Manufacturability of Lab on Chip Devices: Reagent-Filled Reservoirs Bonding Process and its Effect on Reagents Flow Pattern

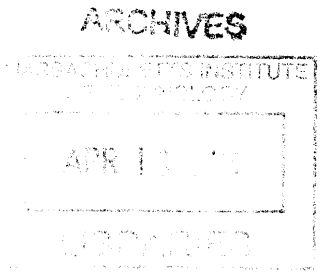
by

Aabed Saber

B.S. Mechanical Engineering (2007)
King Fahd University of Petroleum and Minerals

Submitted to the Department of Mechanical Engineering
in Partial Fulfillment of the Requirements for the Degree of

Master of Engineering in Manufacturing
at the
Massachusetts Institute of Technology



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Abstract

In its lab-on-a-chip product, Daktari Diagnostics utilizes "reagent-filled reservoirs" as a means of storing and delivering the liquid reagent. During the clinical trials of the product, undesired reagent flow patterns (namely, flow anomaly 1 & flow anomaly 2) were noticed. This work focused on optimizing the bonding process of the reagent-filled reservoirs to the backbone. Also, the relationship between the bonding process parameters and the reagent flow pattern was studied in depth. To achieve the objective of this thesis, an experiment was designed in which independent variables were the heat sealing parameters (x, y, z) and accelerated aging and the dependent variables were bond strength and the reagent flow pattern. Experiments showed that optimal Heat Sealing parameters are: parameter x = 4.5, parameter y = 110 and parameter z = 1.5. At the optimal settings of bonding process, the highest bond strength was attained and the reagent flow improved considerably but flow anomalies were not completely resolved. Also, results showed that accelerated aging affected the bond strength negatively. Accelerated aging also affected the flow pattern negatively, but this effect was not statistically significant.

Thesis Supervisor: Dr. Brian W. Anthony
Title: Lecturer in Mechanical Engineering

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Chapter 1: Introduction

This research focuses on various aspects of manufacturing in the CD4 diagnostic microfluidic cartridge produced by Daktari Diagnostics. The ability to accurately measure CD4 counts with a low cost, portable, and easy to use device will benefit millions of HIV infected patients who cannot access expensive diagnostics.

1.1 Company Background

Daktari Diagnostics is a medical diagnostic device company located in Cambridge, Massachusetts, is actively developing a microfluidic CD4 level counter for patients with HIV in the developing world. The device is designed to deliver results at the point-of-care (POC) and is quick, portable, robust, and cost effective. Quickly getting results allows doctors to identify the candidates eligible for antiretroviral therapy (ART), monitor a HIV/AIDS compromised immune system, and track the disease progression of the patients.

1. 2 HIV & AIDS

Human Immunodeficiency Virus (HIV) is a virus that attacks the human body's immune system. Specifically, HIV affects CD4+ cells (also known as T cells or T-helper cells, a type of white blood cell) coordinate the immune system to fight diseases by sending signals to activate the body's immune response once foreign bodies like viruses and bacteria have been detected. [1] CD4+ cells are destroyed by HIV, until the body's immune system reaches a point where it looses its ability to combat disease and leads to an increased risk to opportunistic infections, a medical condition known as Acquired Immune Deficiency Syndrome (AIDS). [1][2]. Healthy, HIV-negative people have a CD4+ counts of 600-1200 cells/mm3. A CD4+ count of less than 200 cells/ mm3 signifies as an AIDS diagnosis. [2]

Since 1981, over 30 million people have died from AIDS. In 2010 alone, it is estimated that 1.8 million died from AIDS and 2.7 million have been infected by HIV. Today, there are

more than 35 million people living with HIV and AIDS worldwide, and ever increasing. [3] Therefore, the measurement of CD4+ is useful for a number of reasons:

- To measure the immune system strength
- To indicate when to start HIV treatment to prevent drug resistance from premature medication.
- To monitor the effectiveness of the HIV treatment every 3-6 months. [4]

1.3 Point-of-Care Development

Typical healthcare conditions found in developing countries are very different than in countries with mature infrastructure. The quality of healthcare facilities vary widely and rural branches commonly have only basic equipment, while healthcare workers may have little training or resources to maintain complex equipment. Even electricity and running water cannot be guaranteed to be available.

Microfluidic systems can be designed to obtain and process measurements from small volumes of complex fluids with efficiency and speed, and without the need for an expert operator; this unique set of capabilities is precisely what is needed to create portable point of-care (POC) medical diagnostic systems.[5][6] In fact, microfluidic instrumentation has been applied to several of the four most common centralized laboratory techniques — blood chemistries, immunoassays, nucleic-acid amplification tests and flow cytometry. [7]

Table 1 Factors Affecting Microfluidic Diagnostic Technology (MDT) and Attributes of a Successful MDT in the Developing World[14]

Key Factors	Attributes
Cost	Low
Accuracy	High
Quality control	Reproducible performance
Level of user training	User interface requires little
Time for result	Short
Use in variety of settings	Reproducible operation in variable environment
Performance over time	Stable storage and low power consumption
Local health education	High perceived need for test
Availability of therapies	Potential for significant health improvements

1.4 Use of Microfluidics

Microfluidic devices show great potential to address the challenges associated with CD4 cells counting in resource-limited settings, ideally revolutionizing the point-of-care (POC) diagnostics industry. [8][9]A microfluidic platform provides a set of fluidic unit operations, which are designed for easy combination within a well-defined (and low cost) fabrication technology. The platform allows the implementation of different application specific systems (assays) in an easy and flexible way, based on the same fabrication technology. [10] Following early efforts in dispensing nano and sub-nanoliter fluid volumes, a wide array of microfluidic components such as micro pumps, valves, mixers and other types were developed. An integrated approach on the lines of the microelectronics industry led to the development of more complicated combined systems, commonly referred to as Lab-on-a-chip microfluidic devices.

Despite the rising popularity of microfluidic devices, the transition from laboratory research to engineering product development is often challenging given the constraints of large scale production and the need for low production cost. These constraints become especially severe the resource-limited settings of developing countries, where Daktari's POC HIV diagnostic will be most beneficial.

1.5 HIV Monitoring Challenges

Typically, appropriate analysis is performed via a process called flow cytometry. This process involves identifying appropriate cells with fluorescent biomarkers, and then pushing the fluid through a controlled stream. A beam of light, typically a laser, is focused on this stream and when it contacts the fluorescent chemical, the corresponding particle can be excited to emit a light of longer wavelength. This brief fluctuation can be detected with a photomultiplier and interpreted to determine chemical and physical characteristics. However, this process requires run time of between 18-24 hours on a stationary, expensive, and complex lab machine under guidance of a trained technician, resulting in significant limitations in access to the targeted developing world populations.

70% of the HIV-infected population worldwide does not have access to proper diagnostics, preventing them from receiving necessary treatment. The complexity of current CD4 counting equipment requires trained lab technicians. The shortage in most African countries is as extreme as 1 technician for every million people. The lack of laboratory infrastructure, reliable power and environmental controlled packaging are also severe constraints in CD4 diagnostics. Conventional CD4 counting equipment are expensive. Flow cytometers, for instance, the standard equipment to estimate CD4 cell counts, cost between $30,000-150,000 per device. [11] [12] [13] These limitations make a compelling argument in favor of the importance of an affordable, practical, quick and accurate means for CD4 counting. [8] [11]

1.6 The Masters of Engineering Capstone Project

This document serves as partial fulfillment of the graduation requirements for the Masters of Engineering in Manufacturing program at the Massachusetts Institute of Technology. Through the Laboratory for Manufacturing Productivity (LMP), co-advised by Professor David Hardt and Research Scientist Brian Anthony. The author conducted research and laboratory experiments documented in this thesis at Daktari Diagnostics. Four students actively worked at Daktari, each focusing on unique challenges in the manufacturing of HIV diagnostic. The author of this thesis, Nikhil Jain, focused on a reducing variability in high-

throughput electrode production, with a primary emphasis on the system-critical impedance measurements. Benjamin Judge developed a new process for induction sealing microfluidic channels with sensitive tolerances. Tejas Inamdar and Aabed Saber focused on characterizing the effect of reagent-filled reservoirs production parameters on bonding strength and reagent performance. Due to similarity in background of work performed at Daktari, the portions of the introductory sections of the four theses were written collaboratively. Together, this work represents an in-depth analysis of a few of the company's most important manufacturing issues at the time of writing.

1.7 Thesis Overview

This body of work is organized in the following manner for clarity, and targeted towards readers of limited technical background in this field: Chapter 1 and 2 outline the company profile, product, and problems being addressed. A thorough technological background follows in Chapter 3. Following, in Chapter 4, this thesis outlines the specific experimental methodologies performed by the author to characterize the development process. A detailed analysis of the results, as well as further experimentation performed to complement this work is shown in Chapter 5. Chapter 6 is comprised of conclusive remarks and recommendations with Chapter 7 outlining paths for future work.

Chapter 2: Background Research

2.1 MEMS

Micromachining and micro-electromechanical system (MEMS) technologies can be used to produce complex structures, devices and systems on the scale of micrometers. A wide variety of transduction mechanisms allow the conversion of real world signals from one form of energy into another thereby enabling many microsensors, microactuators, and microsystems.[14] The scaling of microsystems dramatically changes material and mechanical properties, performance and cost of production of these systems. All MEMS devices exploit one of the following advantages offered by microscale behavior:

1. Advantageous scaling properties – Some physical phenomena perform much better or are more efficient on a micrometer scale.
2. Batch Fabrication – Lithographic processes and batch fabrication work better with economies of scale.
3. Circuit Integration – Tremendous value can be derived by integrating circuits with MEMS devices. [14]

2.2 Microfluidics

Microfluidics is an extension of the MEMS technology. It is the science and technology of systems that process or manipulate small (10^{-9} to 10^{-18} liters) amounts of fluids, using channels with proportional dimensions of tens to hundreds of micrometers.[11] In microscale fluidic systems, surface tension, energy dissipation and fluidic resistance significantly contribute to flow dynamics. In particular, the Reynolds number, which compares the effect of the fluid momentum to the effect of its viscosity, can become very low, resulting in a highly laminar flow system in which fluids do not regularly mix. [15]

Some of the main advantages of Microfluidic Devices can be outlined as follows:

1. Efficient use of reagents helps minimize costs.
2. Modular design allows flexibility.
3. Faster results (potential for real time analysis)

4. Precise control over small fluid volumes.

5. Low cost of production.

2.3 Lab-on-a-Chip Technology

With the recent development of technology in microfluidics, small systems capable of performing laboratory functions on small chips using microliters of fluid began to be developed and were coined "Lab-on-a-Chip" devices. Initially this technology was commonly referred to as Micro Total Analysis Systems, or microTAS, because of an initial focus purely on laboratory-based chemical analysis. However, as platforms became broader, the new term was coined to indicate Micro Electro Mechanical Systems (MEMS) devices integrating microfluidic technology. Areas of application are constantly expanding- currently technology exists in chemical analysis, environmental monitoring, cellomics, and medical diagnostics as is seen at Daktari.

Lab-on-a-Chip technology and microfluidics in particular have become rapidly growing area for over 10,000 papers have been published on new developments in the past 10 years alone [Microfluidic lab-on-a-chip platforms: requirements, characteristics, and applications]. These small scale systems are advantageous for many reasons; the low fluid volumes required mean lower storage volume requirements, lower cost with reduced material usage, and less waste. Also, small channels allow for more rapid testing procedures including heating, mixing, and diffusion as necessary. Smaller size and lower energy requirements allow for high parallel processing for increased throughput, all while permitting the use of disposable systems, an unimaginable characteristic when considering the multi-million dollar laboratory machines that currently occupy most hospital and clinics. However, these benefits come with new challenges as well- microscopic system are far more susceptible to physical anomalies that are typically ignored otherwise. Tolerances must be scaled accordingly which is increasing difficult, as well as physical phenomena such as capillary forces must be accounted for.

2.3.1 Generic Microfluidic Components

All microfluidic devices must have a series of generic components – a method of introducing reagents and samples; methods for moving these fluids around on the chip and for combining and mixing them (usually referred to as the microfluidic plumbing); and other features such as detectors for most micro analytical work and purification of products for systems used in synthesis.[16]

Sample injection can take place primarily in one of the two ways – capillary action or an external device such as a syringe or a pump. The sample can then flow through the fluidic channels on its own pressure differential or it can be driven by a reagent flowing through the fluidic channels. The storage, injection and flow of reagents are under significant research activity in the microfluidics community. The entire fluidic channel is composed of fluidic interconnects, microfluidic mixers, pumps and valves which allow greater control over the flow rates and the flow directions of the reagents. The microfluidic cartridge also commonly includes a waste channel to store used samples and reagents once the assay has been performed.

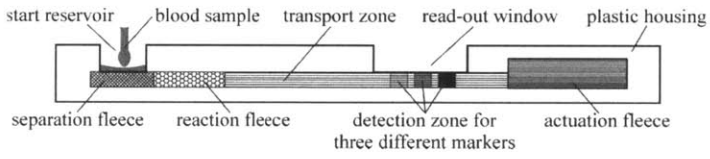


Figure 1 Simplified Cross Section of a Typical Driven Immunoassay Test Strip [11]

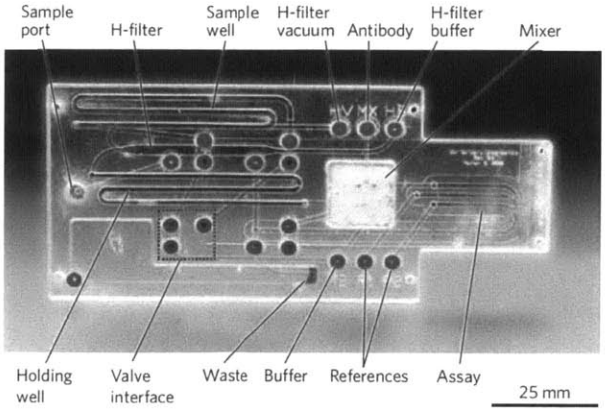


Figure 2 Example of an Integrated Disposable Diagnostic [14]

2.3.2 Microfluidic Device Architecture

The Microfluidic Device Architecture is heavily influenced by microelectronics. Similar to the Printed circuit boards (PCBs), these devices are formed by different layers performing a specific function. Figure 3 represents the typical arrangement of components in a microfluidic device.

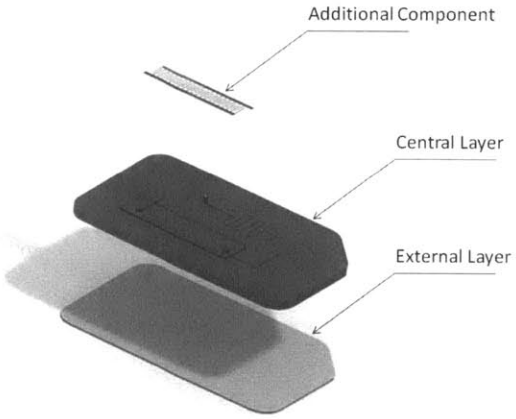


Figure 3 Microfluidic Device Architecture [18]

Micro-channel Plate

The Microchannel Plate is often the defining component of a microfluidic cartridge. It made of clear or opaque polymethyl methacrylate (PMMA), commonly known as acrylic. This layer houses the open microfluidic channels. These channels may include the mixers, the reservoirs, waste channels, vials, sensors, and other features. The complexity of the features may wary widely depending upon the assay.

Microfluidic Channel Seal

The Microfluidic Channel seal is an additional layer meant to seal the open section of the features in the backbone to create a fully enclosed channel. This seal may in some case have additional functionality buy using PCBs, sensors and outputs from other systems.

Additional Components

Microfluidic Devices typically also have additional components which perform fluid flow control, external flow control and sensing. Many microfluidic devices have several ways of sensing changes in optical, temperature, pressure and electrical properties (impedance, capacitance etc) to estimate assay results.

Chapter 3: Product and Project Overview

3.1 Product Description

The Daktari system includes an array of channels on its disposable cards which serve to control the flow of blood and reagents to appropriate areas. Using actuators from the device, metered quantities of fluid can be pushed from card storage areas and routed through microfluidic channels. These actuators then also determine the direction of flow by opening and closing valves. In Daktari's system, a fixed amount of blood is passed through the channels and the particular CD4 cell desired is separated and counted. More on this process will be detailed below, but the use of microfluidics allows for a small volume of liquid and high surface area to volume channels to make accurate diagnostic reports with minimal preparation and processing. All of this work can be completed within minutes in small portable systems, eliminating the need for large-scale laboratories with extremely high capital costs. Figure 1 shows how Daktari's system is used to get a CD4 T-Cell count. The assay process has three main stages. The stages are: (A) The blood sample flows through the assay chamber and CD4 cells stick to the antibody. (B) Other cells are washed out of the chamber. (C) CD4 cells' cell membranes are ruptured, or lysed by a high-impedance solution, and the difference in impedance is measured.

