendix F: Standing Time Statistical Analysis

Fit Group

Oneway Analysis of Average Gliding Force By Standing Time

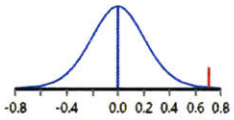


t Test

3-0

Assuming unequal variances

Difference	0.70500	t Ratio	3.351141
Std Err Dif	0.21038	DF	14.86762
Upper CL Dif	1.15375	Prob > |t|	0.0044*
Lower CL Dif	0.25625	Prob > t	0.0022*
Confidence	0.95	Prob < t	0.9978



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.07387	0.05

LSD Threshold Matrix

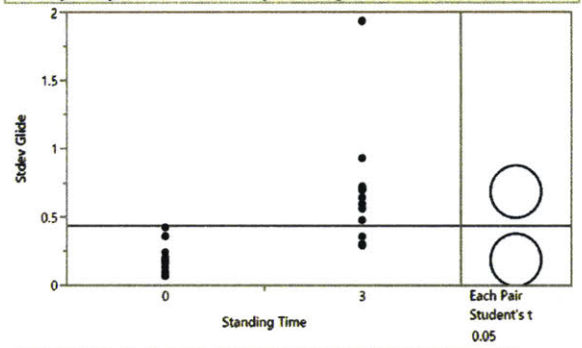
Abs(Dif)-LSD

	3	0
3	-0.43629	0.26871
0	0.26871	-0.43629

Positive values show pairs of means that are significantly different.

Fit Group

Oneway Analysis of Stdev Glide By Standing Time

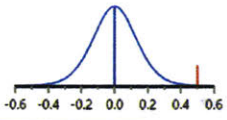


t Test

3-0

Assuming unequal variances

Difference	0.500489	t Ratio	3.837735
Std Err Dif	0.130413	DF	12.41898
Upper CL Dif	0.783574	Prob > |t|	0.0022*
Lower CL Dif	0.217404	Prob > t	0.0011*
Confidence	0.95	Prob < t	0.9989



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.07387	0.05

LSD Threshold Matrix

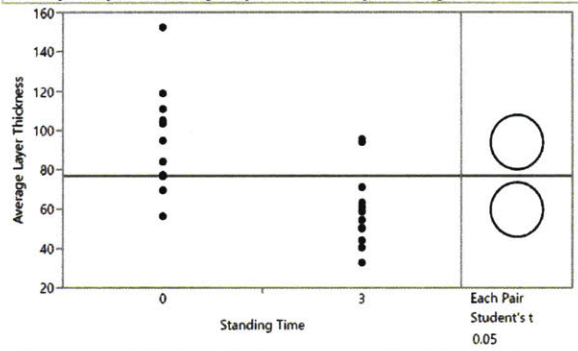
Abs(Dif)-LSD

	3	0
3	-0.27046	0.23003
0	0.23003	-0.27046

Positive values show pairs of means that are significantly different.

Fit Group

Oneway Analysis of Average Layer Thickness By Standing Time

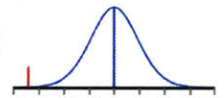


t Test

3-0

Assuming unequal variances

Difference	-34.227	t Ratio	-3.63832
Std Err Dif	9.407	DF	20.33364
Upper CL Dif	-14.624	Prob > |t|	0.0016*
Lower CL Dif	-53.829	Prob > t	0.9992
Confidence	0.95	Prob < t	0.0008*



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.07387	0.05

LSD Threshold Matrix

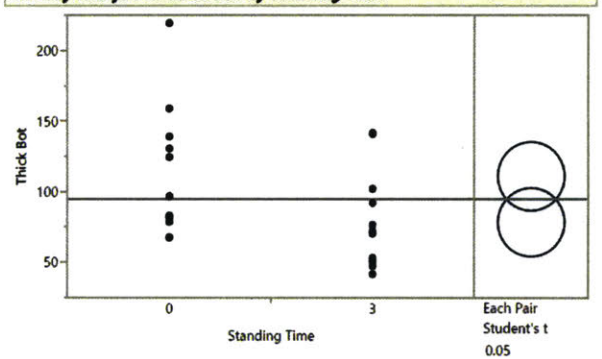
Abs(Dif)-LSD

	0	3
0	-19.509	14.717
3	14.717	-19.509

Positive values show pairs of means that are significantly different.

Fit Group

Oneway Analysis of Thick Bot By Standing Time



t Test

3-0

Assuming unequal variances

Difference	-32.644	t Ratio	-1.9714
Std Err Dif	16.559	DF	20.54804
Upper CL Dif	1.838	Prob > |t|	0.0623
Lower CL Dif	-67.127	Prob > t	0.9689
Confidence	0.95	Prob < t	0.0311*

Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.07387	0.05

LSD Threshold Matrix

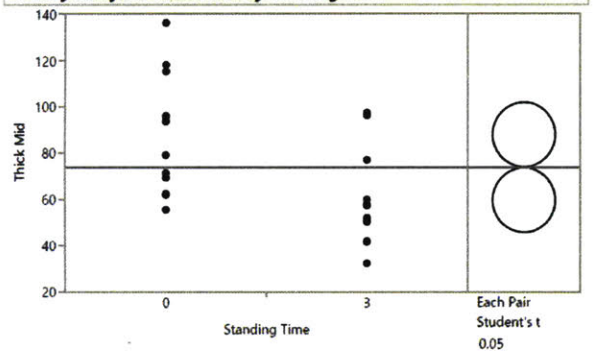
Abs(Dif)-LSD

	0	3
0	-34.341	-1.697
3	-1.697	-34.341

Positive values show pairs of means that are significantly different.

Fit Group

Oneway Analysis of Thick Mid By Standing Time

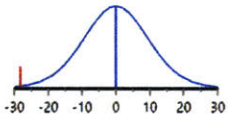


t Test

3-0

Assuming unequal variances

Difference	-28.314	t Ratio	-2.98003
Std Err Dif	9.501	DF	21.04384
Upper CL Dif	-8.558	Prob > |t|	0.0071*
Lower CL Dif	-48.071	Prob > t	0.9964
Confidence	0.95	Prob < t	0.0036*



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.07387	0.05

LSD Threshold Matrix

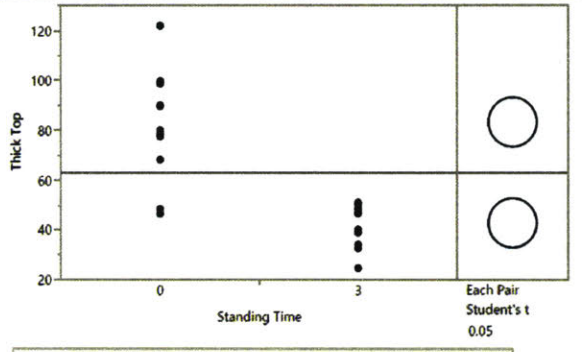
Abs(Dif)-LSD

	0	3
0	-19.705	8.610
3	8.610	-19.705

Positive values show pairs of means that are significantly different.

