The Effects of Laser Welding on Biodegradable Materials

Mark Dolan

Institute of Technology Sligo

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Original Work Statement

I, Mark Dolan indicate that this thesis is a fair representation of my own work.

Signed

Print Name	Signature	Date
Mark Dolan		
Dr. Richard Sherlock (Supervisor)		

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Mark

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Chapter 1 Introduction

This chapter discusses the current and future applications of Biomaterials in medical devices and summarises the Material Selection process in the initial stages of the Laser welding project. It will give a brief outline of each of the materials that were shortlisted as possible candidates for this project, and may include reasons as to why they were accepted/rejected. Also, a brief introduction to Laser Welding processes and applications.

INTRODUCTION

Laser welding and Biodegradable materials are used in diverse fields of science and engineering. Whether as an aid for joining materials in different constructions or as materials for such constructions, laser welding and biodegradable materials have insinuated themselves into almost all aspects of our lives. Biodegradable materials can be found in many areas including packaging, medical devices, waste management, building constructs, agriculture and clothing. Laser welding processes are also routinely used in many products that we consume, ranging in fields as diverse as automobile construction, Information Technology infrastructure, electronics manufacture and medical devices.

Despite the ubiquitous nature of these terms, very little work has been carried out to date on how one aspect affects the other. There are many bodies of knowledge present describing the laser welding process and or processes involving biodegradable material constructs but very little exists on how the former affects the latter. To this end, this body of knowledge aims to start a discussion on how laser welding affects the characteristics of biodegradable materials, specifically focussing on the medical device industry.

The reason for focussing on medical devices is due to the opinion of this researcher that at some point in the medical device lifecycle, laser welding may be incorporated into part or perhaps all of the medical device production cycle. The medical device industry is often highly regulated, especially when the device may be used in the area of human therapeutics. Because of these regulatory requirements, the manufacturers of these devices must be aware of all interactions between the material which the device is made from and the biological tissues surrounding it in order to be compliant with the regulatory authority. But, does the laser welding process affect the biodegradable properties of the material, and consequently, its interactions with the surrounding tissue? This is the question that this work intends to explore.

BIOMATERIALS

The term 'Biomaterial' is an umbrella name that covers a multitude of materials that are considered to biodegradable, bioresorbable, biocompatible or bioactive. Biomaterials occupy a central role over many fields and disciplines ranging from Waste Management, Energy production, Food Technology and Medical Sciences. This body of work will be more focused on possible applications within Medical Sciences, specifically Tissue Engineering, Drug Delivery and Medical Devices.

Biomaterials can be defined as substances in therapeutic or diagnostic systems that are in contact with biological fluids. Biomaterials require certain essential properties depending on the functionality of the final device. Properties such as blood compatibility, size, shape, and porosity must be controlled. For instance, for cardiovascular implants the devices have certain size requirements in order to avoid clotting; in drug delivery, the requirements are different: drug permeability, good release properties, etc.(Stamatialis et al. 2008)

The ideal material for use as a biomaterial would have the following properties:

1. does not evoke an inflammatory/toxic response, disproportionate to its beneficial effect,
2. is metabolized in the body after fulfilling its purpose leaving no trace,
3. is easily processed into the final product form, has acceptable shelf life,
4. is easily sterilized. (Middleton & Tipton 2000)

Biomaterials fall into three distinct categories of materials which are discussed below:

Ceramic Biomaterials

Most ceramics biomaterials are used to repair hard tissues in the body such as bone and dental work. Ceramics have good osteoconductivity properties (i.e. formation of hydroxyapaptites which are naturally occurring minerals that have a role in bone regrowth), but have a very low bioresorbabilty with the exception of tricalcium phosphate. Ceramics are relatively inert to body fluids, have high compressive strength and are difficult to shear due to the ionic nature of the chemical bonds. Ceramics have also found use as reinforcing components for implantable devices that are manufactured from different set of biomaterials. (Park & Bronzino 2002)