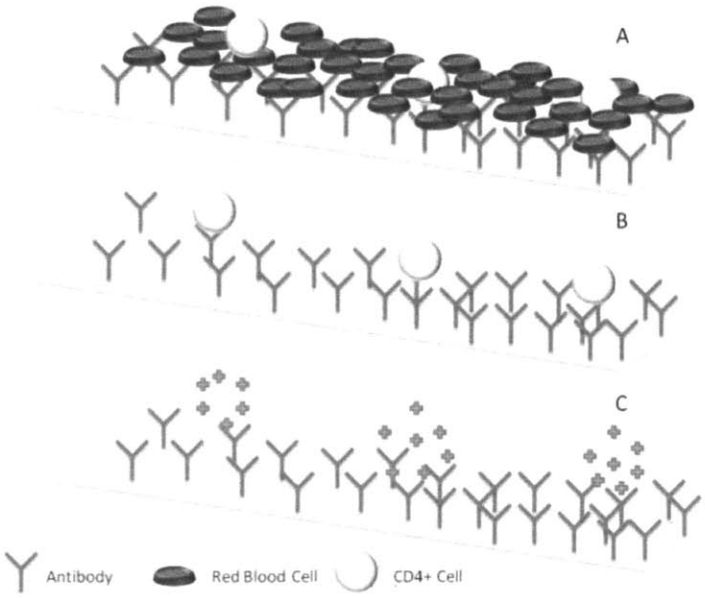


Figure 4 Assay Process Diagram [18]

This product would typically be used by a trained operator carrying the portable instrument and a supply of disposable cartridges to patients in remote locations. The device is to be used where a flow cytometer is not easily accessible. The operator pricks the patient's finger with a lancet and allows the blood to flow into the sample entry port of the card. Once a sufficient amount of blood has entered the card, the operator caps the card, which seals the cartridge, and helps the patient with a bandage to reduce the risk of exposure. The capped card then goes into the instrument, and the test begins. Solenoids in the instrument drive the fluid reagents, which are stored in reservoirs on the card, out of the reservoirs in a controlled manner. Actuation of valves guides the sample through an assay chamber. Antibodies that were deposited to the electrode foil capture the CD4 cells. The captured cells' membranes are ruptured (lysed) by a high-impedance solution. The contents of the cells reduce the impedance of the solution. This reduction of impedance is measured and is correlated to the concentration of CD4 cells in the blood sample; subsequently the concentration is displayed on the instrument's LCD display.

3.1.1 The Instrument

The battery-powered instrument is designed for the simplest possible user interaction and portability. The standalone instrument contains the actuators for driving the reagents and operating the valves. The instrument connects to the electrode in the cartridge to read the impedance measurements in the assay chamber. The measurements are used to determine the CD4 cell count in the sample, and the rest of the electronics needed to display the results and drive the actuators are contained in the instrument. Figure 2 shows how the disposable cartridge will go into the unit. Inserting the cartridge is similar to how a cassette goes into a cassette player. All of the tasks are met by the subassemblies listed below.

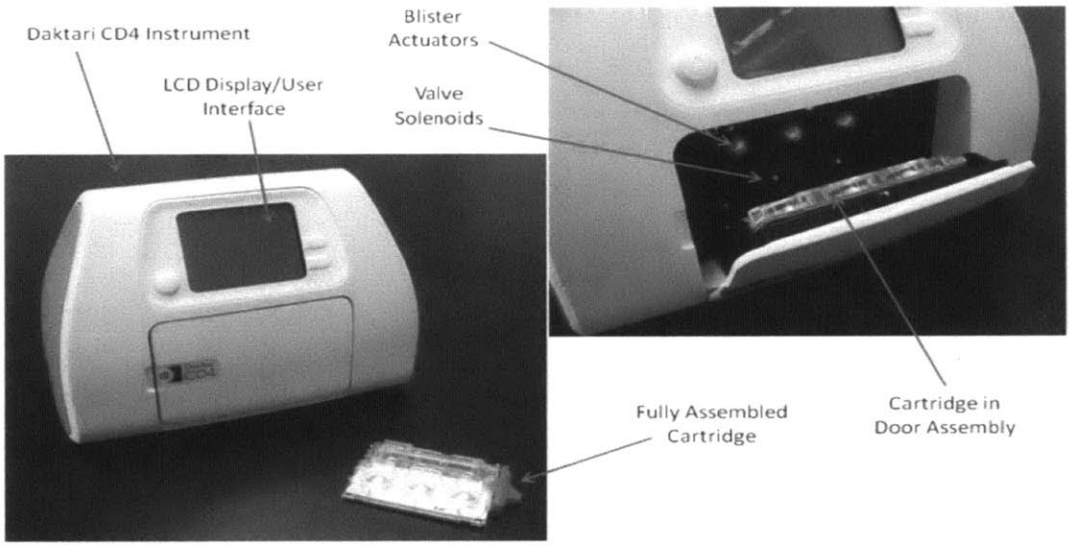


Figure 5 Daktari Instrument [14]

1. Frame - the structural element of the instrument. All of the other subassemblies are located using the frame.
2. Door Subassembly - locates the cartridge, punctures a vent hole and ensures no deformation of the card.
3. Actuator Subassembly – holds the actuators perpendicular to the frame.
4. Solenoid Subassembly – holds the valve actuators perpendicular to the frame.
5. Outer Casing – protects the internal components from impact and debris and also provides an aesthetic appeal.

3.1.2 The Cartridge

Each test cartridge is consumable for the test, to be immediately disposed of after the assay. The cartridge is a microfluidic device with reagents and the sensing mechanism to measure the amount of CD4 cells in a sample of blood. Figure 3 shows a recent iteration of the design. Each cartridge contains the following 7 parts:

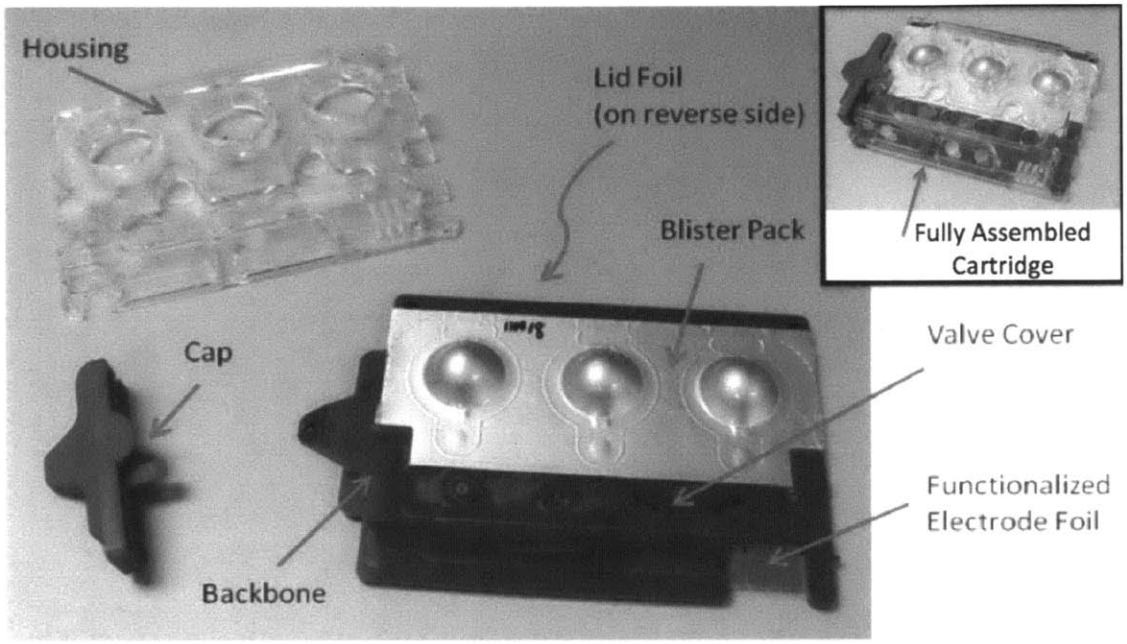


Figure 6 Daktari Cartridge with all Seven Components Labeled [14]

1. Backbone – an injection molded PMMA (polymethylmethacrylate) card with microfluidic channels.
2. Lid foil - a transparent PMMA sheet that is joined to one side of the backbone to seal the microfluidic channels on the backbone.
3. Functionalized electrode foil – a PMMA foil that covers the 'assay chamber' where the CD4 cell count is performed. This foil has an electrode layer on it. It is then coated with antibody solution, which is used to trap the desired CD4 cells.
4. Reagent-filled reservoirs – the three semispherical objects in Figure 3 contain the three liquid reagents that perform tasks as they flow through the system.
5. Valve cover- a layer of polymer used to create a seal on the valves that are used to direct flow through the system.

6. Housing - an injection molded PMMA element that protects the reagent-filled reservoirs and functionalized foil.

7. Cap – a polymer component that seals the blood entry port after the blood is sampled and also closes vents that were necessary to allow capillary flow of blood into the card.

3.1.3 Reagents-Filled Reservoirs

There are three dome shaped reagent-filled reservoirs – each carrying around 600 μL of reagents. Reagents perform a specific function in the assay. The reagent reservoirs are hollow domes filled with ionic solutions of varying degrees. The reservoirs are named in the order of their operation. Reservoir 1 is popped releasing R1 the most ionic solution that first drives blood through the cuvette and then clears the cuvette. B2 is popped later releasing R2 and has slightly lesser ionic concentration and clears the R1 solution. Finally B3 is popped releasing R3 the least ionic solution which drives out the R2 direction in the same direction as the R2 flow. Once R3 resides in the cuvette volume, the CD4 lysis begins and changes the impedance of the solution.

This reagent-filled reservoir shape has also been extensively studied in Selvakumar's thesis in 2010. His research indicates that there is no significant change in flow rate as a result of imperfect application of plunger force either angular or axial. His theoretical predictions have later been validated by experiments.

3.2 Background on the Problem

Previous research on the formation of the reagent-filled reservoirs and modeling the flow behavior in order to determine the effects of formed geometries and instrument alignment on both the flow characteristics and assay performance. [17], [18] Additionally, instrument and cartridge interactions at the valves and electrode pads were also analyzed. This work provided extensive information on component behavior during product operation. Conclusions from this work have led to the optimization of reagent-filled reservoirs geometry.

3.2.1 Reagent-Filled Reservoirs Bonding

The definitive nature of the medical device, the intended use, expiration date, transport, and storage all influence the design and manufacturing of the device. Reagent-filled reservoirs consist of a formed foil and a lid foil, joined together, which is then joined to the backbone through thermal bonding. Reagent-filled reservoirs, once bonded, shall perform efficiently, safely, and adequately in the end-user's hands. [19] Any flaw in the bonding process might result in delamination leading to undesired flow patterns -or even worse- loss of containment of the reagents.

3.2.2 Reagent-Filled Reservoirs Failure

The reagent-filled reservoirs production process should result in a final assembly that meets all performance specifications, including reagent storage and delivery. Failure of any process can result in failure of one or more performance attributes.

Changes in key operating parameters can result in changes in reagent delivery. [19]

3.2.3 Reagent Delivery

The flow pattern in this microfluidic structure is designed to ensure that the assay can be successfully performed. This means that the flow must satisfy two key characteristics – The reagent flow rate must follow a predefined predictable pattern and it must not wash away the CD4 cells due to high flow rates. In an ideal situation the reagent-filled reservoirs flow must follow a square wave pattern. The flow initiation must be instantaneous and be constant for a period of time followed by an instantaneous drop of flow rate. Flow is often redirected at its initiation as well as it's conclusion to the waste channel (referred to as priming) to utilize a section of the flow in control. This is done through a set of valves designed into the backbone and is operated by servo motor actuation in the instrument. The flow exiting the reservoirs at a port called the reservoir via is measured using flow sensors. The experiments conducted so far indicate that there are several anomalies observed in the actual flow rate patterns.

3.2.3.1 Anomaly 1

This flow anomaly is defined as the flow rate higher than the upper limit of the requested flow rate. Flow anomaly 1 is analogous to a signal *overshoot* in control theory. The source of flow anomaly 1 is unknown but flow anomaly 1 mimics a build-up and valve release of higher flow rate during actuator movement. This anomaly may have unknown consequences such as lack of knowledge about the amount of waste volume needed, washing away of the CD4 cells and the lack of repeatability. Flow anomaly 1 is postulated to be associated with the reagent-filled reservoirs and backbone bonding. [19]

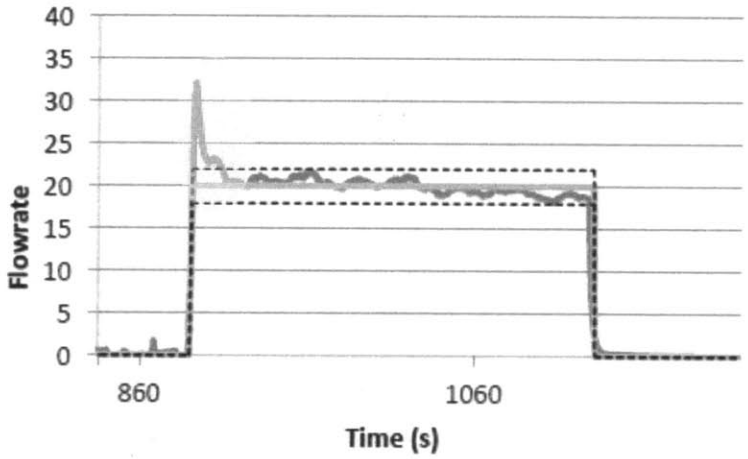


Figure 7Flow Anomaly 1 Case

3.2.3.2 Anomaly 2

The response time required to achieve requested flow rate is termed as Flow anomaly 2. This could be shifting from zero flow rate to the desired flow rate and vice versa. This phenomenon can be thought of as the delay characteristics in a control theory or signal processing. In essence, the presence of Flow anomaly 2 is not as serious a problem as compared to flow anomaly 1, however the unpredictability in Flow anomaly 2 duration makes it challenging to program reagent-filled reservoirs sequencing and priming operations. Flow anomaly 2 seems to be associated with the seal. [19]

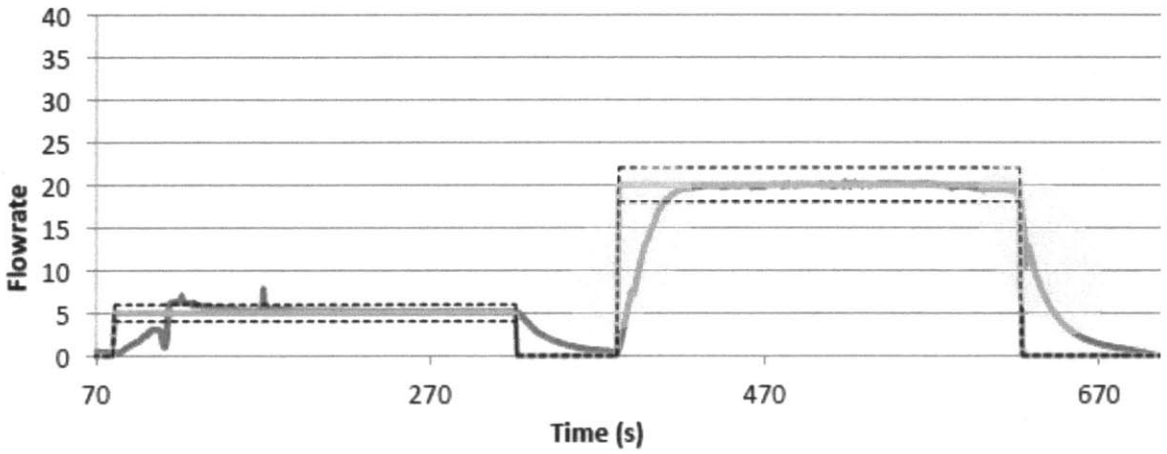


Figure 8 Anomaly 2

3.4 Project Objectives

The main goals of this thesis are:

- Optimize the reagent-filled reservoirs production process to produce the highest possible reagent-filled reservoirs performance.
- The hypothesis is that optimizing the reagent-filled reservoirs production process parameters would improve the reagent-filled reservoirs performance. Here I would investigate the relationship between reagents performance and the reagent-filled reservoirs production process.
- Study the effect of accelerated aging on reagent-filled reservoirs / backbone bond strength.

Chapter 4: Methodology

4.1 Overview

To achieve the objectives of this thesis, an experiment was designed in which independent variables were: heat sealing parameters time, temperature and pressure (X,Y,Z), accelerated aging and dependent variables were: reagent flow and reagent-filled reservoirs to backbone bond strength. In this chapter, we will focus on sample preparation and give general background on the experiment procedure. Results of the experiment, however, would be discussed in the Results chapter.

4.2 Sample Preparation

4.2.1 Materials

Materials used in the sample preparation included the reagent-filled reservoirs and the PMMA backbone.