Fit Group

Oneway Analysis of Thick Top By Standing Time

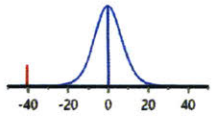


t Test

3-0

Assuming unequal variances

Difference	-40.515	t Ratio	-5.98651
Std Err Dif	6.768	DF	14.33716
Upper CL Dif	-26.032	Prob > |t|	<.0001*
Lower CL Dif	-54.999	Prob > t	1.0000
Confidence	0.95	Prob < t	<.0001*



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.07387	0.05

LSD Threshold Matrix

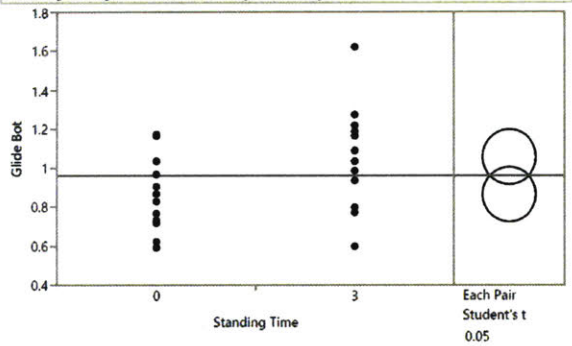
Abs(Dif)-LSD

	0	3
0	-14.035	26.480
3	26.480	-14.035

Positive values show pairs of means that are significantly different.

Fit Group

Oneway Analysis of Glide Bot By Standing Time

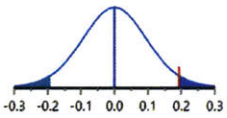


t Test

3-0

Assuming unequal variances

Difference	0.19258	t Ratio	2.010106
Std Err Dif	0.09581	DF	19.9348
Upper CL Dif	0.39247	Prob > |t|	0.0581
Lower CL Dif	-0.00731	Prob > t	0.0291*
Confidence	0.95	Prob < t	0.9709



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.07387	0.05

LSD Threshold Matrix

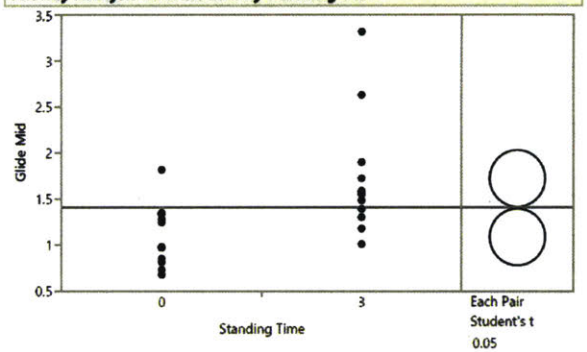
Abs(Dif)-LSD

	3	0
3	-0.19869	-0.00611
0	-0.00611	-0.19869

Positive values show pairs of means that are significantly different.

Fit Group

Oneway Analysis of Glide Mid By Standing Time

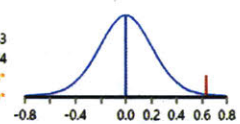


t Test

3-0

Assuming unequal variances

Difference	0.63672	t Ratio	3.02983
Std Err Dif	0.21015	DF	16.30474
Upper CL Dif	1.08155	Prob > |t|	0.0078*
Lower CL Dif	0.19190	Prob > t	0.0039*
Confidence	0.95	Prob < t	0.9961



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.07387	0.05

LSD Threshold Matrix

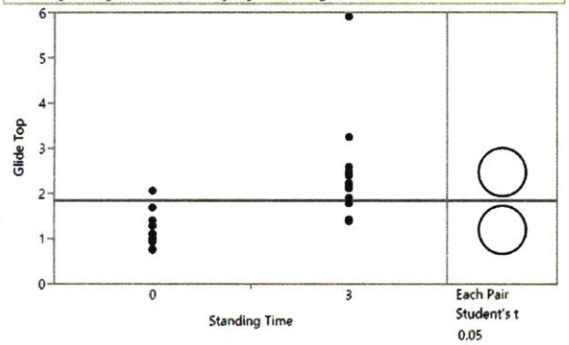
Abs(Dif)-LSD

	3	0
3	-0.43583	0.20090
0	0.20090	-0.43583

Positive values show pairs of means that are significantly different.

Fit Group

Oneway Analysis of Glide Top By Standing Time

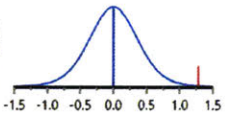


t Test

3-0

Assuming unequal variances

Difference	1.27596	t Ratio	3.514352
Std Err Dif	0.36307	DF	13.20934
Upper CL Dif	2.05906	Prob > |t|	0.0037*
Lower CL Dif	0.49285	Prob > t	0.0019*
Confidence	0.95	Prob < t	0.9981



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.07387	0.05

LSD Threshold Matrix

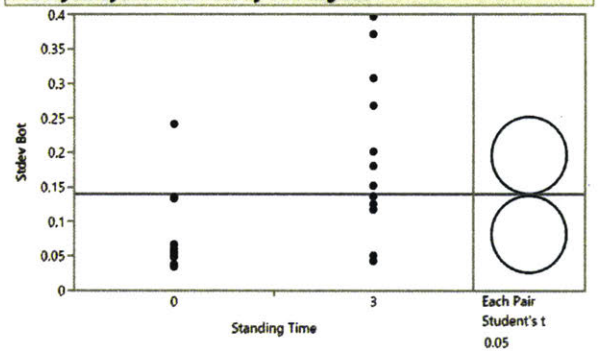
Abs(Dif)-LSD

	3	0
3	-0.75296	0.52299
0	0.52299	-0.75296

Positive values show pairs of means that are significantly different.

Fit Group

Oneway Analysis of Stdev Bot By Standing Time

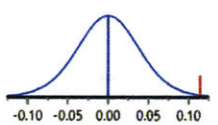


t Test

3-0

Assuming unequal variances

Difference	0.114283	t Ratio	3.010846
Std Err Dif	0.037957	DF	16.47379
Upper CL Dif	0.194562	Prob > |t|	0.0081*
Lower CL Dif	0.034005	Prob > t	0.0040*
Confidence	0.95	Prob < t	0.9960



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.07387	0.05

LSD Threshold Matrix

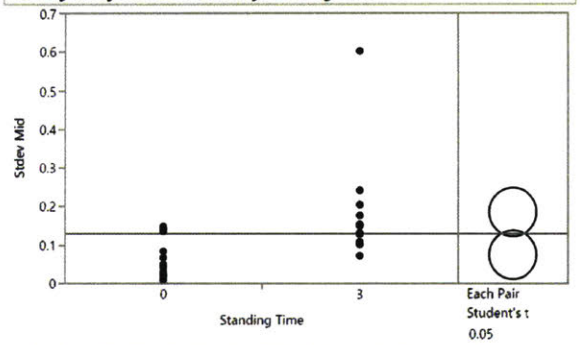
Abs(Dif)-LSD

	3	0
3	-0.07872	0.03556
0	0.03556	-0.07872

Positive values show pairs of means that are significantly different.