Metallic Biomaterials

Metals are used as biomaterials due to their excellent electrical and thermal conductivity and mechanical properties. Some metals are passive substitutes for hard tissue replacement such as total hip and knee joints, fracture healing aids, bone plates and screws, spinal fixation devices and dental implants. (Park & Bronzino 2002) Although some metallic components can degrade *in vivo* due to the presence of bodily fluids, this characteristic is not often encouraged because high levels of free metallic particles can be harmful and can cause toxic responses that outweigh their beneficial effects. Because of this, most metallic implants require surgical removal after their therapeutic lifecycle has come to an end. As a result more research is being undertaken to find substitute materials that can eliminate the need for subsequent surgical procedures.

Polymer Biomaterials

Polymers are molecules consisting of a large number of individual structural units, (called monomers) all joined together by covalent bonds to form chains. Polymers first came to light after the discovery of the tapping of *Hevea* rubber trees in the middle of the eighteenth century. Early technological applications of *Hevea* rubber began with efforts to discover the chemical nature of rubber, starting with the determination of its elemental composition in 1826. (Morawetz 2000). Despite been known to early explorers in the 16th Century, rubber remained a curiosity only until 1839 where it was found that through treatment with sulphur and heat, rubber's elastic properties could be made more permanent.(Dean 1987). This marked the beginning of scientific interest in polymeric materials. Since then numerous attempts have being made to adapt natural occurring polymers for use in the diverse fields to which we are familiar with today.

All polymers come in two distinct categories, natural and synthetic. Natural polymers are present in all organisms are produced during the growth cycles for example, protein expression in insects to create their chitin exoskeletons. Synthetic polymers are engineered molecules created under controlled conditions, such as ring opening polymerization to create materials with specific characteristics.

The most recognisable family of natural polymers are in the polysaccharide groups. Common members of the polysaccharide family are cellulose and starch. Both cellulose and starch are composed of hundreds or thousands of d-glucopyranoside repeating units. These units are linked together by acetal bonds formed between the hemi- acetal carbon atom, C1, of the cyclic glucose structure in one unit and a hydroxyl group at either the C3 (for cellulose and amylose) or the C6 (for the branch units in amylopectin) atoms in the adjacent unit. Both of these natural polymers are produced in green plants.