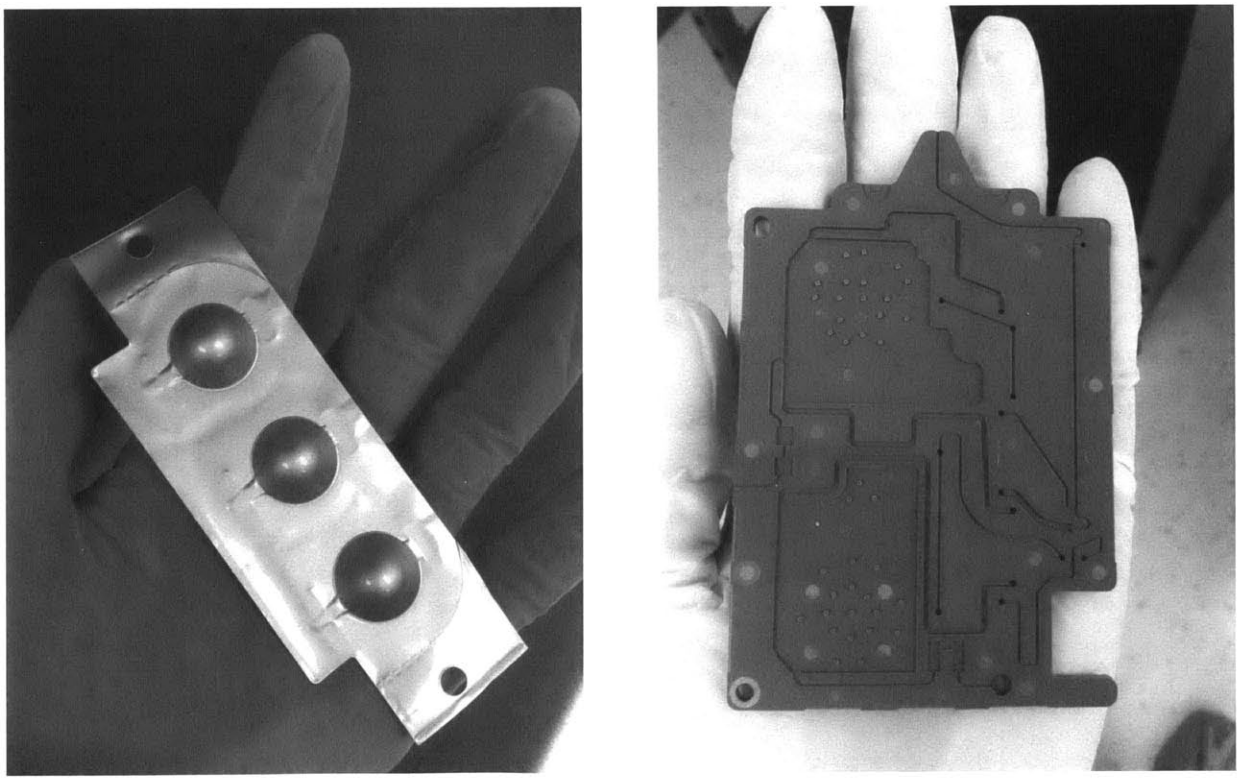


Figure 9 Reagent-filled reservoirs (left) and the Latest Version of the Backbone (right)

4.2.2 Processes

4.2.2.1 Reagent-filled Reservoirs Filling

Each reagent-filled reservoir is filled with 600 uL of deionized water using HandyStep®, an automated micro volume liquid dispenser. The deionized water was used here to minimize variability only. In the product, fluid other than deionized water will be used.

4.2.2.2 Bonding the Reagent-filled Reservoirs to the Backbone

4.2.2.2.1 Background on Bonding Processes

Heat sealing is a process of joining two or more thermoplastic films or sheets by heating areas in contact with each other to the temperature at which fusion occurs and it is usually aided by pressure. Heat sealing can join both similar and dissimilar materials together. [20] Sometimes a low melting point sealant material is placed between the two-bonded surfaces to ease the bonding process. There are many factors affecting the seal strength resulted from the heat-sealing process. Those factors are related to the characteristics of the bonded materials and the heat sealing parameters. Yuan and Hassan did some work on the effect of sealing parameters on OPP/MCPP heat seal strength. They concluded that jaw temperature and dwell time are interrelated in attaining the heat seal strength. It was found, however, that jaw temperature is more influential than dwell time. Also, they noticed that there is a threshold point below which the bonding does not occur. Furthermore, it was shown that pressure applied did not have significant effect on the seal strength. The pressure, as it was the case with the temperature, needs to exceed a threshold for the bonding to occur. [21]

4.2.2.2.2 Heat Sealing of the Reservoirs

Bonding parameters were varied to identify optimal bond strengths.

4.3 Accelerated Aging

4.3.1 Background:

Usually, especially at early stages of product development, actual lifespan data is not available. In those cases, accelerated Aging -a testing method used to estimate the useful lifespan of a product- can be utilized. This occurs with products that have not existed long enough to have gone through their useful lifespan. Accelerated aging data is recognized by regulatory bodies as an acceptable means to generate data quickly, but is only accepted until those tests can be repeated on ambient condition aged ("real time") samples. An accelerated aging test is carried out by subjecting the product to unusually high levels of stress (rapid, but controlled, changes in temperature, humidity, pressure, strain, etc.) designed to mimic the effects of normal use. [22] The nature of Daktari product requires increasing the temperature only- as a means for accelerated aging.

ISO 11607 states "For medical devices with a defined shelf-life, the manufacturer shall have documented evidence that the performance of the packing is not adversely affected by storage under specified conditions for a period not less than the shelf-life of the medical device. This shall be demonstrated by real time aging testing. Accelerated aging testing may be undertaken in addition to real time aging under conditions of increased severity." [19]

Accelerated aging techniques are based on the assumption that the chemical reactions involved in the deterioration of materials follow the Arrhenius reaction rate function. This function states that a 10°C increase or decrease in temperature of a homogeneous process results in, approximately, a two times or 1 /2 -time change in the rate of a chemical reaction. The accelerated aging time (AAT) needed to establish equivalence to Real Time (RT) aging is determined by dividing the desired (or required) shelf life by the Accelerated Aging Factor (AAF).

Accelerated Aging Time (AAT) = Desired (RT)/AAF

Equation 1

An accelerated aging factor (AAF) estimate is calculated by the following equation:

$$AAF = Q_{10}^{[(TAA-TRT)/10]}$$

Equation 2

Where:

TAA is the Accelerated Aging Temperature (°C), and

TRT is Ambient Temperature (°C).

Q10 equals 2. This is a common and conservative means of calculating an aging factor. A more aggressive reaction rate coefficient, for example, Q10 of 2.2 to 2.5, may be used if the system under investigation is sufficiently well characterized in the literature. [23]

4.3.2 Equivalent Real Time Aging:

For the purpose of our experiment, a set of samples was exposed to accelerated aging for two weeks (AAT) at 50° C using the aging oven in the company's lab. Using Eq.1 and Eq.2 , with following values:

AAT= 17 days

TAA= 50° C

TRT= 25° C

Q10 = 2

we get a desired real time aging of 96.2 days = 3.2 months. This period is almost half the expected maximum shelf life (6 months) of the first phase of the product launch.

The bond strength and the reagent flow of the accelerated-aged set were compared against those of non-accelerated-aged set to gauge the effect of aging on the bond strength and the flow pattern.

4.4 Tests

Each sample after being prepared goes through two tests, namely; flow test and peel test.

4.4.1 Flow Test

Samples were put in instrument that simulates the actual instrument operation.

In conjunction with flow measurement equipment, software program was capturing flow measurement data.

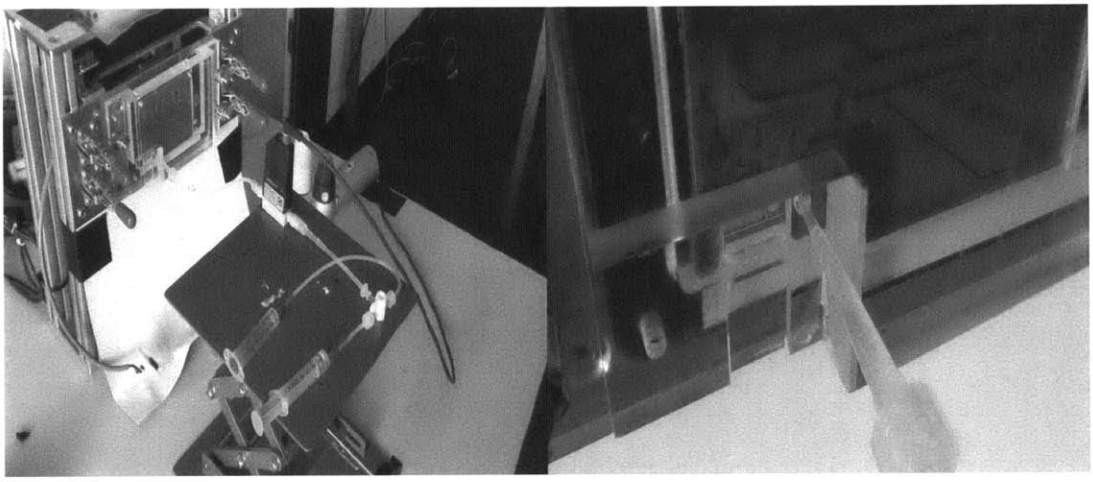


Figure 10 Flow Measurement Equipment

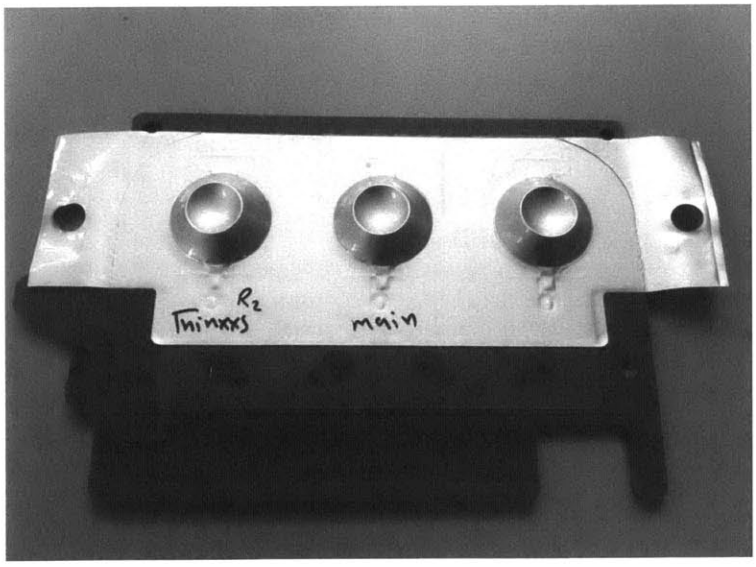


Figure 11 One of the Samples after Being Tested for Reagent Delivery

4.4.2 Peel Test

4.4.2.1 Background

The peel strength is the measure of the average force to separate two bonded materials like tape, labels, textile or plastic films. The strength is calculated during a peel test at a constant peel rate by dividing the average force required during the test by the unit width of the bonded samples. Depending on materials, norms, products, the tests can be done with different angles: 90° and 180° are commonly used. Also, there is what is called the T-peel test.

The 90 and 180 degree tests are commonly used where a flexible material with an adhesive or other bonding method is adhered to a more rigid substrate. The 90 is preferred over the 180 degree peel test if the flexible substrate can't be bent cleanly back to 180 degrees. The T-Peel is used when both materials are either similar or both flexible. [24]

Like friction, peeling is a discontinuous phenomenon: there is a peak and then a plateau with saw tooth. This peak is the start peak that is generally used to characterize the peel strength as shown in figure 8. In the case of adhesive materials, the first peak is not measured, but rather the average force during the test divided by the width of the sample. The unit of the resistance value is in N/mm. [24] [25]

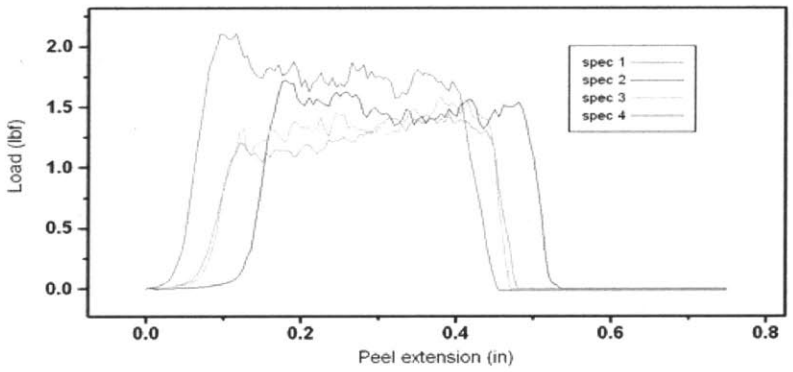
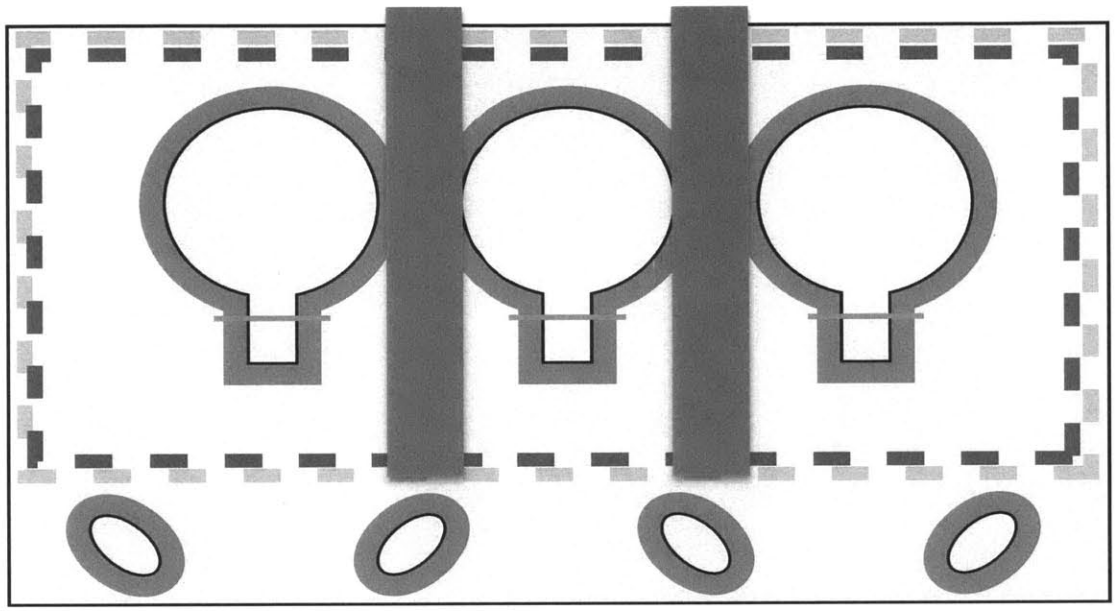


Figure 12 Typical Peel Test Graph

4.4.2.2 Sample Preparation and Test Machine Settings

The card is of complex geometry for a peel test. Hence two locations where there is no geometry variation were chosen to be peel tested (fig.19).



gure 13 Schematic Top View of the Reagent-filled reservoirs (Peel Tests Locations are ılored in Red, the stripe on the right is referred to as location 1 and the one on the left is referred to as location 2)

Upon preparing the sample for peel test, a modified ASTM D903 was conducted as shown in Figure 21. The bond strength was the average of the readings of the two peel tests conducted on the two strips.

4.5 Reagent Parameters:

Currently, reagent anomalies are characterized qualitatively. Here, we tried to characterize the flow anomalies quantitatively. The measures are related to the average flow of the reagents.

4.5.1 Average Flow:

During the flow test and after being popped, each reagent-filled reservoir is pushed twice (each is referred to as flow step). For some unknown reasons, the average flow rates resulting from the two flow steps are not the same. Hence, we calculated the average flow rate of each flow step separately.

Nominal flow rate resulting from the first flow step:

The nominal flow rate was calculated by averaging out the flow rates of five samples as follows:

Table 2 Average Flow Rate of the First Flow Step

Sample #	Flow rate
1	25.15
2	23.1
3	24.6
4	20.74
5	23.45
Average (X)	23.41
Standard Deviation (s)	1.71

Using the following formula:

$$X - t_{\alpha/2,n-1}\frac{s}{\sqrt{n}} \leq \mu \leq X + t_{\alpha/2,n-1}\frac{s}{\sqrt{n}}$$

Equation 3

Where:

S: the sample standard deviation

X: the sample average

N: number of samples

μ: the nominal average

100 (1-α) % = 95 → $\alpha = .01$ → $t_{\alpha/2,n-1} = 2.776$

Plugging the data in the above formula yields→ 21.2874< μ < 25.529. We can say, with 95% confidence, that the mean falls within this range and we opted to choose the middle point of this range which is 23.408.