Fit Group

Oneway Analysis of Stdev Mid By Standing Time

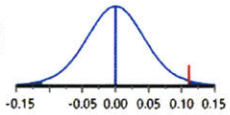


t Test

3-0

Assuming unequal variances

Difference	0.110868	t Ratio	2.573885
Std Err Dif	0.043074	DF	14.2046
Upper CL Dif	0.203128	Prob > |t|	0.0219*
Lower CL Dif	0.018608	Prob > t	0.0109*
Confidence	0.95	Prob < t	0.9891



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.07387	0.05

LSD Threshold Matrix

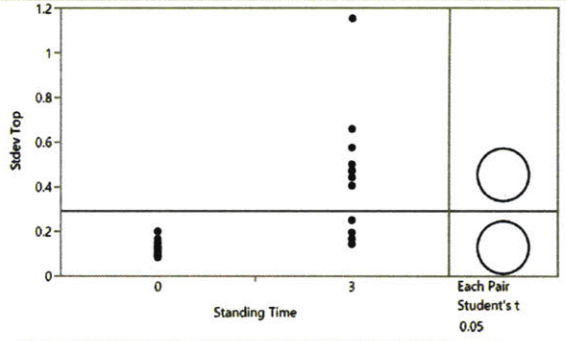
Abs(Dif)-LSD

	3	0
3	-0.08933	0.02154
0	0.02154	-0.08933

Positive values show pairs of means that are significantly different.

Fit Group

Oneway Analysis of Stdev Top By Standing Time

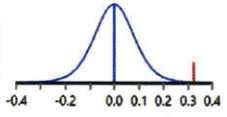


t Test

3-0

Assuming unequal variances

Difference	0.325195	t Ratio	4.049438
Std Err Dif	0.080306	DF	11.33084
Upper CL Dif	0.501320	Prob > |t|	0.0018*
Lower CL Dif	0.149070	Prob > t	0.0009*
Confidence	0.95	Prob < t	0.9991



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.07387	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

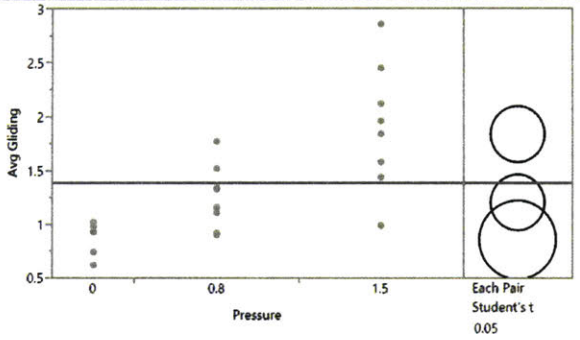
	3	0
3	-0.16654	0.15865
0	0.15865	-0.16654

Positive values show pairs of means that are significantly different.

Appendix G: Air Pressure Statistical Analysis

Fit Group

Oneway Analysis of Avg Gliding By Pressure



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.07387	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	1.5	0.8	0
1.5	-0.36680	0.26620	0.53276
0.8	0.26620	-0.36680	-0.10024
0	0.53276	-0.10024	-0.51874

Positive values show pairs of means that are significantly different.

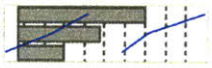
Connecting Letters Report

Level		Mean
1.5	A	1.8400000
0.8	B	1.2070000
0	B	0.8580000

Levels not connected by same letter are significantly different.

Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
1.5	0	0.9820000	0.2166194	0.532759	1.431241	0.0002*
1.5	0.8	0.6330000	0.1768690	0.266196	0.999804	0.0017*
0.8	0	0.3490000	0.2166194	-0.100241	0.798241	0.1214



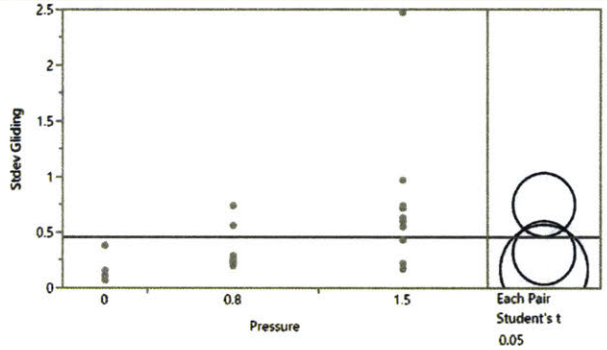
Fit Group

Oneway Analysis of Avg Gliding By Pressure

Missing Rows 1

Excluded Rows 10

Oneway Analysis of Stdev Gliding By Pressure



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.07387	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	1.5	0.8	0
1.5	-0.40349	0.02851	0.08983
0.8	0.02851	-0.40349	-0.34217
0	0.08983	-0.34217	-0.57062

Positive values show pairs of means that are significantly different.

Connecting Letters Report

Level		Mean
1.5	A	0.75000000
0.8	B	0.31800000
0	B	0.16600000

Levels not connected by same letter are significantly different.

Fit Group

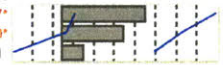
Oneway Analysis of Stdev Gliding By Pressure

Means Comparisons

Comparisons for each pair using Student's t

Ordered Differences Report

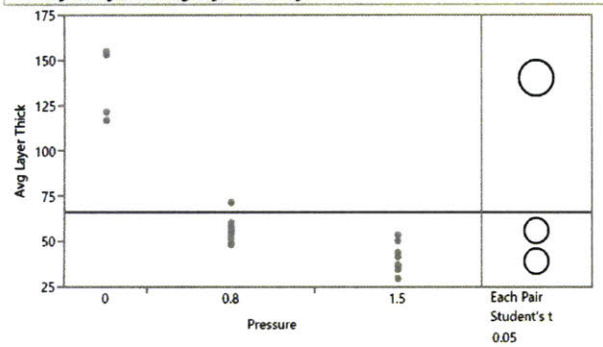
Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
1.5	0	0.5840000	0.2382859	0.089825	1.078175	0.0227*
1.5	0.8	0.4320000	0.1945596	0.028508	0.835492	0.0370*
0.8	0	0.1520000	0.2382859	-0.342175	0.646175	0.5301



Missing Rows 1

Excluded Rows 10

Oneway Analysis of Avg Layer Thick By Pressure



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.07387	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	0	0.8	1.5
0	-13.923	72.112	88.934
0.8	72.112	-9.845	6.977
1.5	88.934	6.977	-9.845

Positive values show pairs of means that are significantly different.

Fit Group

Oneway Analysis of Avg Layer Thick By Pressure

Means Comparisons

Comparisons for each pair using Student's t

Connecting Letters Report

Level		Mean
0	A	140.30003
0.8	B	56.13044
1.5	C	39.30847

Levels not connected by same letter are significantly different.

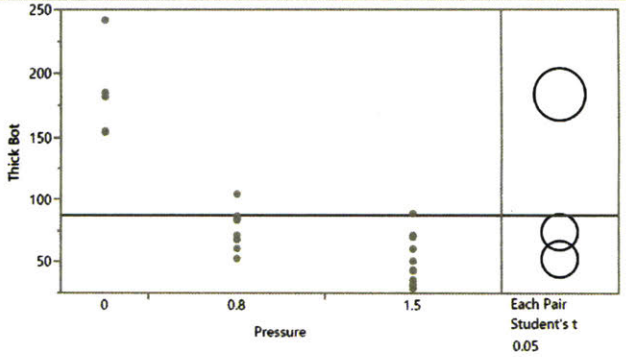
Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
0	1.5	100.9916	5.814149	88.93375	113.0494	<.0001*
0	0.8	84.1696	5.814149	72.11179	96.2274	<.0001*
0.8	1.5	16.8220	4.747233	6.97680	26.6671	0.0018*

Missing Rows 1

Excluded Rows 10

Oneway Analysis of Thick Bot By Pressure



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.07387	0.05

Fit Group

Oneway Analysis of Thick Bot By Pressure

Means Comparisons

Comparisons for each pair using Student's t

LSD Threshold Matrix

Abs(Dif)-LSD

	0	0.8	1.5
0	-28.95	84.40	105.93
0.8	84.40	-20.47	1.05
1.5	105.93	1.05	-20.47

Positive values show pairs of means that are significantly different.

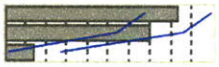
Connecting Letters Report

Level		Mean
0	A	183.46238
0.8	B	73.98854
1.5	C	52.46656

Levels not connected by same letter are significantly different.

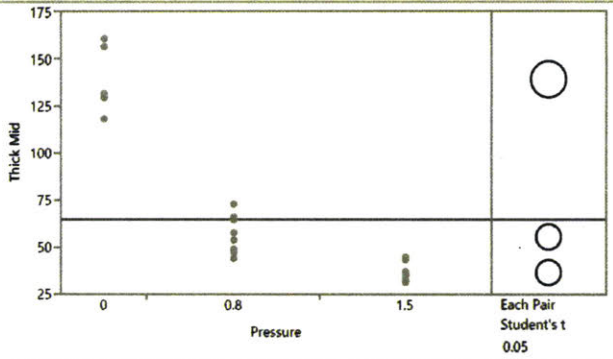
Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
0	1.5	130.9958	12.08828	105.9263	156.0654	<.0001*
0	0.8	109.4738	12.08828	84.4043	134.5434	<.0001*
0.8	1.5	21.5220	9.87004	1.0528	41.9912	0.0402*



Fit Group

Oneway Analysis of Thick Mid By Pressure



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.07387	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	0	0.8	1.5
0	-13.519	72.049	91.046
0.8	72.049	-9.559	9.437
1.5	91.046	9.437	-9.559

Positive values show pairs of means that are significantly different.

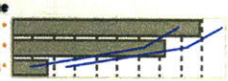
Connecting Letters Report

Level		Mean
0	A	139.30799
0.8	B	55.55121
1.5	C	36.55500

Levels not connected by same letter are significantly different.

Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
0	1.5	102.7530	5.645186	91.04559	114.4604	<.0001*
0	0.8	83.7568	5.645186	72.04938	95.4642	<.0001*
0.8	1.5	18.9962	4.609275	9.43716	28.5553	0.0004*



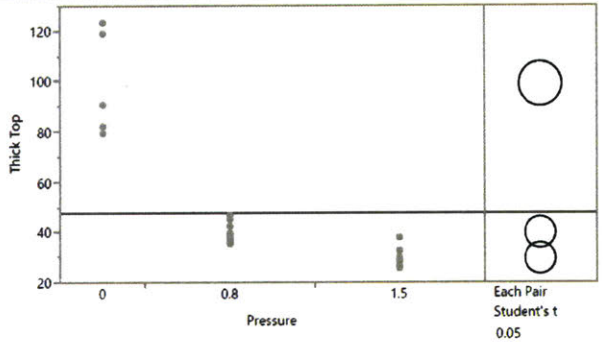
Fit Group

Oneway Analysis of Thick Mid By Pressure

Missing Rows 1

Excluded Rows 10

Oneway Analysis of Thick Top By Pressure



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.07387	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	0	0.8	1.5
0	-12.444	48.207	58.545
0.8	48.207	-8.799	1.539
1.5	58.545	1.539	-8.799

Positive values show pairs of means that are significantly different.

Connecting Letters Report

Level		Mean
0	A	98.864811
0.8	B	39.880944
1.5	C	29.543231

Levels not connected by same letter are significantly different.

Fit Group

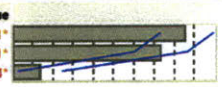
Oneway Analysis of Thick Top By Pressure

Means Comparisons

Comparisons for each pair using Student's t

Ordered Differences Report

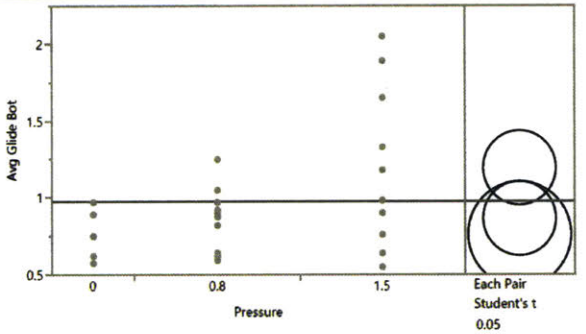
Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
0	1.5	69.32158	5.196325	58.54506	80.09810	<.0001*
0	0.8	58.98387	5.196325	48.20735	69.76039	<.0001*
0.8	1.5	10.33771	4.242782	1.53872	19.13670	0.0234*



Missing Rows 1

Excluded Rows 10

Oneway Analysis of Avg Glide Bot By Pressure



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.07387	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	1.5	0.8	0
1.5	-0.34175	-0.01244	0.01362
0.8	-0.01244	-0.34175	-0.31570
0	0.01362	-0.31570	-0.48331

Positive values show pairs of means that are significantly different.

Fit Group

Oneway Analysis of Avg Glide Bot By Pressure

Means Comparisons

Comparisons for each pair using Student's t

Connecting Letters Report

Level		Mean
1.5	A	1.1930724
0.8	A B	0.8637571
0	B	0.7608986

Levels not connected by same letter are significantly different.