Nominal flow rate resulting from the second flow step:

The nominal flow rate was calculated by averaging out the flow rates of five samples as follows:

Table 3 Average Flow Rate of the Second Flow Step

Sample #	Flow rate
1	20.54
2	20.52
3	20.75
4	20.78
5	20.82
Average (X)	20.68
Standard Deviation (s)	0.141

Using the following formula:

$$X - t_{\alpha/2,n-1}\frac{s}{\sqrt{n}} \leq \mu \leq X + t_{\alpha/2,n-1}\frac{s}{\sqrt{n}}$$

Equation 4

Where:

S: the sample standard deviation

X: the sample average

N: number of samples

μ: the nominal average

100 (1-α) % = 95 → $\alpha = .01$ → $t_{\alpha/2,n-1} = 2.776$

Plugging the data in the above formula yields→ 20.507< μ < 20.857. We can say with 95% confidence that the mean falls within this range and we opted to choose the middle point of this range which is 20.682.

4.5.2 Flow Anomalies:

Flow anomalies refer to the flow patterns that deviate from the desired rectangular wave patterns. There are two types of flow anomalies, namely; flow anomaly 2 and flow anomaly 1.

4.5.2.1 Flow Anomaly 1:

This flow anomaly is defined as a value greater than the upper limit of the requested flow rate. The upper limit is defined as 110% of the nominal target level of flow rate. Mathematically:

Anomaly 1 = Peak Value – 110% target level of flow rate

Equation 5

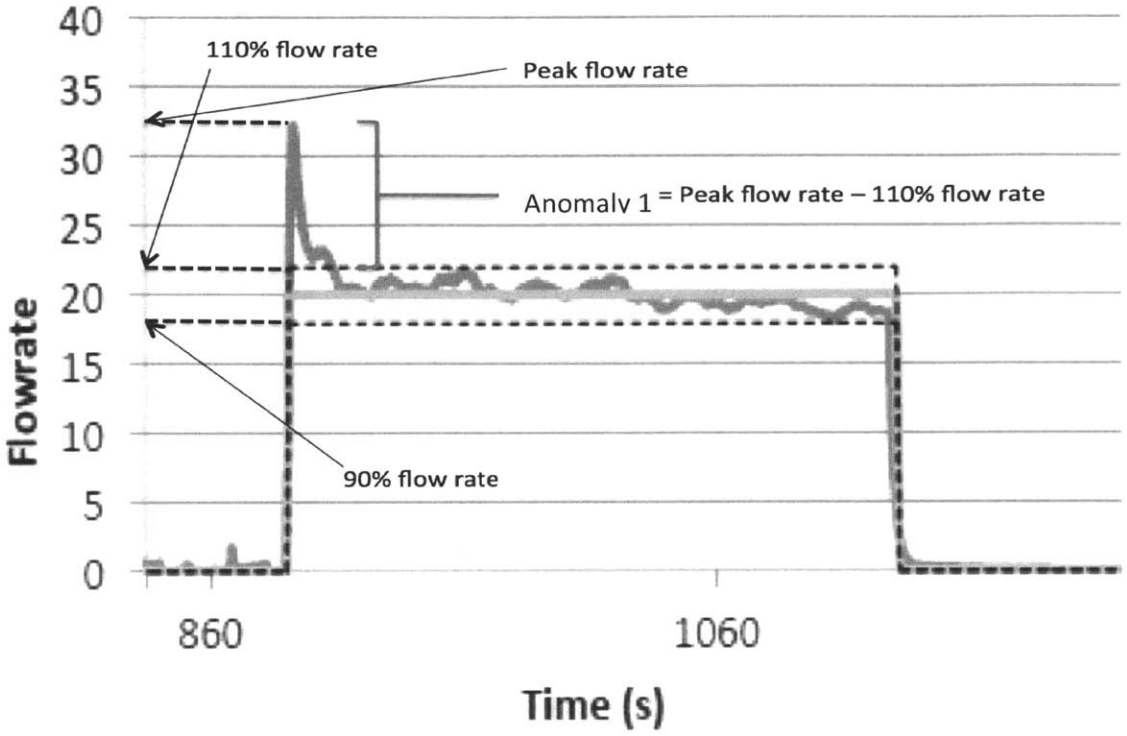


Figure 14 Flow Anomaly 1 Calculations

All the flow anomaly 1 for each flow step is averaged out.

4.5.2.2 Flow Anomaly 2

Flow anomaly 2 is the response time required to achieve requested value of flow rate. Hence, it will be quantitatively characterized as the time required to reach 50% of the nominal target level of Q during the rise or the drop of each phase. Mathematically:

For the rise: Flow Anomaly 2 (seconds) = Time @ %50 target level of flow rate – time @ 0 flow rate

Equation 6

For the drop: Flow Anomaly 2 (seconds) = Time @ average flow rate – time @%50 target level of flow rate

Equation 7

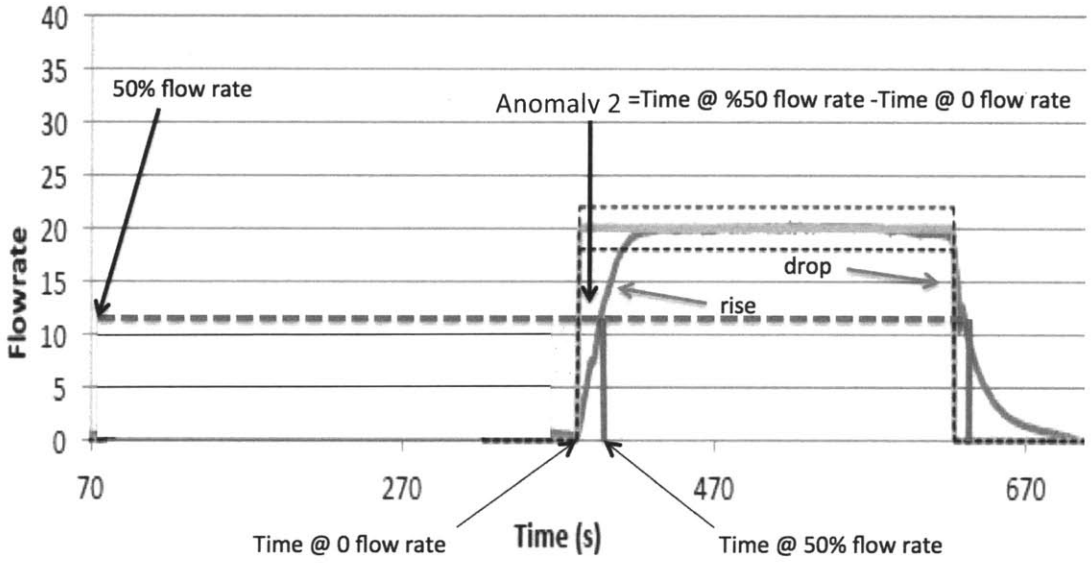


Figure 15 Flow Anomaly 2 Calculations

All the flow anomaly 2 times for the rises and drops of the two flow steps are averaged out.

5 Results and Discussion

Before carrying out the main experiment, a preliminary experimentation was needed to refine the design of the main experiment in terms of appropriate limits and levels of the independent variables.

5.1 Preliminary Analysis:

In the preliminary analysis, 4 sets of samples were tested for bond strength. In the first set, a handful of samples were prepared under the same production parameters. The purpose of testing the first set was to determine the variation in the results and hence decide on the need for having replicates at each of the settings in the main experiment. At each of the remaining set of samples, one of the production parameters was varied while the other two were kept unchanged. The purpose of the testing the remaining three sets was to test the relationship between each of the three production parameters and the resulted bond strength so we can decide on the levels and limits of each of the production parameters in the main experiment.

5.1.1 Variability of the Production Parameters (Set 1):

Three samples were run under identical production parameters and the results are shown in table 4.

Table 4 Bond Strength Data for Set 1

#	Heat Sealing Parameters			Bond strength at location 1 (N/mm)	Bond strength at location 2 (N/mm)	Average bond strength (N/mm)
	X	Y	Z			
1	4.5	110	1.5	5.68	5.87	5.78
2	4.5	110	1.5	6.17	5.70	5.93
3	4.5	110	1.5	5.07	6.00	5.54

It was noticed that the average of the bond strength was 5.75 N/mm and the standard deviation is 0.1967 which yield and coefficient of variation of .0342. Hence, replicates at each corner are needed in the main experiment.

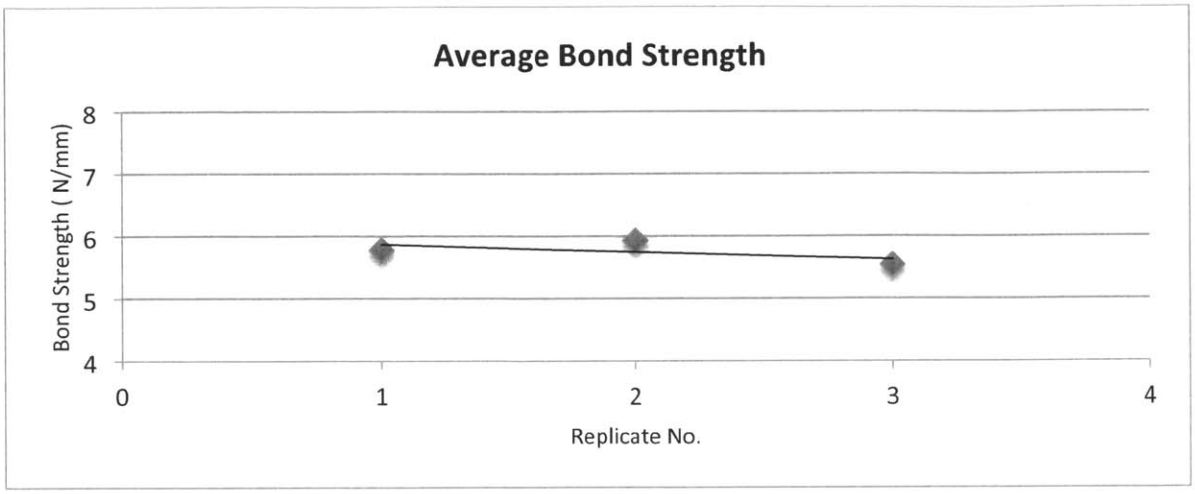


Figure 16 Bond Strength Data for Set1

5.1.2 Varying Parameter Z (Set 2)

Four experiments were run with parameter Z varying from 0.5 to 4.0 while keeping other parameters constant.

Table 5 Bond Strength Data for Set 2

#	Heat Sealing Parameters			Bond strength at location 1 (N/mm)	Bond strength at location 2 (N/mm)	Average bond strength (N/mm)
	X	Y	Z			
1	4.5	110	0.5	1.73	1.36	1.55
2	4.5	110	2.0	5.29	5.19	5.24
3	4.5	110	3.0	4.74	4.47	4.60
4	4.5	110	4.0	5.67	5.97	5.8

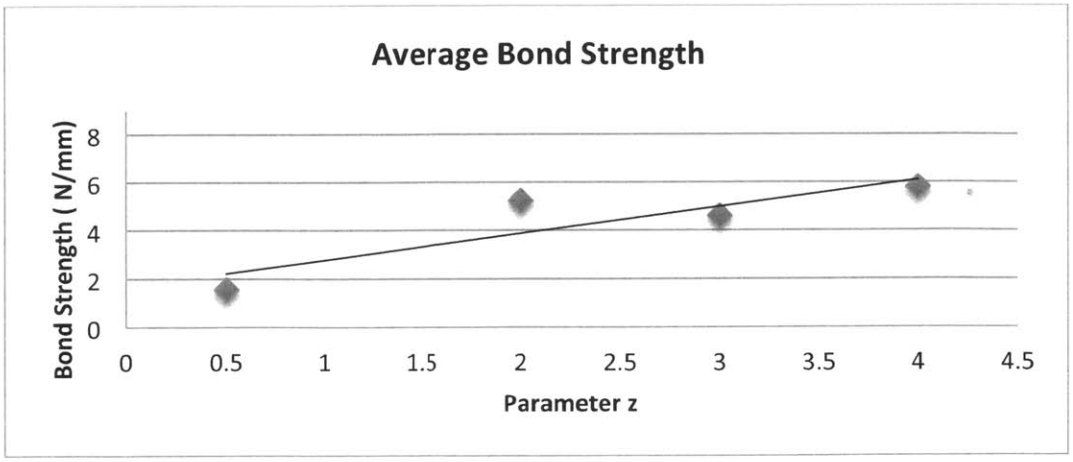


Figure 17 Bond Strength Data for Set 2

From Fig. 25, it can be concluded that there is a direct linear relationship between parameter Z and the bond strength. Thus, there is no need to take center points in the design of the main experiment i.e. parameter z will be run in two levels.

5.1.3 Varying Parameter X (Set 3)

Three experiments were run with Parameter X varying from 3.5 to 4.5 while keeping other parameters constant.

Table 6 Bond Strength Data for Set 3

#	Heat Sealing Parameters			Bond strength at location 1 (N/mm)	Bond strength at location 2 (N/mm)	Average Bond Strength (N/mm)
	X	Y	Z			
1	4.0	110	1.5	3.94	4.55	4.24
2	5.5	110	1.5	5.47	5.29	5.38
3	6.3	110	1.5	5.84	5.37	5.61

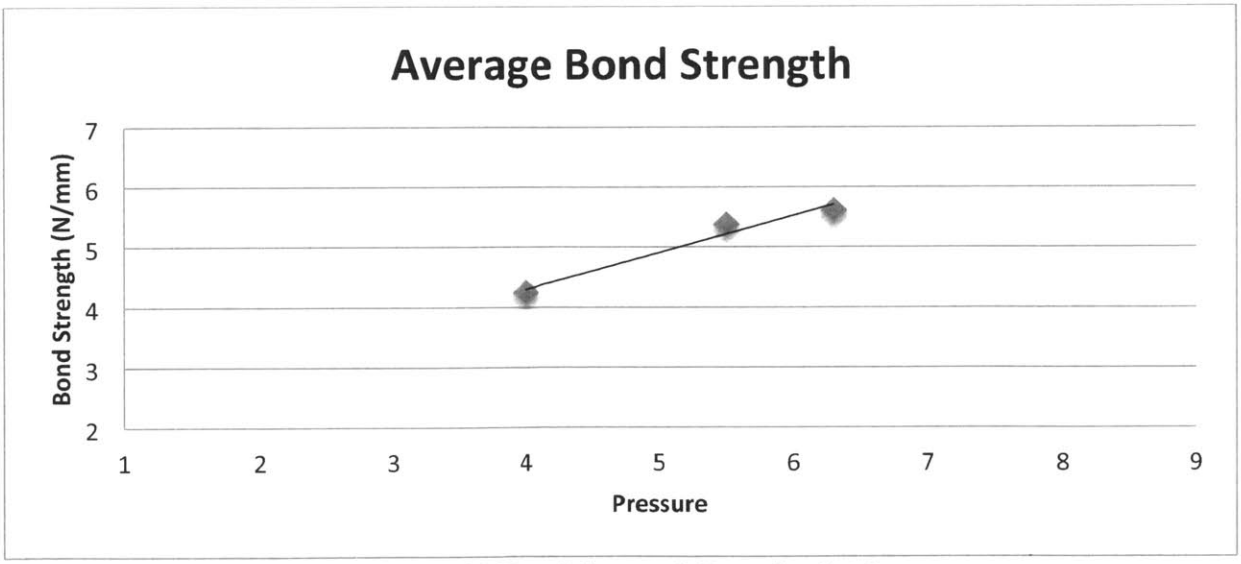


Figure 18 Bond Strength Data for Set 3

From fig. 26, it can be concluded that there is a direct linear relationship between the parameter X and the bond strength. Thus, there is no need to take center points in the design of the main experiment.

5.1.4 Varying Parameter y (Set 4)

Four experiments were run with the parameter y while keeping other parameters constant.

Table 7 Bond Strength Data for Set 4

#	Heat Sealing Parameters			Bond strength at location 1 (N/mm)	Bond strength at location 2 (N/mm)	Average bond Strength (N/mm)
	X	Y	Z			
1	4.5	75	1.5	0.62	0.48	0.5
2	4.5	95	1.5	2.38	1.78	2.08
3	4.5	125	1.5	3.94	2.91	3.42
4	4.5	140	1.5	4.18	2.94	3.56

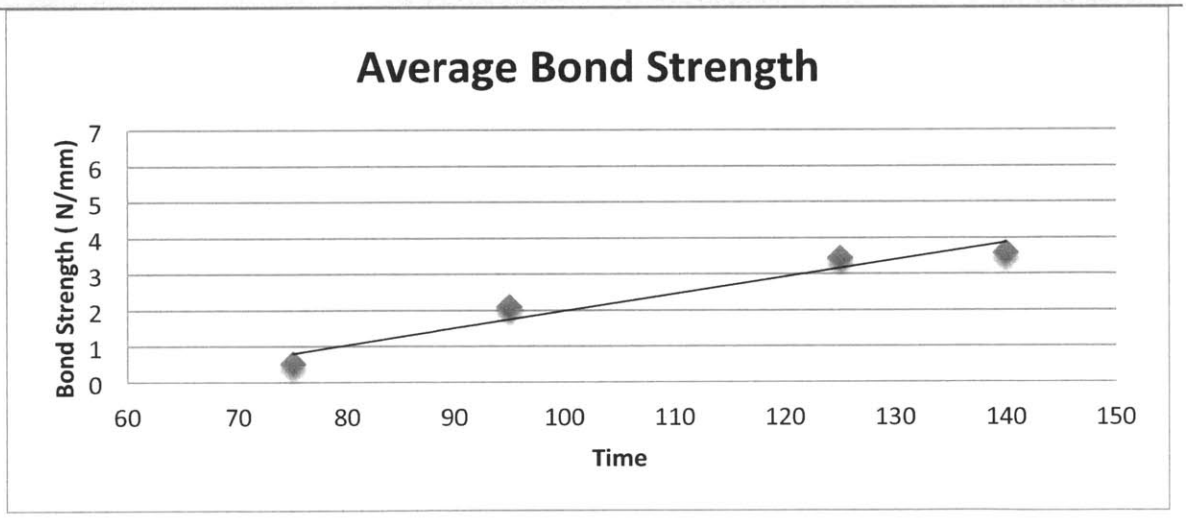


Figure 19 Bond Strength Data for Set 4

From fig. 27, it can be concluded that there is a direct linear relationship between parameter Y and the bond strength. Thus, there is no need to take center points in the design of the main experiment.