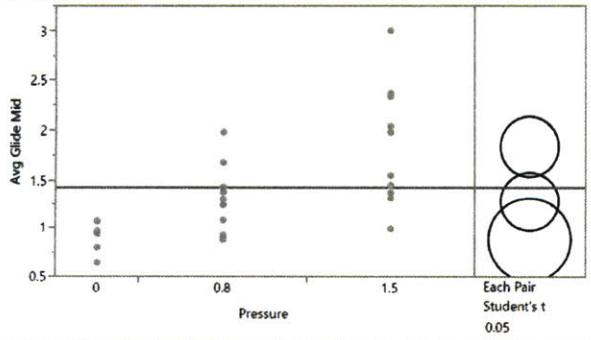
Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
1.5	0	0.4321738	0.2018238	0.013617	0.8507308	0.0436*
1.5	0.8	0.3293153	0.1647885	-0.012435	0.6710657	0.0582
0.8	0	0.1028584	0.2018238	-0.315699	0.5214155	0.6154

Missing Rows 1

Excluded Rows 10

Oneway Analysis of Avg Glide Mid By Pressure



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.07387	0.05

Fit Group

Oneway Analysis of Avg Glide Mid By Pressure

Means Comparisons

Comparisons for each pair using Student's t

LSD Threshold Matrix

Abs(Dif)-LSD

	1.5	0.8	0
1.5	-0.42643	0.13438	0.43332
0.8	0.13438	-0.42643	-0.12749
0	0.43332	-0.12749	-0.60306

Positive values show pairs of means that are significantly different.

Connecting Letters Report

Level		Mean
1.5	A	1.8404385
0.8	B	1.2796255
0	B	0.8848525

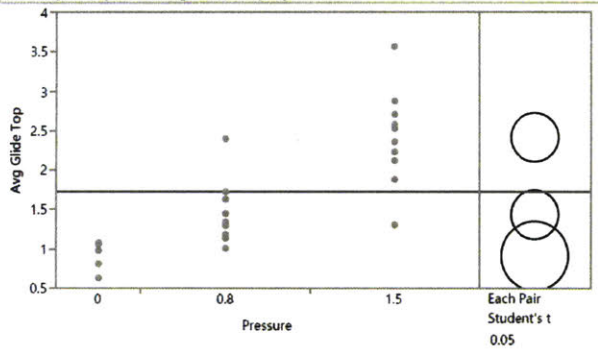
Levels not connected by same letter are significantly different.

Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
1.5	0	0.9555860	0.2518311	0.433320	1.477852	0.0010*
1.5	0.8	0.5608130	0.2056192	0.134385	0.987241	0.0123*
0.8	0	0.3947730	0.2518311	-0.127493	0.917039	0.1312

Fit Group

Oneway Analysis of Avg Glide Top By Pressure



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.07387	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	1.5	0.8	0
1.5	-0.43945	0.54119	0.96670
0.8	0.54119	-0.43945	-0.01394
0	0.96670	-0.01394	-0.62148

Positive values show pairs of means that are significantly different.

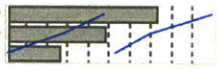
Connecting Letters Report

Level		Mean
1.5	A	2.4167498
0.8	B	1.4361103
0	B	0.9118324

Levels not connected by same letter are significantly different.

Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
1.5	0	1.504917	0.2595239	0.966698	2.043137	<.0001*
1.5	0.8	0.980639	0.2119004	0.541185	1.420094	0.0001*
0.8	0	0.524278	0.2595239	-0.013942	1.062497	0.0557



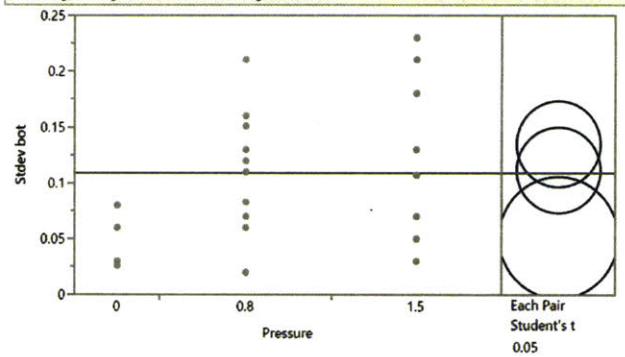
Fit Group

Oneway Analysis of Avg Glide Top By Pressure

Missing Rows 1

Excluded Rows 10

Oneway Analysis of Stdev bot By Pressure



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.07387	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	1.5	0.8	0
1.5	-0.05425	-0.03095	0.01706
0.8	-0.03095	-0.05425	-0.00624
0	0.01706	-0.00624	-0.07672

Positive values show pairs of means that are significantly different.

Connecting Letters Report

Level		Mean
1.5	A	0.13470000
0.8	A B	0.11140000
0	B	0.05120000

Levels not connected by same letter are significantly different.

Fit Group

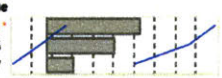
Oneway Analysis of Stdev bot By Pressure

Means Comparisons

Comparisons for each pair using Student's t

Ordered Differences Report

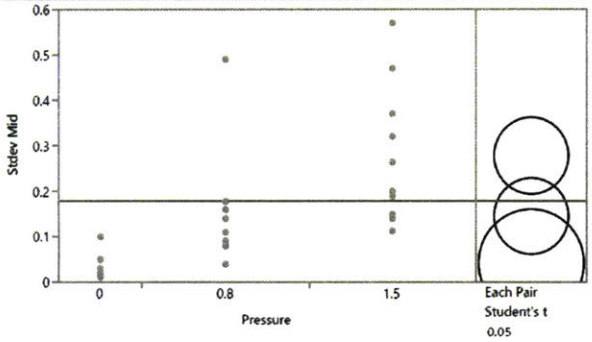
Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
1.5	0	0.0835000	0.0320370	0.017059	0.1499408	0.0161*
0.8	0	0.0602000	0.0320370	-0.006241	0.1266408	0.0735
1.5	0.8	0.0233000	0.0261581	-0.030949	0.0775487	0.3827



Missing Rows 1

Excluded Rows 10

Oneway Analysis of Stdev Mid By Pressure



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.07387	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	1.5	0.8	0
1.5	-0.11880	0.01400	0.09080
0.8	0.01400	-0.11880	-0.04200
0	0.09080	-0.04200	-0.16801

Positive values show pairs of means that are significantly different.

Fit Group

Oneway Analysis of Stdev Mid By Pressure

Means Comparisons

Comparisons for each pair using Student's t

Connecting Letters Report

Level		Mean
1.5	A	0.27870000
0.8	B	0.14590000
0	B	0.04240000

Levels not connected by same letter are significantly different.

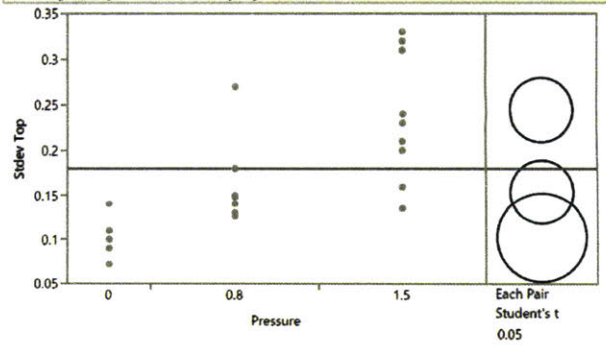
Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
1.5	0	0.2363000	0.0701602	0.090797	0.3818034	0.0028*
1.5	0.8	0.1328000	0.0572856	0.013997	0.2516030	0.0301*
0.8	0	0.1035000	0.0701602	-0.042003	0.2490034	0.1543

Missing Rows 1

Excluded Rows 10

Oneway Analysis of Stdev Top By Pressure



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.07387	0.05

Fit Group

Oneway Analysis of Stdev Top By Pressure

Means Comparisons

Comparisons for each pair using Student's t

LSD Threshold Matrix

Abs(Dif)-LSD

	1.5	0.8	0
1.5	-0.05008	0.04102	0.08077
0.8	0.04102	-0.05008	-0.01033
0	0.08077	-0.01033	-0.07082

Positive values show pairs of means that are significantly different.

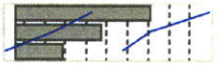
Connecting Letters Report

Level		Mean
1.5	A	0.24450000
0.8	B	0.15340000
0	B	0.10240000

Levels not connected by same letter are significantly different.

Ordered Differences Report

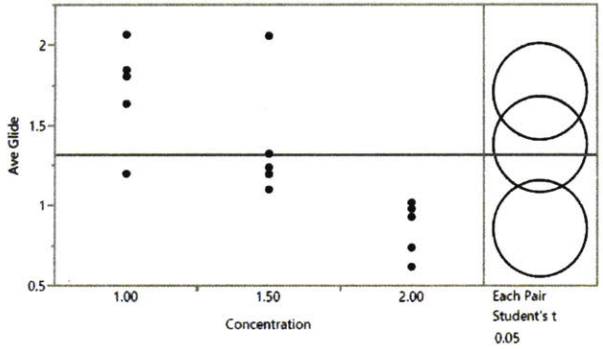
Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
1.5	0	0.1421000	0.0295747	0.080766	0.2034342	<.0001*
1.5	0.8	0.0911000	0.0241477	0.041021	0.1411792	0.0010*
0.8	0	0.0510000	0.0295747	-0.010334	0.1123342	0.0987



Appendix H: Concentration Statistical Analysis

Fit Group

Oneway Analysis of Ave Glide By Concentration



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.17881	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	1.00	1.50	2.00
1.00	-0.42431	-0.09559	0.43169
1.50	-0.09559	-0.42431	0.10297
2.00	0.43169	0.10297	-0.42431

Positive values show pairs of means that are significantly different.

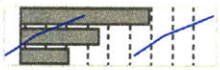
Connecting Letters Report

Level		Mean
1.00	A	1.7140000
1.50	A	1.3852781
2.00	B	0.8580000

Levels not connected by same letter are significantly different.

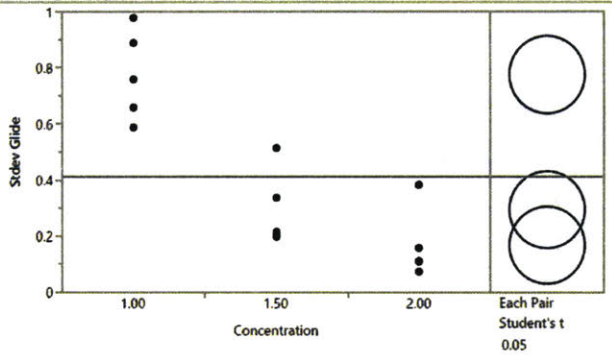
Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
1.00	2.00	0.8560000	0.1947427	0.431692	1.280308	0.0009*
1.50	2.00	0.5272781	0.1947427	0.102970	0.951586	0.0190*
1.00	1.50	0.3287219	0.1947427	-0.095586	0.753030	0.1172



Fit Group

Oneway Analysis of Stdev Glide By Concentration



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.17881	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	1.00	1.50	2.00
1.00	-0.19447	0.28648	0.41367
1.50	0.28648	-0.19447	-0.06728
2.00	0.41367	-0.06728	-0.19447

Positive values show pairs of means that are significantly different.

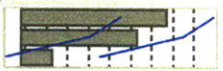
Connecting Letters Report

Level		Mean
1.00	A	0.77600000
1.50	B	0.29505271
2.00	B	0.16786113

Levels not connected by same letter are significantly different.

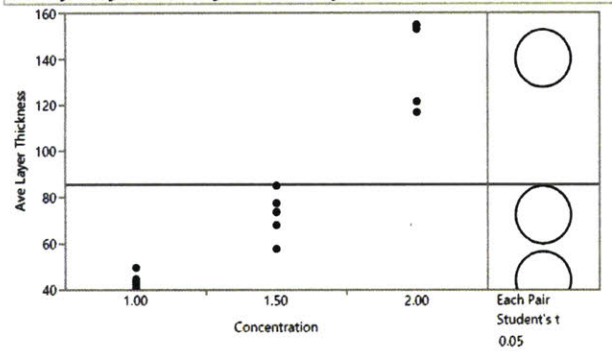
Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
1.00	2.00	0.6081389	0.0892546	0.413670	0.8026079	<.0001*
1.00	1.50	0.4809473	0.0892546	0.286478	0.6754164	0.0002*
1.50	2.00	0.1271916	0.0892546	-0.067277	0.3216606	0.1796



Fit Group

Oneway Analysis of Ave Layer Thickness By Concentration



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.17881	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	2.00	1.50	1.00
2.00	-17.531	50.224	78.525
1.50	50.224	-17.531	10.770
1.00	78.525	10.770	-17.531

Positive values show pairs of means that are significantly different.

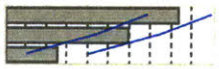
Connecting Letters Report

Level		Mean
2.00	A	140.30071
1.50	B	72.54579
1.00	C	44.24477

Levels not connected by same letter are significantly different.