5.1.5 Conclusions from the preliminary Analysis

There is a considerable variation in the peel strength in the samples prepared under the same production parameters. Thus, the main experiment needs to be run with replicates (in this case and due to time limitations it would be 3) at each corner. Also, the relationship between production parameters and the bond strength is linear (in most of the cases) indicating there is no need for taking center points in the main experiment. Hence, the main experiment will be of two levels for each of the independent variables.

5.2 Main Experiment:

5.2.1 Background on Design of Experiment (DOE):

Objectives of DOE include but are not limited to:

1. Determining which independent variables are most influential on the response.
2. Determining where to set the influential independent variables to optimize the response.

In a DOE, Independent variables are varied intentionally in a systematic way to assess the effect of independent variables on the dependent ones. DOE, if well done, helps in reducing variability in quality characteristics and in optimizing the process.

The process, as shown in Fig. 28, can be visualized as some combination of machines, methods, and people that transforms an input material into an output product. This output product has one or more observable quality characteristics or responses. Some of the independent variables **x1** , **x2** , . . . , **xp** and the y is the response or the dependent variables.

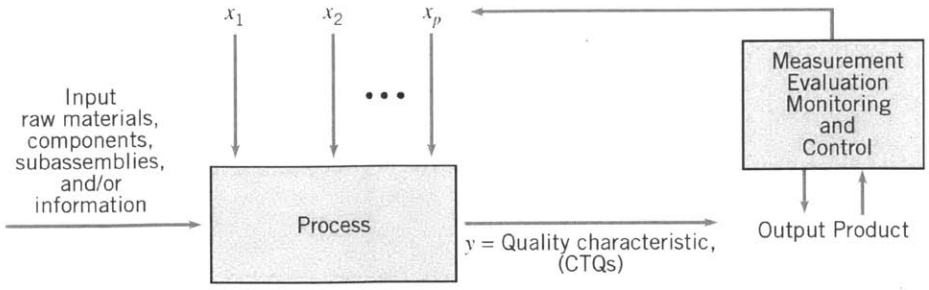
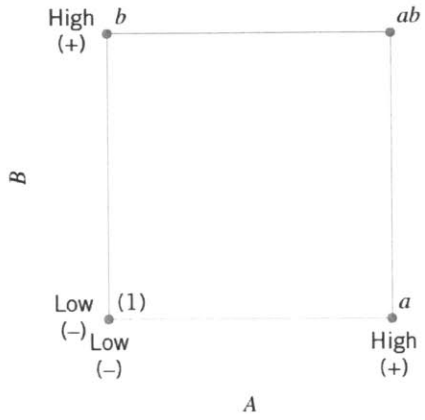


Figure 20 A Typical Process [19]

There are a handful of designed experiments types. One of the important ones is the factorial design, an experiment consisting of two independent variables or more varied

until all possible combinations of factors levels had been achieved.

One of the common factorial designs is the 2^2, i.e. 2 factors each with two levels. The number of runs associated with such common factorial design is 4 as shown in figure 5.



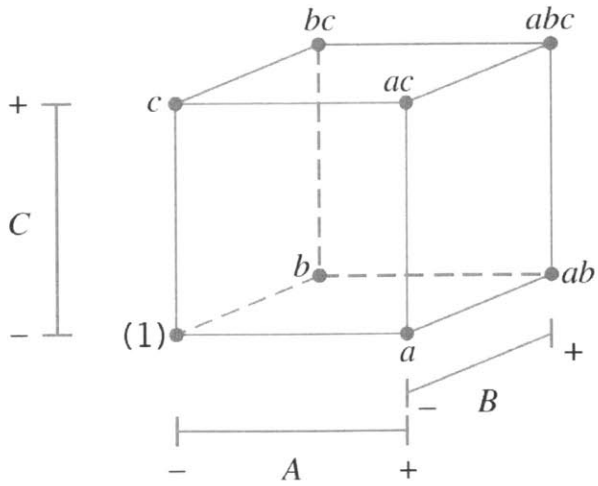
(*a*) Design geometry

A	B
–	–
+	–
–	+
+	+

(*b*) Test matrix

Figure 21 2^2 Factorial Design [19]

Another common factorial design is 2^3 factorial design (3 independent variables each with two levels). Number of runs for this design is 8 as shown in figure 2^3.



A	B	C
–	–	–
+	–	–
–	+	–
+	+	–
–	–	+
+	–	+
–	+	+
+	+	+

(*a*) Design geometry

(*b*) Test matrix

Figure 22 2^3 Factorial Design [19]

In general, for K number of factors, the number of runs is 2^K. As the number of factors in a 2^K design increases, the number of runs required increases accordingly. It is not possible and sometimes meaningless to do all the runs especially with high number of factors and levels. Hence arises the importance of fractional factorial design of experiment, which is defined by the American Society of Quality (ASQ) as " A factorial experiment in which only an adequately chosen fraction of the treatment combinations required for the complete factorial experiment is selected to be run". [26] [27]

5.2.2 Main Experiment Design Space

From the preliminary analysis data, it can be concluded that there is some variability in the results indicating the need for having replicates at each corner. Also, the same data have shown that, when varying one variable, there is linearity in the relationship between the varied variable and the results, indicating there is no need for center points, i.e. two levels for each variable are enough. Hence we will be having a 2^3 full factorial experiment with three replicates at each corner. Dependent variables are the bond strength and the flow pattern. Limits of the independent variables are shown in the following table.

Table 8 Coding of the Independent Variables of the Experiment

Independent variables					
Parameter X		Parameter Y		Parameter Z	
-1	+1	-1	+1	-1	+1
5	5	100	120	1	3

5.2.3 Discussion on the Bond Strength Results

5.2.3.1 Results:

Table 9 Bond Strength Data of the Main Experiment

Run #	X	Z	Y	Avg. Bond Strength
1	4	1	100	3.19
2	5	1	100	3.66
3	4	3	100	3.09
4	5	3	100	4.2
5	4	1	120	4.2
6	5	1	120	5.38
7	4	3	120	5.44
8	5	3	120	5.33
9	4	1	100	3.23
10	5	1	100	3.65
11	4	3	100	3.27
12	5	3	100	4
13	4	1	120	4.73
14	5	1	120	4.21
15	4	3	120	5.42
16	5	3	120	5
17	4	1	100	3.14
18	5	1	100	2.92
19	4	3	100	2.7
20	5	3	100	4.38
21	4	1	120	4.08
22	5	1	120	4
23	4	3	120	5
24	5	3	120	5.68
25	4.5	1.5	110	5.05
26	4.5	1.5	110	5.02
27	4.5	1.5	110	4.75

5.2.3.2 Results Analysis:

Regression model

The following regression model was attained:

Avg. Bond Strength = - 6.00 + 0.410 Parameter X + 0.297 Parameter Z + 0.0710 Parameter Y

Equation 8

Where:

4 < Parameter X < 5

110 < Parameter Y < 120

1 < Parameter Z < 3

R^2 for this model is 0.729.

Weight and effect of each parameter:

It was found that the most influential factors are: parameter y followed by parameter z followed by parameter x as shown in figure 32.

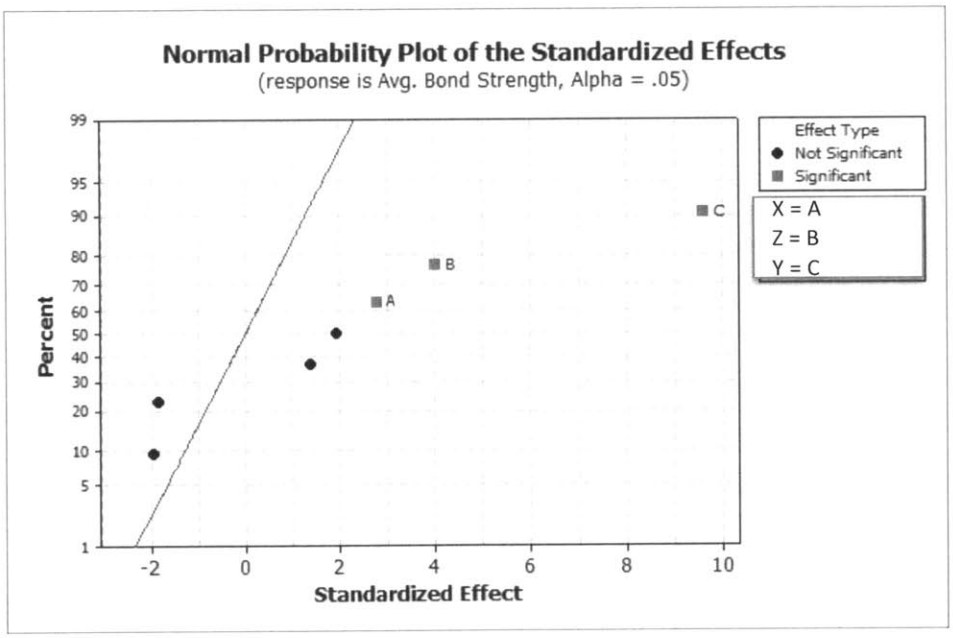


Figure 23 Standardized Effects of the Process Parameters on the Resulting Bond Strength

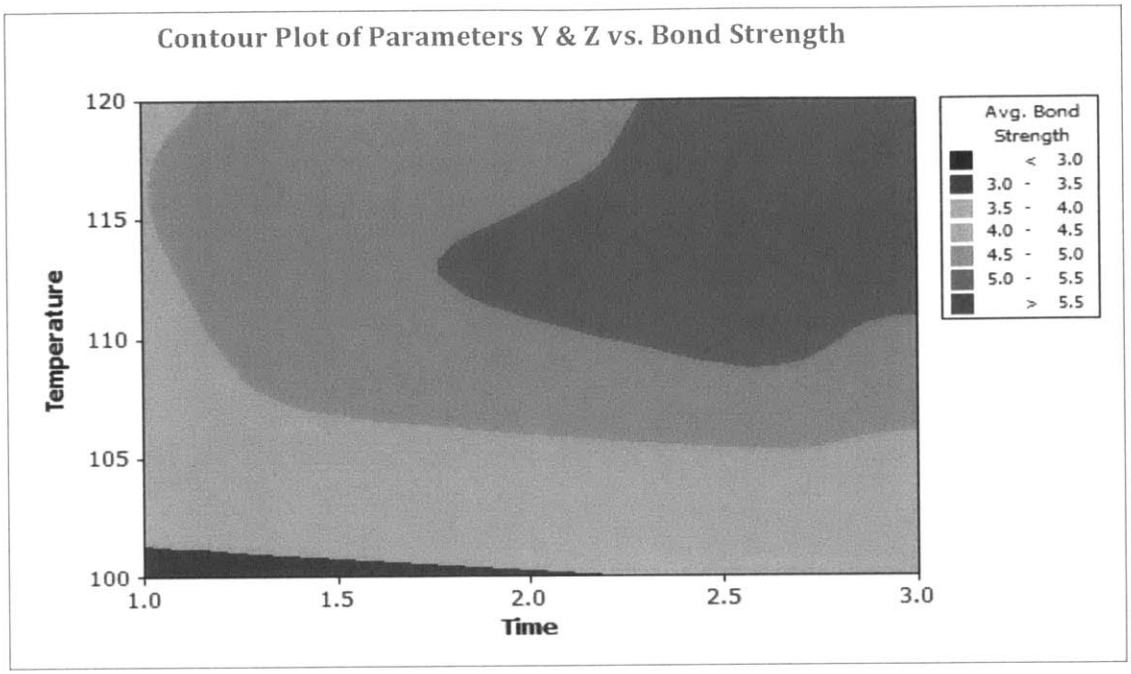


Figure 24 Contour Plot of Parameters Y & Z vs. Bond Strength

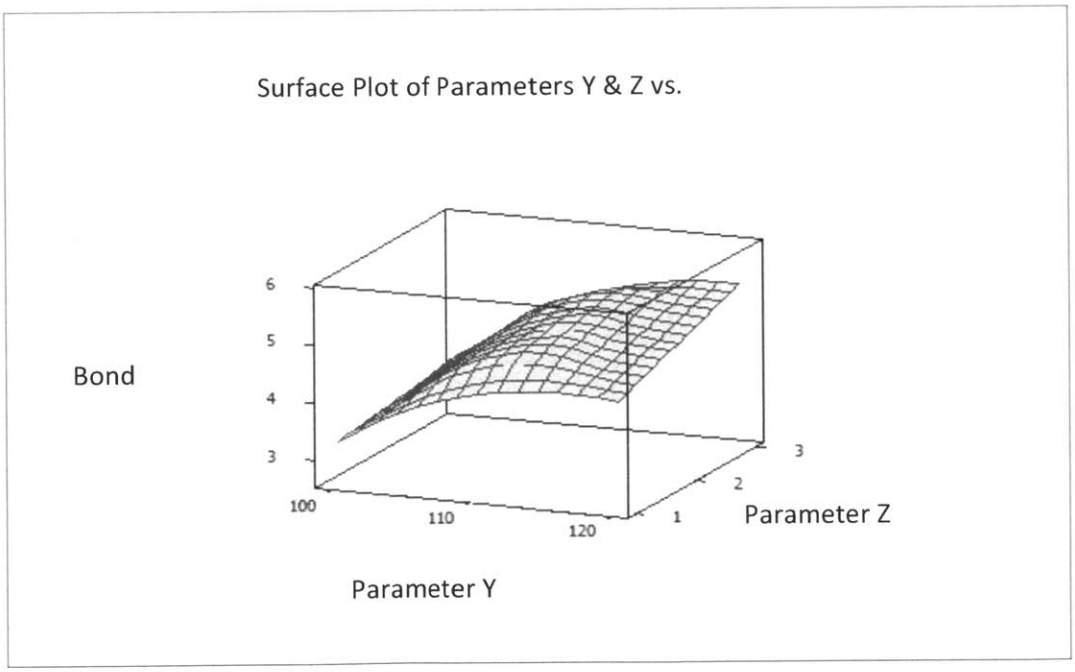


Figure 25 Surface Plot of the Parameters Y & Z vs. Bond Strength

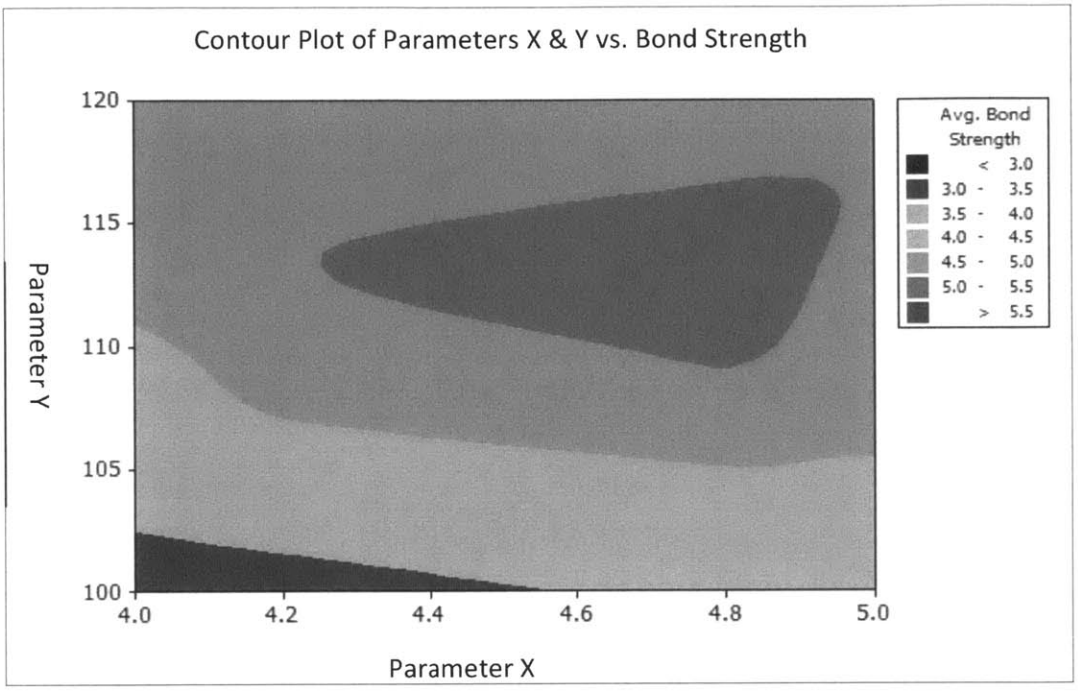


Figure 26 Contour Plot of Parameters X & Y vs. Bond Strength

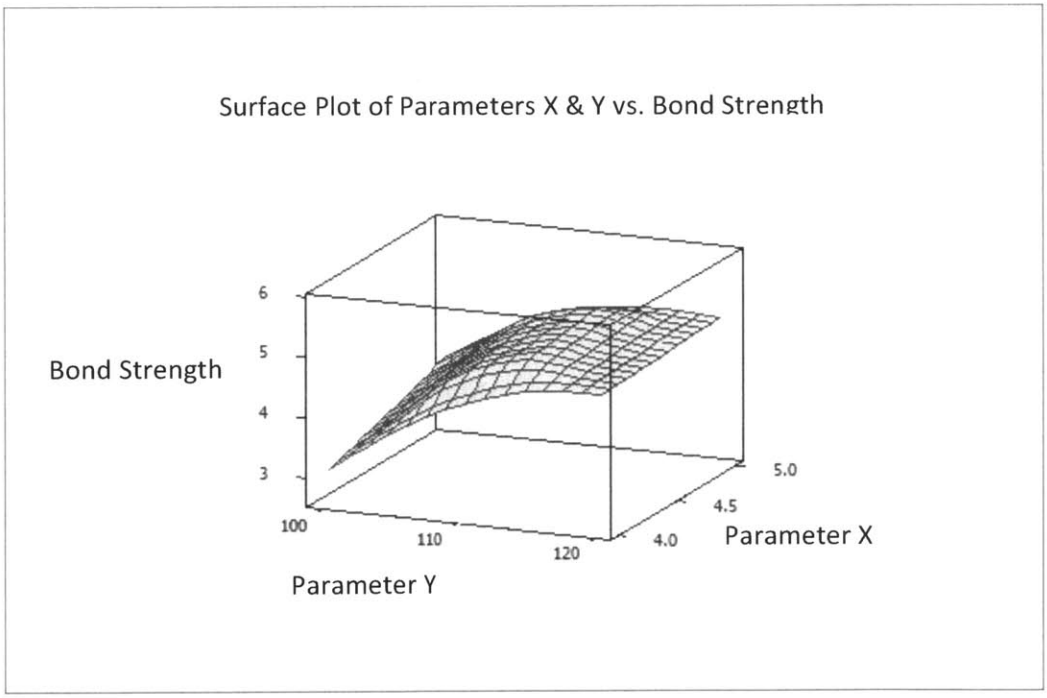


Figure 27 Surface Plot of Parameters X & Y vs. Bond Strength

5.2.3.3 Bond Strength distribution across the reagent-filled reservoirs:

The bond strength values are the averages of the whole length of the peeled stripes. It was noticed, however, that the bond strength over the peeled stripes is not equally distributed. At the optimal settings, the bond strength was even all over the peeled stripe as shown in fig. 39.

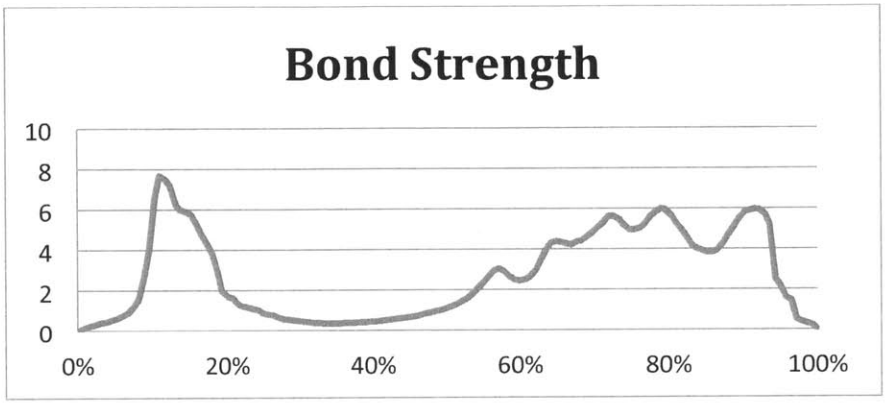


Figure 28 Bond Strength Profile of A Sample Prepared under a certain set of parameters

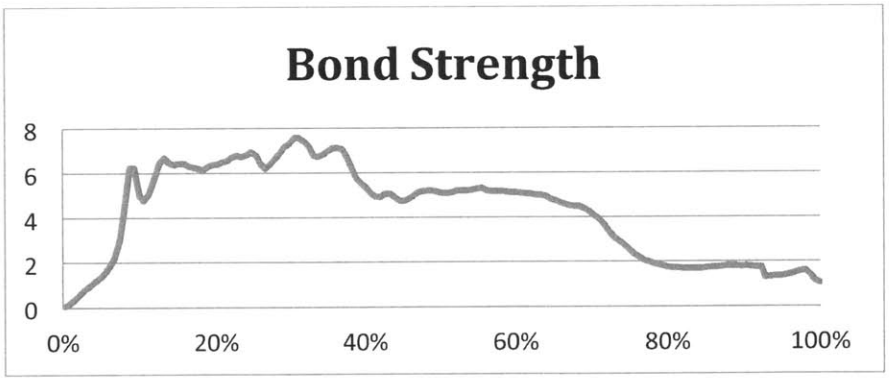


Figure 29 Bond Strength Profile of a Sample Prepared under a different set of parameters

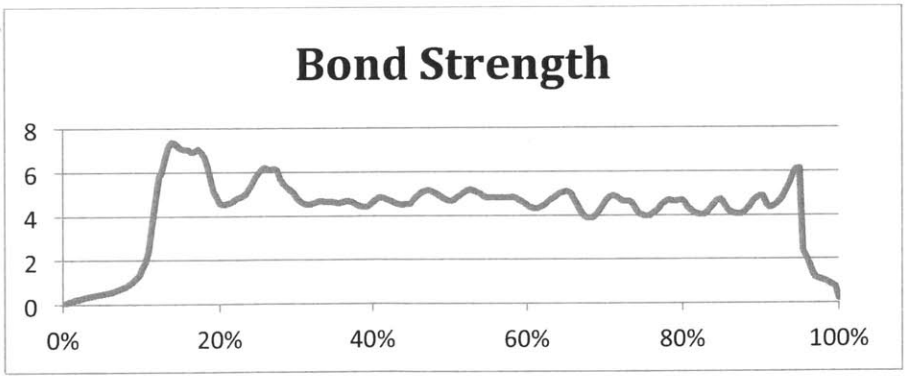


Figure 30 Bond Strength Profile of a Sample Prepared under optimal parameters

5.2.3.4 Flow Anomaly 1:

Flow Anomaly 1 Calculations were discussed in the methodology section.

5.2.3.4.1 Results

Table 10 Results of Flow Anomaly 1

Run	Parameter X	Parameter Z	Parameter Y	Flow Anomaly 1
1	4	1	100	1.10167
2	5	1	100	0.47
3	4	3	100	3.31383
4	5	3	100	2.178
5	4	1	120	1.29438
6	5	1	120	6.27667
7	4	1	100	1.09273
8	5	1	100	0
9	4	3	100	3.72
10	5	3	100	4.55667
11	4	1	120	1.39833
12	5	1	120	3.83667
13	4	1	100	0
14	5	1	100	0.31
15	4	3	100	4.18783
16	5	3	100	2.114
17	4	1	120	3.27
18	5	1	120	4.955
19	4.5	2	110	2.755
20	4.5	2	110	2.83533
21	4.5	2	110	4.80067

5.2.3.4.2 Results Analysis:

Parameters that affect flow anomaly 1 the most is parameter Y followed by parameter Z followed by the interaction of Parameters X & Y.

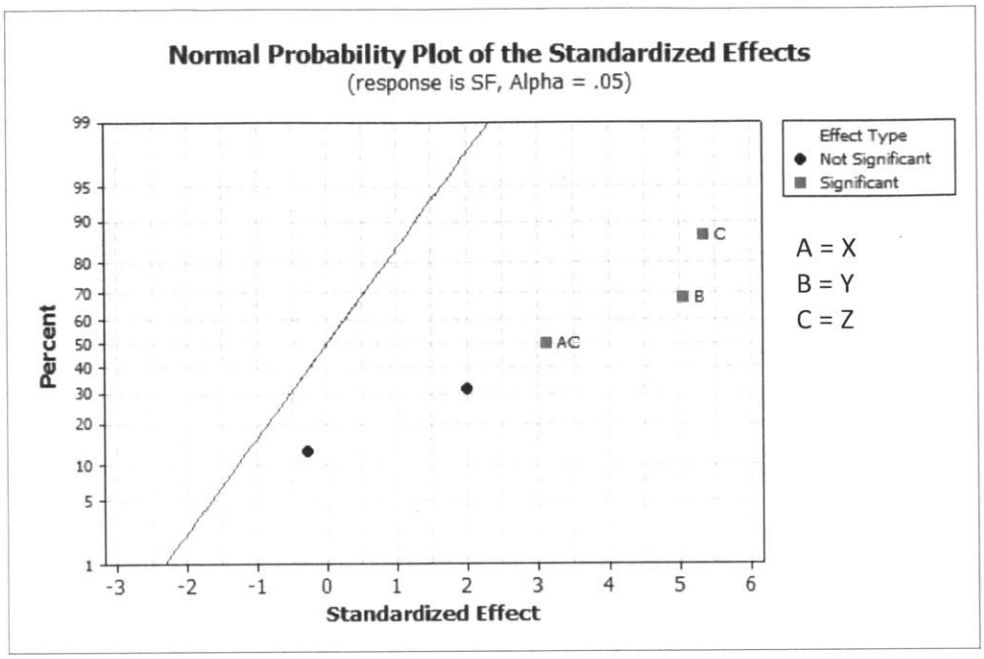


Figure 31 Significant Factors Affecting Flow Anomaly 1

5.2.3.4.3 Optimal Settings:

Optimal settings as shown in the previous figures are parameter X of 4 , parameter Z of 1 and parameter Y of 100. However, those settings result in high flow anomaly 2 as shown in the previous sections.

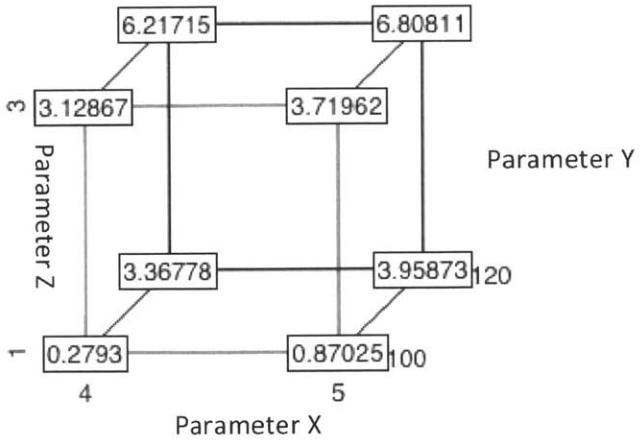


Figure 32 Cube Plot of Parameters X, Y & Z vs. Flow Anomaly 1

5.2.3.4 Flow Anomaly 2:

5.2.3.4.1 Results:

Flow Anomaly 2 Calculations were discussed in the methodology section.

Table 11 Average Flow Anomaly 2 Results

Run	X	Z	Y	Anomaly 2
1	4	1	100	2.32
2	5	1	100	1.25333
3	4	3	100	0.72
4	5	3	100	0.64
5	4	1	120	0.56
6	5	1	120	0.74667
7	4	1	100	1.57333
8	5	1	100	2.85091
9	4	3	100	0.66667
10	5	3	100	0.69333
11	4	1	120	0.85333
12	5	1	120	0.88
13	4	1	100	2.48
14	5	1	100	1.64
15	4	3	100	0.77333
16	5	3	100	1.09333
17	4	1	120	1.36
18	5	1	120	0.85333
19	4.5	1.5	110	0.74667
20	4.5	1.5	110	0.41333
21	4.5	1.5	110	1.01333

5.2.3.4.2 Results Analysis:

Factors that have significant effect on anomaly 2 are Parameters Y & Z.

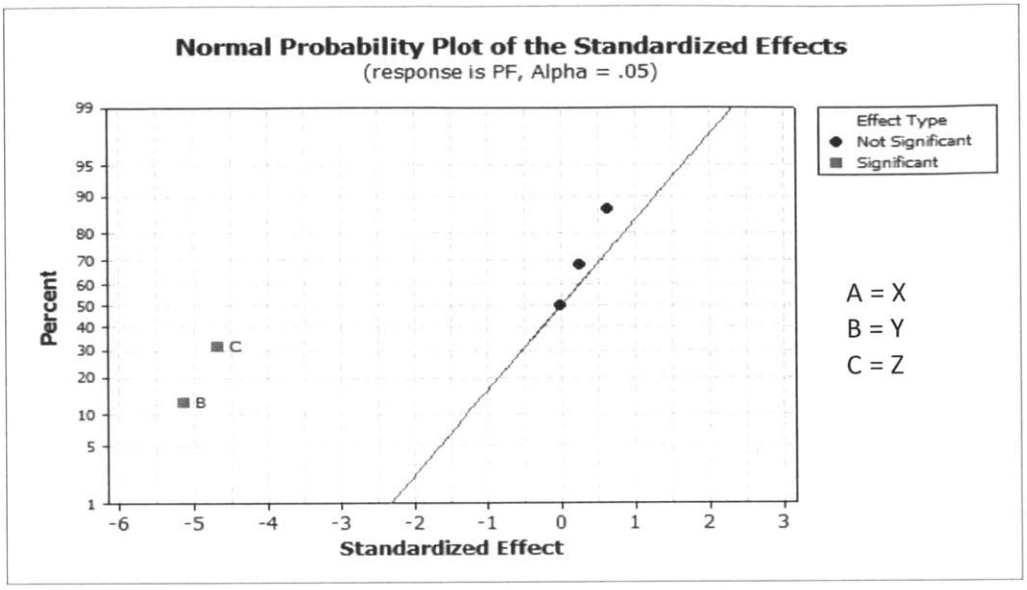


Figure 33 Standardized Effects of Process Parameters on Flow Anomaly 2

5.2.3.4.3 Optimal Settings:

As shown in fig.63 and fig.64, Anomaly 2 is more likely to occur at low settings of parameters Y & Z. Anomaly 2 values tend to improve (i.e. get lower) toward the high settings of parameters Y & Z.