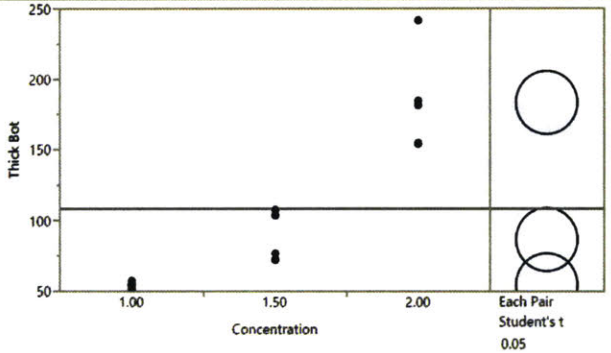
Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
2.00	1.00	96.05594	8.046307	78.52454	113.5873	<.0001*
2.00	1.50	67.75492	8.046307	50.22353	85.2863	<.0001*
1.50	1.00	28.30102	8.046307	10.76962	45.8324	0.0042*



Fit Group

Oneway Analysis of Thick Bot By Concentration



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.17881	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	2.00	1.50	1.00
2.00	-31.665	65.104	97.283
1.50	65.104	-31.665	0.514
1.00	97.283	0.514	-31.665

Positive values show pairs of means that are significantly different.

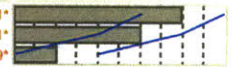
Connecting Letters Report

Level		Mean
2.00	A	183.46208
1.50	B	86.69284
1.00	C	54.51336

Levels not connected by same letter are significantly different.

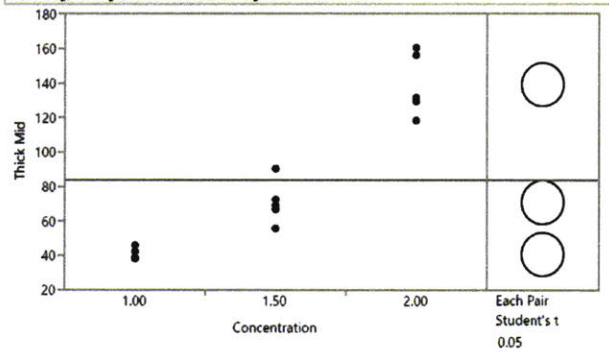
Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
2.00	1.00	128.9487	14.53328	97.28341	160.6140	<.0001*
2.00	1.50	96.7692	14.53328	65.10393	128.4345	<.0001*
1.50	1.00	32.1795	14.53328	0.51417	63.8448	0.0469*



Fit Group

Oneway Analysis of Thick Mid By Concentration



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.17881	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	2.00	1.50	1.00
2.00	-17.862	50.429	80.610
1.50	50.429	-17.862	12.320
1.00	80.610	12.320	-17.862

Positive values show pairs of means that are significantly different.

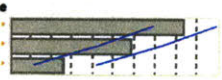
Connecting Letters Report

Level		Mean
2.00	A	139.30730
1.50	B	71.01662
1.00	C	40.83527

Levels not connected by same letter are significantly different.

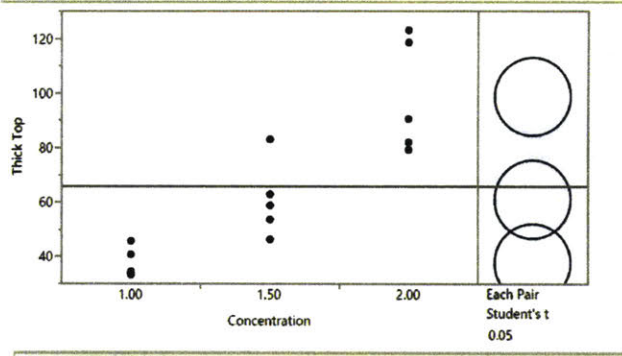
Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
2.00	1.00	98.47203	8.197928	80.61028	116.3338	<.0001*
2.00	1.50	68.29069	8.197928	50.42893	86.1524	<.0001*
1.50	1.00	30.18134	8.197928	12.31959	48.0431	0.0031*



Fit Group

Oneway Analysis of Thick Top By Concentration



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.17881	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	2.00	1.50	1.00
2.00	-20.316	17.493	40.883
1.50	17.493	-20.316	3.074
1.00	40.883	3.074	-20.316

Positive values show pairs of means that are significantly different.

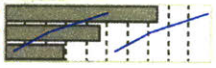
Connecting Letters Report

Level		Mean
2.00	A	98.864811
1.50	B	61.055375
1.00	C	37.665299

Levels not connected by same letter are significantly different.

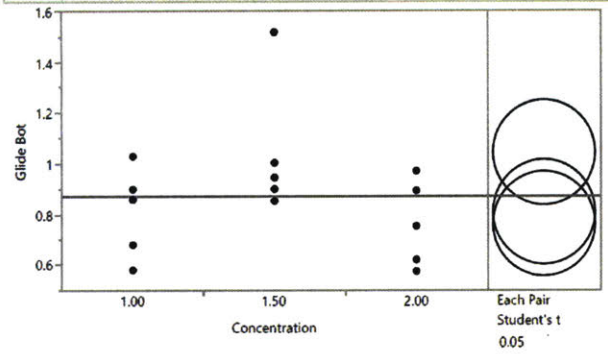
Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
2.00	1.00	61.19951	9.324441	40.88330	81.51572	<.0001*
2.00	1.50	37.80944	9.324441	17.49322	58.12565	0.0016*
1.50	1.00	23.39008	9.324441	3.07386	43.70629	0.0275*



Fit Group

Oneway Analysis of Glide Bot By Concentration



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.17881	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	1.50	1.00	2.00
1.50	-0.29231	-0.05699	-0.01027
1.00	-0.05699	-0.29231	-0.24559
2.00	-0.01027	-0.24559	-0.29231

Positive values show pairs of means that are significantly different.

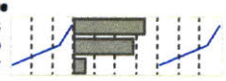
Connecting Letters Report

Level		Mean
1.50	A	1.0453216
1.00	A	0.8100000
2.00	A	0.7632797

Levels not connected by same letter are significantly different.

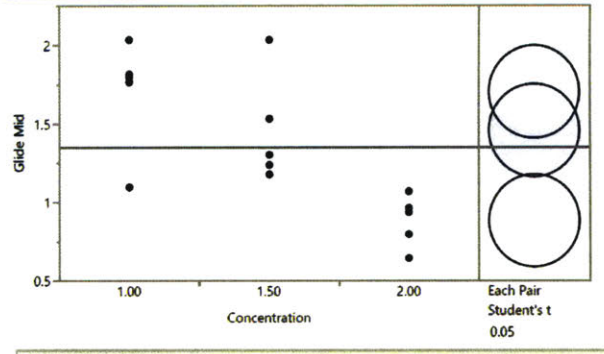
Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
1.50	2.00	0.2820419	0.1341621	-0.010272	0.5743560	0.0573
1.50	1.00	0.2353216	0.1341621	-0.056992	0.5276357	0.1049
1.00	2.00	0.0467203	0.1341621	-0.245594	0.3390344	0.7337



Fit Group

Oneway Analysis of Glide Mid By Concentration



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.17881	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	1.00	1.50	2.00
1.00	-0.41839	-0.17236	0.40384
1.50	-0.17236	-0.41839	0.15781
2.00	0.40384	0.15781	-0.41839

Positive values show pairs of means that are significantly different.

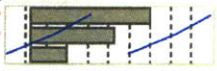
Connecting Letters Report

Level		Mean
1.00	A	1.7060000
1.50	A	1.4599713
2.00	B	0.8837688

Levels not connected by same letter are significantly different.

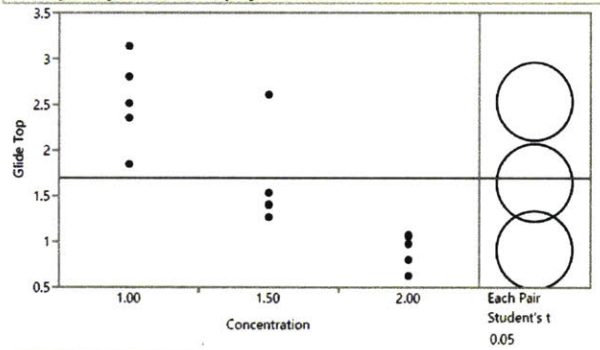
Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
1.00	2.00	0.8222312	0.1920280	0.403838	1.240624	0.0011*
1.50	2.00	0.5762025	0.1920280	0.157810	0.994595	0.0111*
1.00	1.50	0.2460287	0.1920280	-0.172364	0.664422	0.2243



Fit Group

Oneway Analysis of Glide Top By Concentration



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.17881	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	1.00	1.50	2.00
1.00	-0.6024	0.2876	1.0244
1.50	0.2876	-0.6024	0.1344
2.00	1.0244	0.1344	-0.6024

Positive values show pairs of means that are significantly different.

Connecting Letters Report

Level		Mean
1.00	A	2.5360000
1.50	B	1.6460146
2.00	C	0.9092082

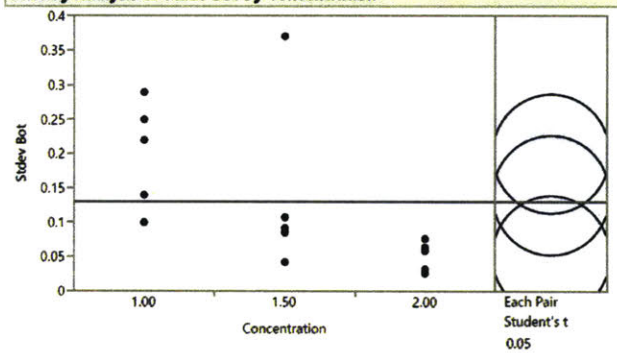
Levels not connected by same letter are significantly different.

Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
1.00	2.00	1.626792	0.2764669	1.024422	2.229161	<.0001*
1.00	1.50	0.889985	0.2764669	0.287616	1.492355	0.0074*
1.50	2.00	0.736806	0.2764669	0.134437	1.339176	0.0206*

Fit Group

Oneway Analysis of Stdev Bot By Concentration



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.17881	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	1.00	1.50	2.00
1.00	-0.12291	-0.06245	0.02546
1.50	-0.06245	-0.12291	-0.03500
2.00	0.02546	-0.03500	-0.12291

Positive values show pairs of means that are significantly different.

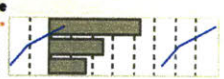
Connecting Letters Report

Level		Mean
1.00	A	0.20000000
1.50	A B	0.13953907
2.00	B	0.05162681

Levels not connected by same letter are significantly different.

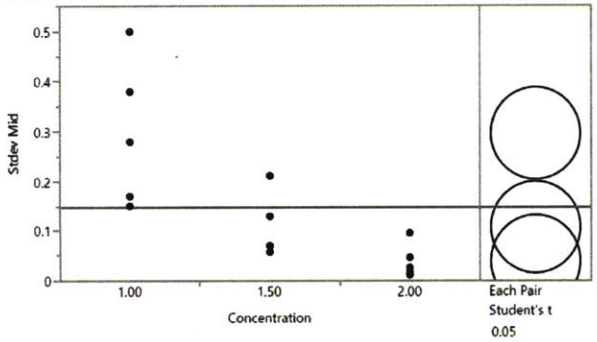
Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
1.00	2.00	0.1483732	0.0564120	0.025462	0.2712844	0.0220*
1.50	2.00	0.0879123	0.0564120	-0.034999	0.2108235	0.1451
1.00	1.50	0.0604609	0.0564120	-0.062450	0.1833722	0.3049



Fit Group

Oneway Analysis of Stdev Mid By Concentration



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.17881	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	1.00	1.50	2.00
1.00	-0.13027	0.05806	0.12636
1.50	0.05806	-0.13027	-0.06198
2.00	0.12636	-0.06198	-0.13027

Positive values show pairs of means that are significantly different.

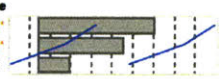
Connecting Letters Report

Level		Mean
1.00	A	0.29600000
1.50	B	0.10766561
2.00	B	0.03936696

Levels not connected by same letter are significantly different.

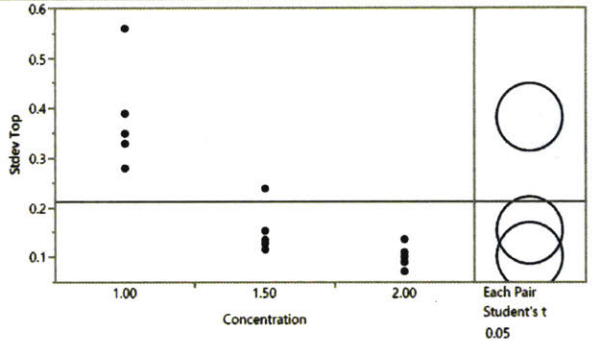
Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
1.00	2.00	0.2566330	0.0597912	0.126359	0.3869070	0.0010*
1.00	1.50	0.1883344	0.0597912	0.058060	0.3186083	0.0084*
1.50	2.00	0.0682986	0.0597912	-0.061975	0.1985726	0.2756



Fit Group

Oneway Analysis of Stdev Top By Concentration



Means Comparisons

Comparisons for each pair using Student's t

Confidence Quantile

t	Alpha
2.17881	0.05

LSD Threshold Matrix

Abs(Dif)-LSD

	1.00	1.50	2.00
1.00	-0.09569	0.13230	0.18456
1.50	0.13230	-0.09569	-0.04343
2.00	0.18456	-0.04343	-0.09569

Positive values show pairs of means that are significantly different.

Connecting Letters Report

Level		Mean
1.00	A	0.38200000
1.50	B	0.15400677
2.00	B	0.10174512

Levels not connected by same letter are significantly different.

Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
1.00	2.00	0.2802549	0.0439192	0.184563	0.3759466	<.0001*
1.00	1.50	0.2279932	0.0439192	0.132301	0.3236850	0.0002*
1.50	2.00	0.0522616	0.0439192	-0.043430	0.1479534	0.2571