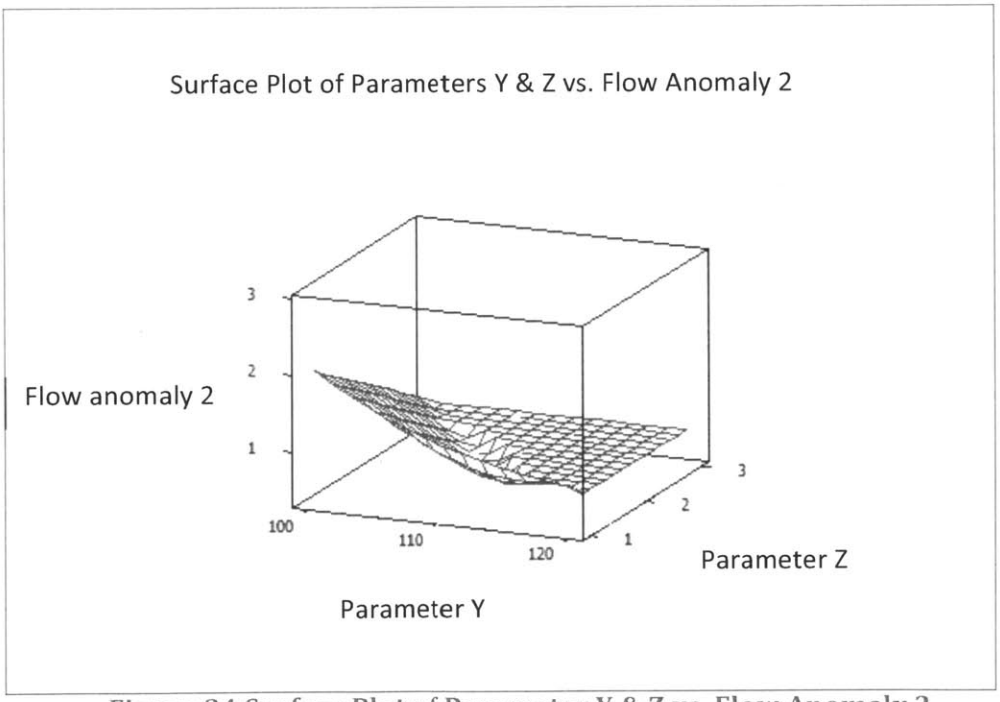


Figure 34 Surface Plot of Parameter Y & Z vs. Flow Anomaly 2

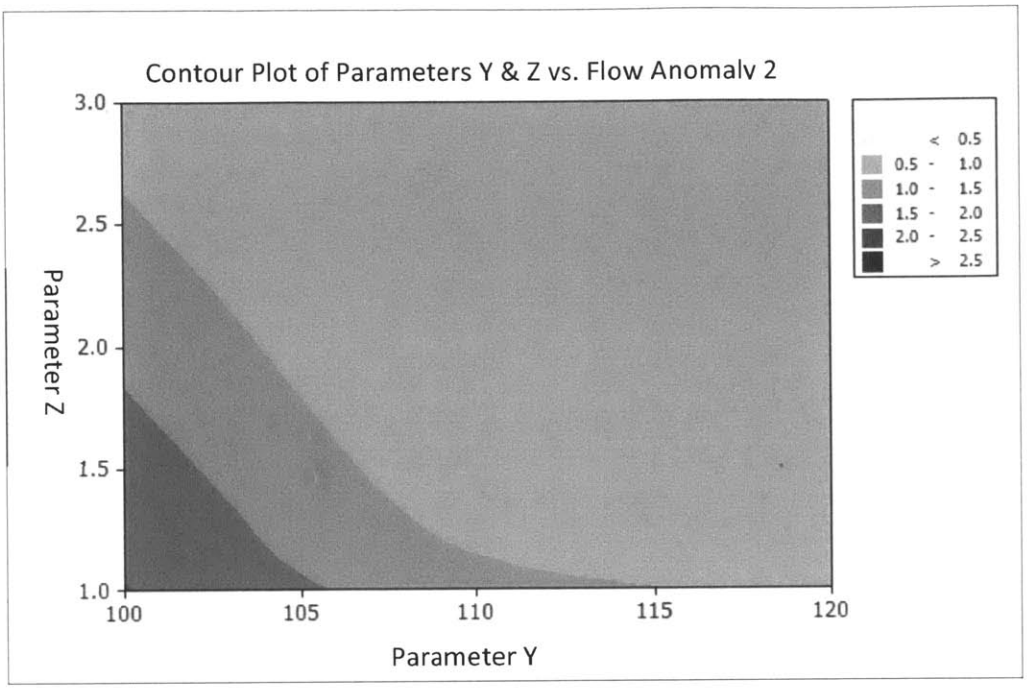


Figure 35 Contour Plot of Parameters Y & Z vs. Flow Anomaly 2

5.3 Overall Optimal Settings

Each of the two flow anomalies and the bond strength has its own optimal points. Hence, there has to be some tradeoffs.

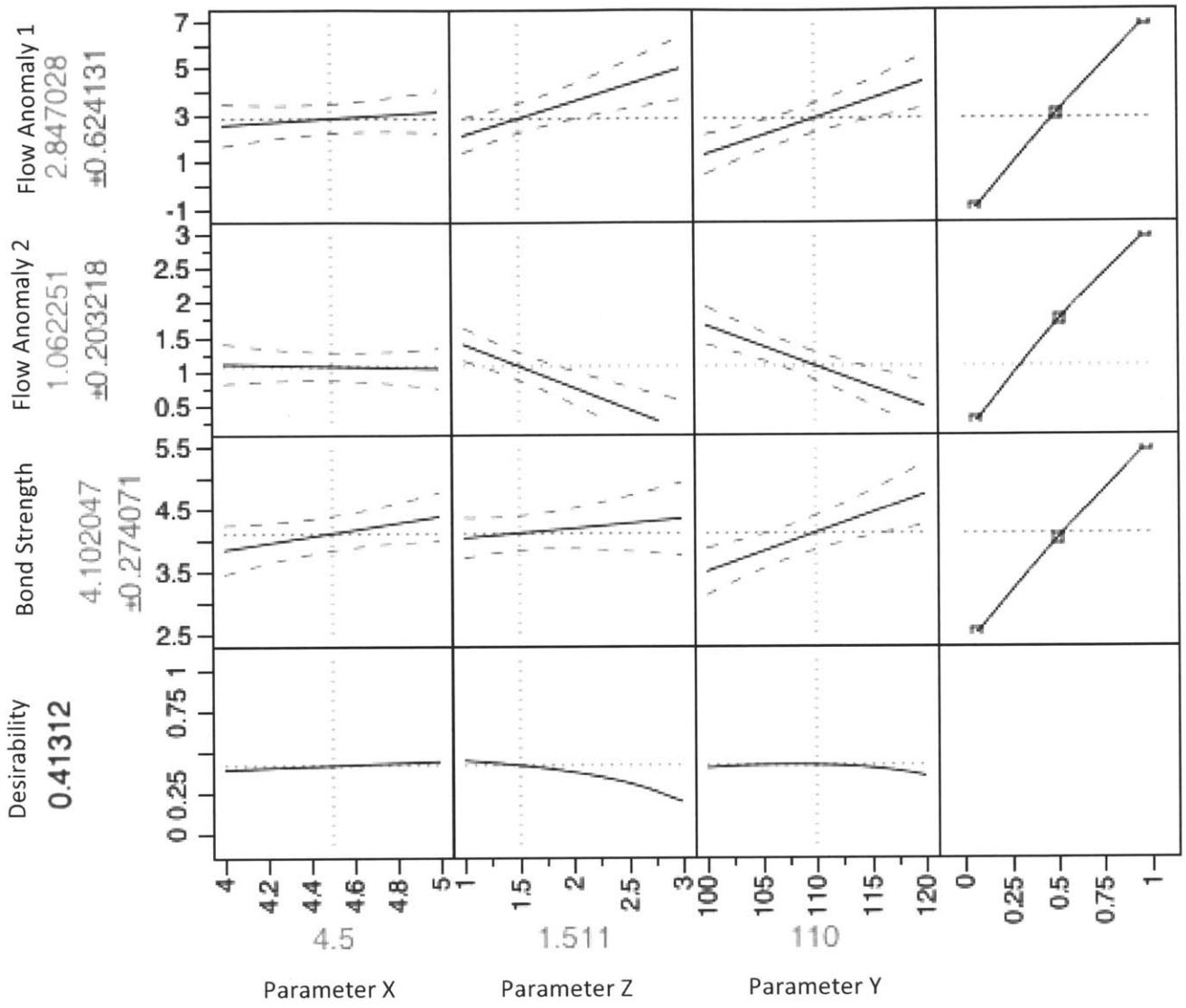


Figure 36 Overall Optimal Settings

5.4 Effect of Accelerated Aging:

5.4.1 On Bond Strength:

Due to the nature of the experiment, accelerated aging independent variable was tested in isolation of the other independent variable. For that purpose, small experiment was designed where the only variable was the accelerated aging. It was a 2^1 experiment with three replicates. The production was done according to the optimal parameters.

Table 12 Bond Strength Data for Aged and Non-Aged Samples

Run	Aging	Avg. Bond Strength
1	-1	5.78
2	-1	5.93
3	-1	6.46
4	1	5.9
5	1	5.215
6	1	5.28

Table 13 ANOVA for the Effect of Aging on the Bond Strength

Source	DF	SS	MS	F	P
Aging	1	0.525	0.525	3.8	0.12
Error	4	0.541	0.135		
Total	5	1.066			

The results show that, with a confidence of 88% , the aging resulted in a drop of the bond strength. That drop was 10.8 % . Peel strength profile was not affected though.

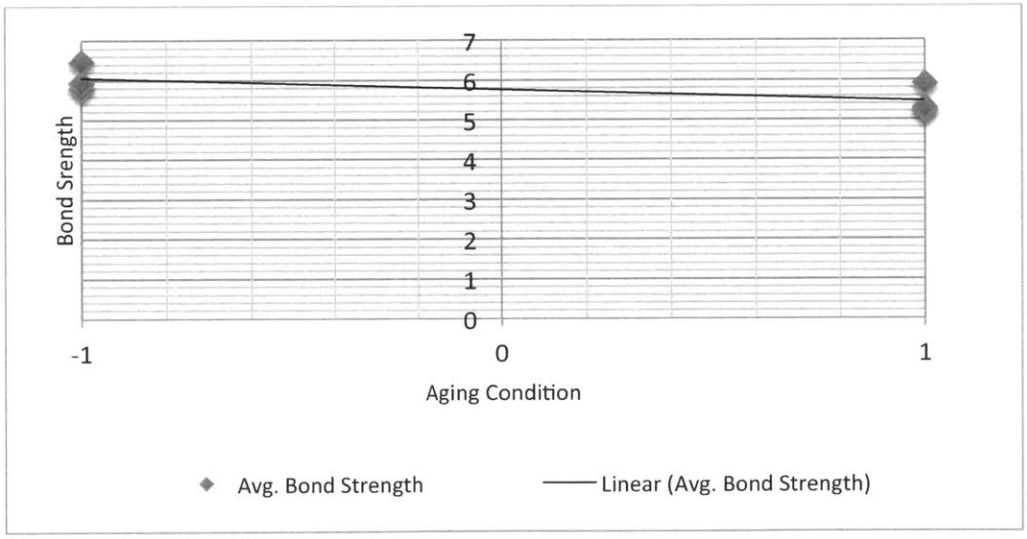


Figure 37 Effect of Accelerated Aging on Bond Strength

5.4.2 On Flow:

5.4.2.1 Flow Anomaly 1:

With a confidence of 48%, it can be said that accelerated aging didn't have an effect on the Flow Anomaly 1 as shown in the following tables.

Table 14 Flow Anomaly 1 Data for the Aging Experiment

Run	Aging	Anomaly 1
1	-1	6.506
2	-1	1.2467
3	1	4.1333
4	1	11.12

Table 15 ANOVA for the Effect of Aging on Flow Anomaly 1

Source	DF	SS	MS	F	P
Aging	1	14.1	14.1	0.74	0.481
Error	2	38.2	19.1		
Total	3	52.3			

5.4.2.2 Flow Anomaly 2:

With a confidence of 68%, it can be said that accelerated aging didn't have an effect on flow anomaly 2 as shown in the following tables.

Table 16 Flow Anomaly 2 Data for the Aging Experiment

Run	Aging	Anomaly 2
1	-1	0.34667
2	-1	2.85333
3	1	2.53333
4	1	1.89333

Table 17 ANOVA for the Effect of Aging on Flow Anomaly 2

Source	DF	SS	MS	F	P
Aging	1	0.38	0.38	0.22	0.682
Error	2	3.35	1.67		
Total	3	3.72			

Chapter 6: Outsourcing for Startups

6.1 Background

One of the most important issues a startup needs to deal with is outsourcing. A startup needs to have answers to questions like: whether to outsource or not, what to outsource, when to outsource and to whom.

Outsourcing as defined by Investopedia "is an effective cost-saving strategy when used properly. It is sometimes more affordable to purchase a good from companies with comparative advantages than it is to produce the good internally. An example of a manufacturing company outsourcing would be Dell buying some of its computer components from another manufacturer in order to save on production costs. Alternatively, businesses may decide to outsource bookkeeping duties to independent accounting firms, as it may be cheaper than retaining an in-house accountant."[28]

Outsourcing should not be done haphazardly. There are things that should be outsourced and things that should not. What should be outsourced depends on the type of the company and its business. In general, companies outsource the non-core functions.

6.2 Reasons to Outsource

There are multiple reasons why companies pursue the outsourcing option. Most common reasons include[30],[29]:

Cost savings:

Companies need to put big investments in internal infrastructure to be able to produce a new product or a new service. Outsourcing that product or service to a specialized vendor would save the company that big investment which makes outsourcing a more economical option at least on the short run. The Duke University study of the Fortune 500 found that "63 percent of respondents achieved greater than 30 percent annual savings. Fourteen percent reported savings greater than 50 percent."

Freeing up Capital Funds:

Instead of investing on peripheral or non-core business to the company, the saved cash can better utilized in growing the company's core business.

Risk Minimization:

The process of launching a new product or a service is inherently risky. Risks include financial, technological, regulatory changes, market, demand fluctuation...etc. Outsourcing helps the company in minimizing the associated risks through sharing them with another party i.e. outsourced-to vendor.

Lack of in House Resources:

Companies often lack some resources. Those resources include cash, time, R & D infrastructure ..etc. Outsourcing could be a viable solution to this problem.

Tapping into new markets:

Some companies also outsource to expand and gain access to new market in different geographic locations, by taking the point of production or service delivery closer to their end users.

Brining Credibility to the Company:

This reason is more of relevance to startups and small companies. Outsourcing the product development, or any other function, to a well-known company brings credibility to the small company and polishes its image in the market. That credibility helps small companies a lot in the early stages of the company's life.

6.3 Reasons not to Outsource

There are many reasons, on the other hand, not to outsource. Those reasons include [29],[30], [32]:

Loss of control:

When outsourcing a service or a product to another company, some of the control over that product or services gets transferred to the as well. Obviously, no company is in favor of losing control over any part of its business.

Hidden/Long term costs:

The vendor company will provide the product or service to the company at a premium. After few years, It would be more economical for the company to produce a product or a service in house. Although the outsourcing is seen as economical on the short run, it turns out to be more costly on the long run.

Also, it could me costly in a different way. Changes and modifications are very common for new services/products. Usually, changes not covered by the contract result in additional charges to the company.

Other hidden costs include the costs associated with:

- Feasibility study of the outsourcing option
- investigating and selecting a vendor
- transitioning work and knowledge to the outsourcer
- ongoing staffing and management of the outsourcing relationship. [29]

Security / Confidentiality Issues:

In some instances, the company needs to release some critical information (trade secret, Intellectual Property-related data..etc.) to the outsourced to vendor. Although, some type of Non Disclosure Agreement (NDA) is usually singed, yet the probability of those pieces of information getting leaked is still not negligible.

Quality issues:

Vendor companies, as it is the case with any company, are profit-driven. In the case of outsourcing, the contract and the price are already fixed and the only way to make more

profit is to cut costs. Apparently, one of the easy ways to do so is to compromise the outsourced product's/service's quality. Also, Controlling the quality of outsourced products/services is more difficult and more costly than controlling the quality of in-house ones.

Employees Morale:

One of the main advantages of outsourcing is reducing costs (short run) by different means including manpower cutoff which takes place usually in the shape of employees layoff. It is needless to say that layoff is one of the most horrible employees' nightmares. The threat of layoff affects the employees morale negatively which in turn either decreases their productivity or incentivizes them to look for more secured jobs.

Dependence on another company:

By outsourcing, companies are depending on other companies to do parts of their business. It is likely that the outsourced to vendor goes bankrupt. Thus, the company is exposing parts of its business to higher risk.

6.4 Outsourcing and the US Labor Market/ Economy

Contrary to popular belief, Mankiw and Swagel in their paper "The Politics and Economics of Offshore Outsourcing", concluded that offshore outsourcing is unlikely to have accounted significantly to the job losses in the 2001-2004 downturn or the slow labor market rebound [35].

In another study on offshore outsourcing, it was found that the US's total gross gain of each dollar worth of work outsourced to India is $1.12 to $1.14[34]. In the same report containing the previous study, Mckinsey Global Institute stated:

"The current debate over offshoring of U.S. jobs is missing the mark. Short-term disruption from job losses must be weighed against the much broader benefit to U.S. consumers and businesses, and the consequences of resisting change. If U.S. companies can't move work abroad, they will become less competitive – weakening the economy and endangering still more jobs – and miss the chance to raise their productivity and concentrate resources on

the creation of higher value jobs. Some workers will need help to make the transition. But globalization's reputation as the enemy is now the real threat to the U.S. economy." [35]

6.5 Insourcing

Opposite to outsourcing is insourcing. Insourcing is defined by the Business Dictionary as "Delegating a job to someone within a company, as opposed to someone outside of the company (outsourcing). One reason for insourcing to occur is if a company had previously outsourced a certain task, but was no longer satisfied with the work being done on that task, so the company could therefore insource the task and assign it to someone within the company who they believe will do a better job."

Over the past 15 years, there was 117 % increase in insourcing in manufacturing sector in the US compared to 82% increase in all sectors.

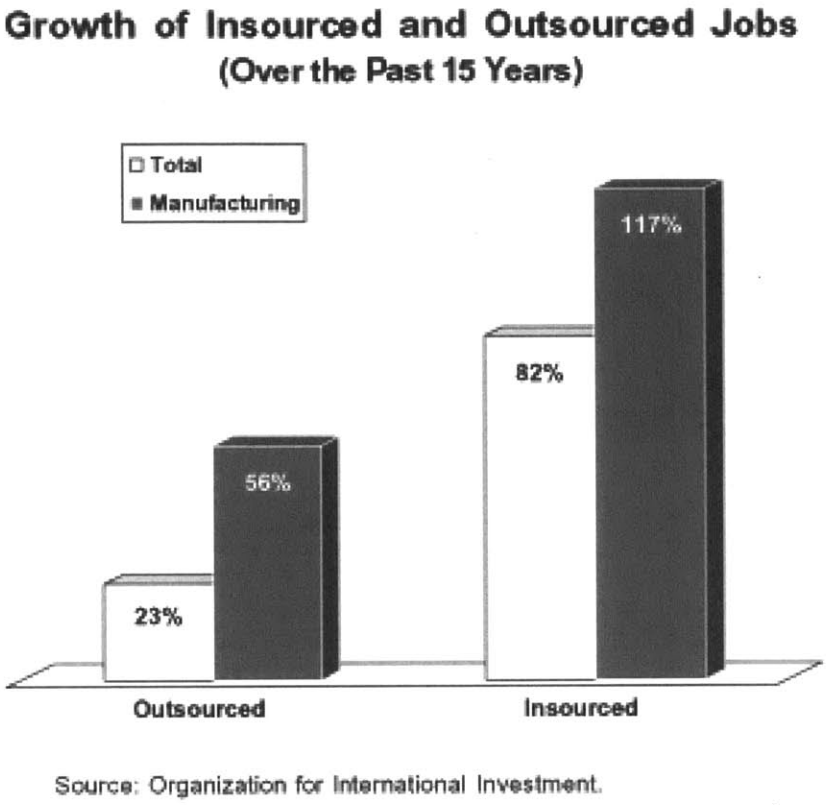


Figure 38 Growth of Insourced and Outsourced Jobs (over the past 15 years) [33]

6.6 Some Companies' Experiences with Outsourcing

Deloitte issued an insightful report on outsourcing /insourcing for a number of companies in different business. More details about the sample used in the report can be found in Fig. 39.

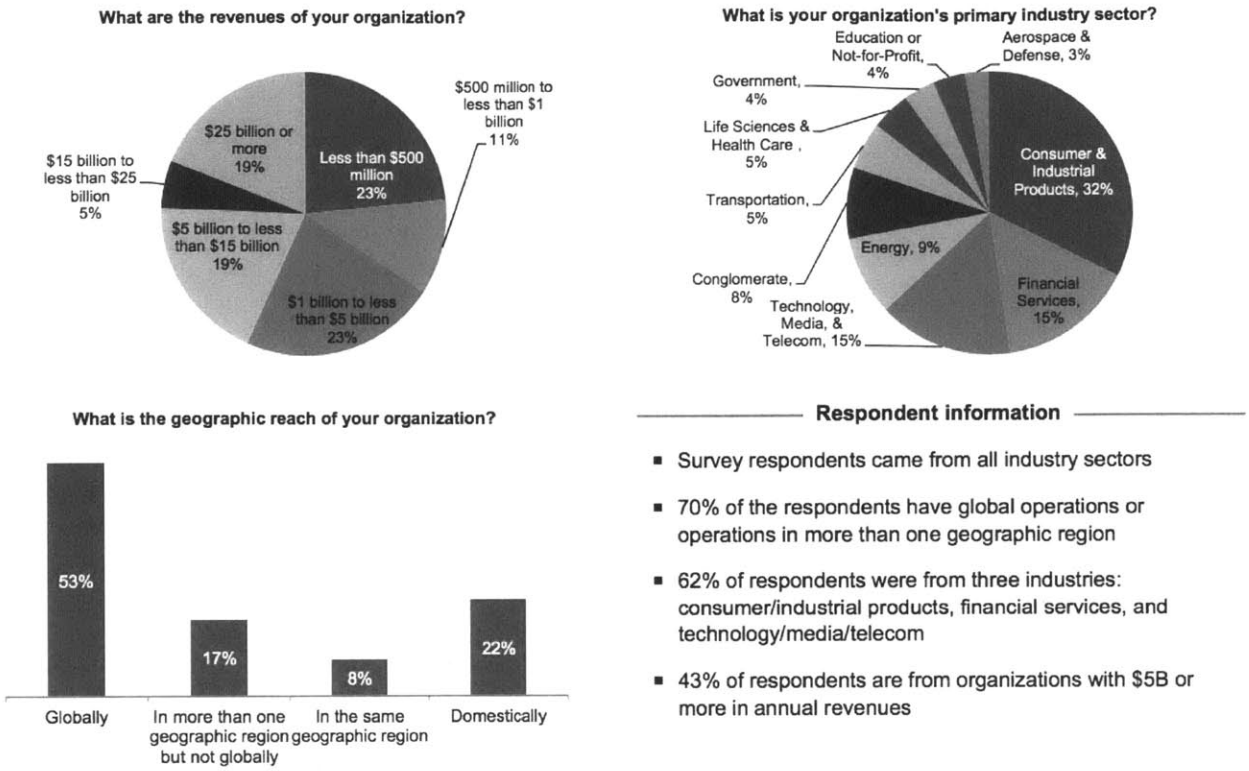


Figure 39 Details of the Sample Used in Deloitte's Study [31]

It was found that almost 70% of the companies were satisfied with their recent outsourcing experience and 7% were extremely satisfied. The rest were either neutral or dissatisfied about their most recent outsourcing experience. The latter group attributed their response to a number of reasons. The two main reasons are the fact that vendors underestimated the scope and the lack of service level attainment. The rest of the reasons are shown in Fig. 40.

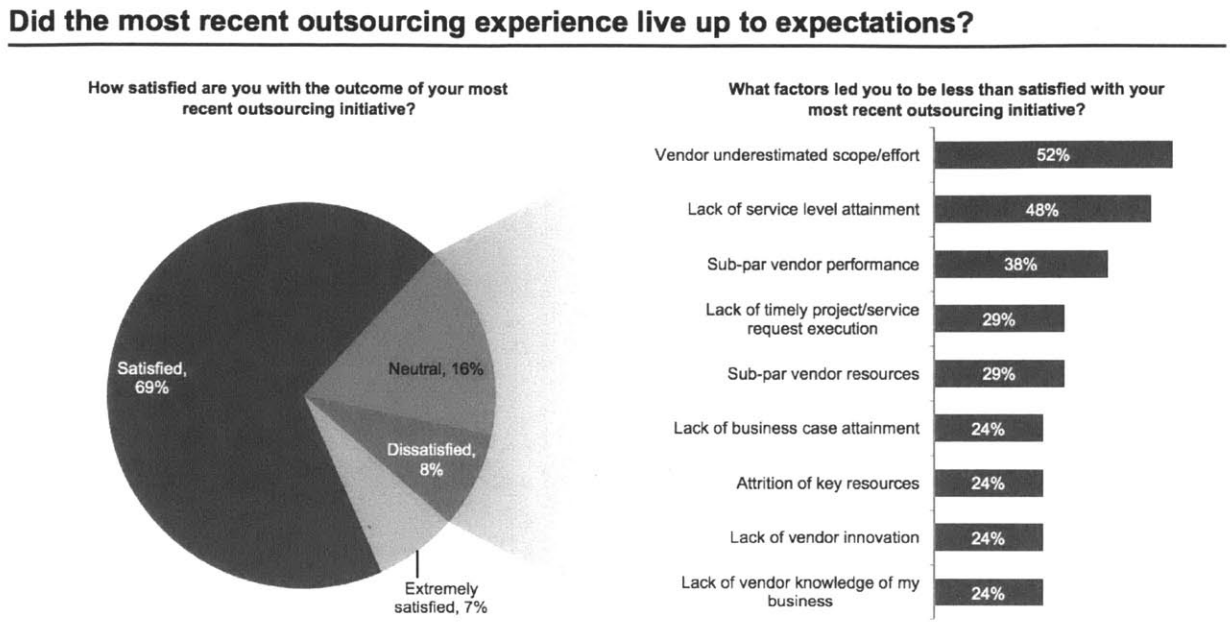


Figure 40 Outsourcing Experience and Expectation [31]

Terminating an outsourcing contract is not an unusual thing to happen. It was found that almost half of the companies usually terminate some of the outsourcing contracts they previously did. The overwhelming majority of those companies attributed the contract termination to the poor overall quality of the service. Other reasons included but were not limited to pricing, communication, and transition-related issues. More insight on the termination reasons is provided in Fig. 41.

How commonly are contracts terminated for cause or convenience?

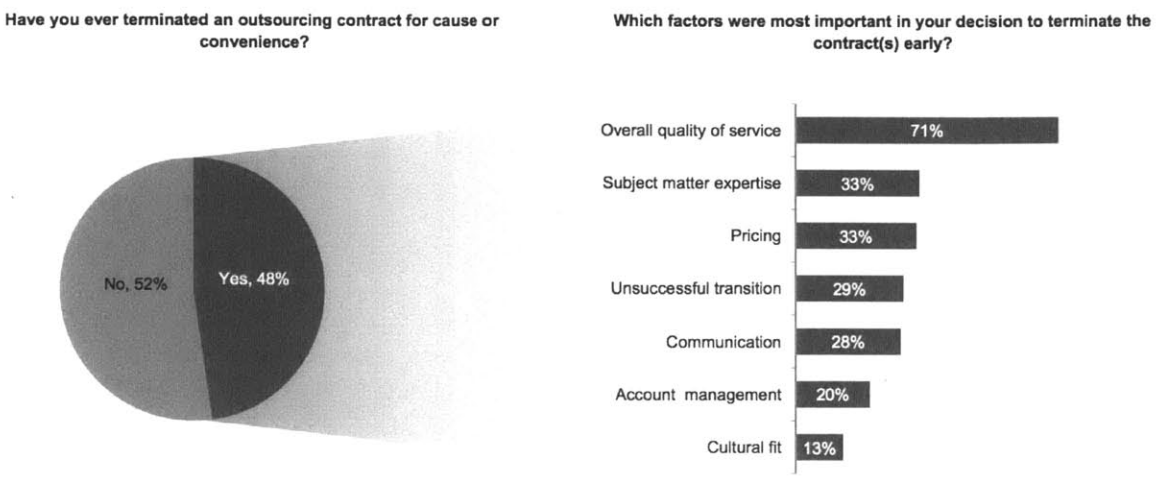


Figure 41 How Common Contracts Are Being Terminated [31]

Of those terminated the contract, 66% continued with outsourcing but switched to another vendor while the remaining 34 % reverted back to doing the previously outsourced function in-house (insourced). Almost 80% of those who insourced, were either extremely satisfied or satisfied with the insourcing option they had pursued and 20% were neutral about the outcome of their decision to insource. Main factors affecting the insource decision, as per the insuring companies, were: improving customers service, improving controls and reducing operation costs. More details are provided in Fig.42.

Having said that, it should be noted that going back and forth between insourcing and outsourcing is not a cost-free process. The decision either to outsource or to insource should be analyzed thoroughly beforehand [31].

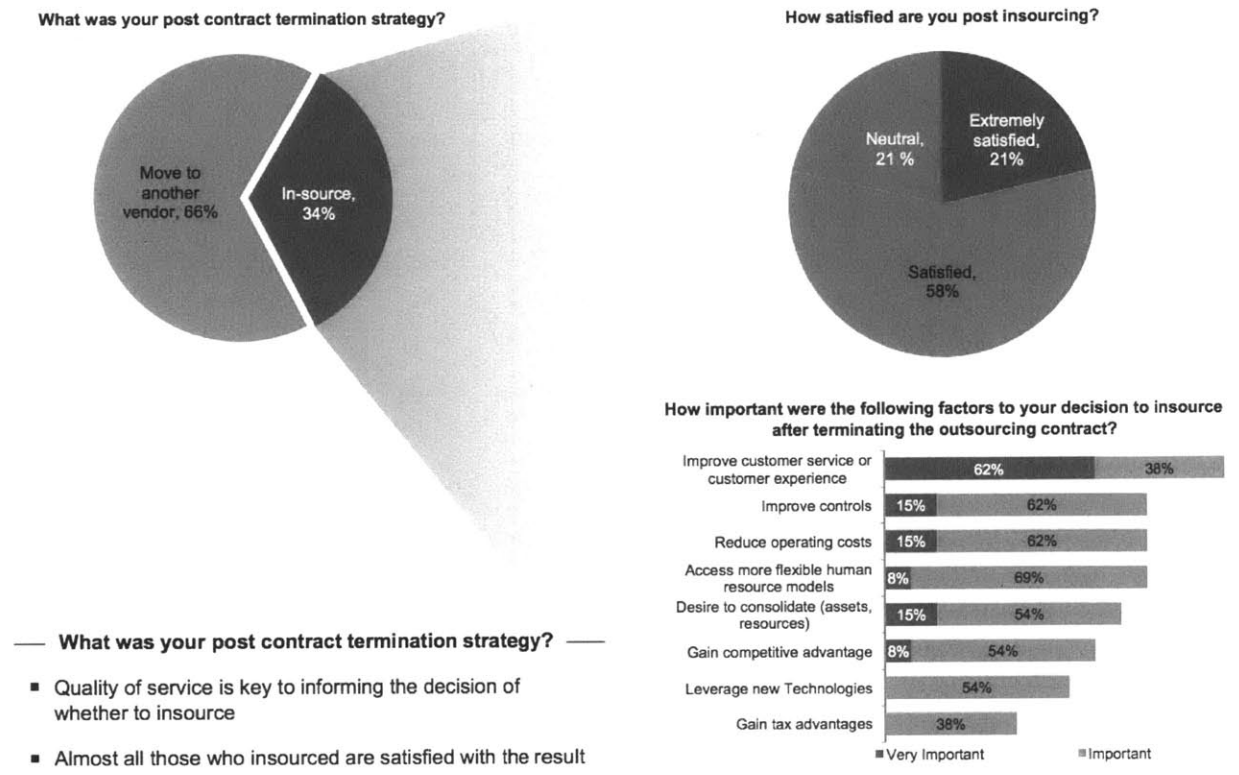


Figure 42 Effectiveness of the Contract Termination [31]

Chapter 7: Conclusions

The most significant factors in the heat-sealing process are parameter y followed by parameter z. The effect of parameter x, however, was negligible.

The best bonding strength was of 5.34 N/mm and it was attained through running the bond process under parameter x = 5, parameter z = 3 , and parameter y = 120. The second best bond strength was 5.29 N/mm and it was attained by running the bond process under parameter x= 4, parameter z = 3 , and parameter y = 120. Those two settings, however, resulted in an excessive melting of the hot melt leading to blockage of the reservoir vias and hence preventing the reagents flow. The optimal settings that produced good bond

strength and don't block the reservoir via are parameter x = 4.5, parameter z = 1.5 and parameter y = 110 which yielded an average bond strength of 5.00 N/mm. This setting, also, resulted in a uniform bond strength profile across the peeled stripes.

Optimizing the bonding process improves the flow patterns but it does NOT eliminate the flow anomalies. Flow anomaly 2 is more likely to occur at the low setting of the bonding process parameters. The optimal settings that produce the best flow anomaly 2 results was found to be parameter x = 4.5, parameter z = 3 and parameter y =110. To the contrary, flow anomaly 1 is more likely to occur at the high settings of the bonding process parameters. Hence, settings that produce best flow anomaly 1 results are parameter x = 4 , parameter z = 1, and parameter y = 100.

Hence, the optimal settings that produce the best possible bond strength and flow pattern are parameter x = 4.5, parameter y = 110 and parameter z = 1.5.

A number of samples went through an accelerated aging at 50^{o} C for 17 days. That accelerated aging period is equivalent to a real time aging of 3.2 months. The accelerated aging resulted, with a confidence of 88%, a 10 % drop in the bond strength. It also affected the flow rate and flow pattern of the reagents. Those effects, however, were not statistically significant.

Chapter 8: Future Work

8.1 Aging Study

As seen in the effect of accelerated aging section (section 5.4), aged samples experienced 10% drop in the bond strength. With a confidence of 88%, that drop is attributed to the accelerated aging that lasted for 2 weeks (equivalent to a real time aging of 3 months). The lifetime of Daktari product, however, is more than 6 months. The product needs to go through accelerated aging for periods that is equivalent to the real lifetime of the product to see the effect on bond strength.

8.2 Uneven Bond Strength Across the Reagent-filled Reservoirs

Peel test results have shown that at some (low and high) bonding settings bond strength is not uniform across the peeled stripes. Uniform bond strength profile was attained by running the bonding process at the optimal settings. Yet, the uneven distribution of the bond strength needs to be studied and analyzed further as it might create some problems ranging from weakening bond strength to loss of containment (reagents in our case).

8.3 Volume of the Reagents in the Reservoirs

In the experiments carried out, the reservoirs were filled with 600 uL of deionized water. I assume that the volume of the deionized water in the reservoirs would affect the flow pattern, however, I didn't have time to vary the liquid volume and see its affect on the flow. That would be a good future work.

8.4 High Variability

Variability in the flow data was quite high. Variability was noticed among flow data of cards prepared under identical bonding settings. It was also noticed also among the flow results of the different reservoirs in the same card. Actually, there was variability even between the first flow step and the second flow step of the same reagent-filled reservoir. Sources of variability have to be further studied and analyzed to eliminate them.

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