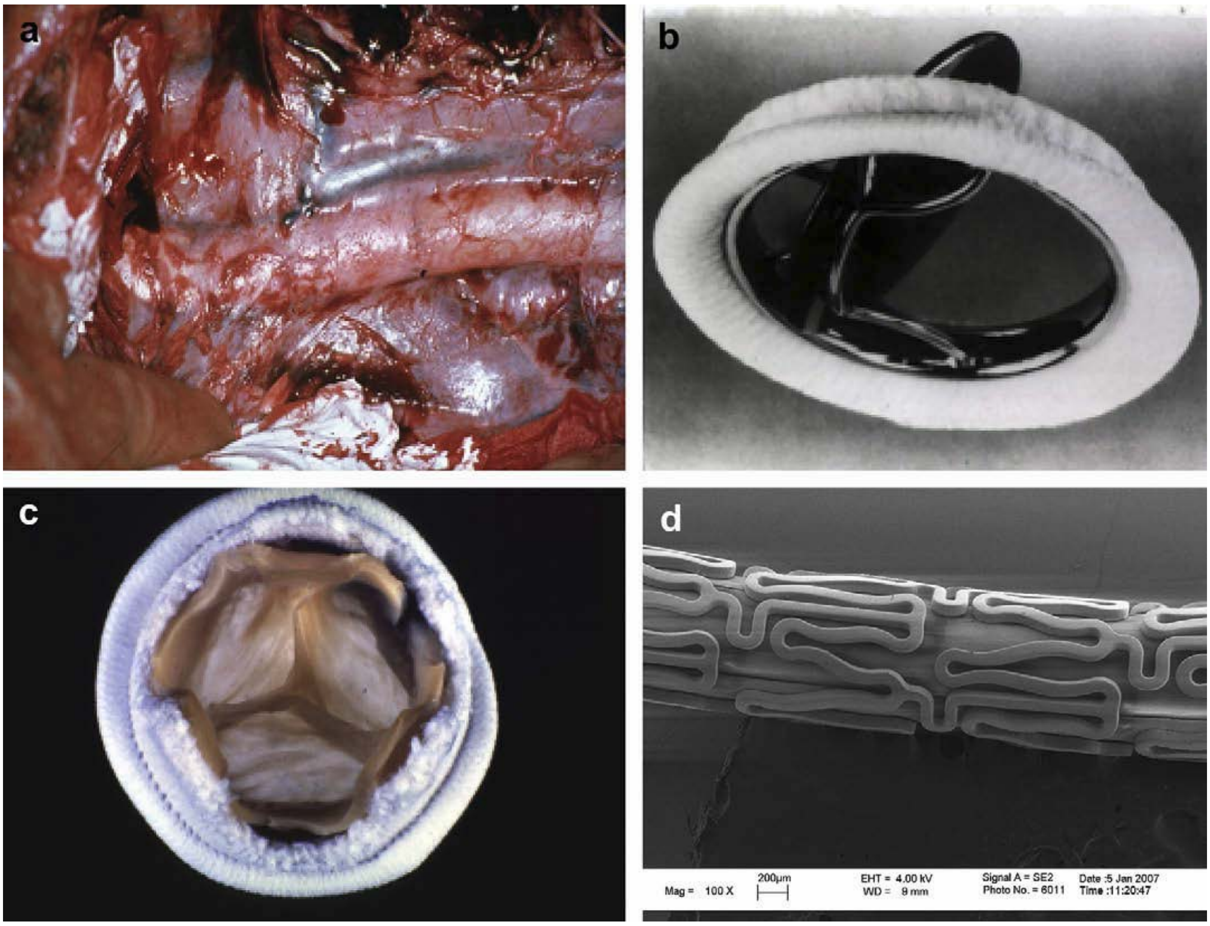


Figure 1 Examples of Biomaterials and their applications **(Williams 2009)**.

(a) Vascular graft; made from conventional textiles (polyethylene terephthalate) or microporous polymers (polytetrafluoro- ethylene), produced by standard textile or polymer processing techniques. (b) Mechanical heart valve; made from an alloy such as one based on titanium or cobalt-chromium, a carbon such as pyrolytic carbon, and a sewing ring made of a textile such as polyethylene terephthalate, produced by standard metal forming processes such as machining and electrochemical milling, chemical vapour deposition of carbon, and textile fabrication processes. (c) Bioprosthetic heart valve; made from natural porcine aortic valve or peri- cardium, with polymer (e.g. acetyl copolymer) or metal (e.g. Elgiloy) frame and sewing ring (as in (b) above), produced by standard materials processing techniques for the frame, and sequences of cutting, sewing and chemical treatment of the animal tissue. (d) Intravascular stent; made from either a self expanding, shape memory alloy such as nickel– titanium or a plastically deformable alloy such as stainless steel, sometimes coated with a drug-loaded polymer such as a paclitaxel or sirolimus loaded styrene–isobutylene–styrene triblock copolymer or polyethylene-co-vinyl acetate/poly n-butyl methacrylate copolymer, typically manufactured by laser cutting and polymer coating techniques. (Williams 2009)

BIODEGRADABLE POLYMERS

Significant advances have been made in the development of biodegradable polymeric materials for biomedical applications since the 1980's. The most promising candidates for developing therapeutic devices have been Degradable Polymeric biomaterials for diverse applications such as temporary prostheses, three-dimensional porous structures as scaffolds for tissue engineering and as controlled/sustained release drug delivery vehicles. In order to develop these applications to provide efficient therapy, specific material demands had to be taken into account for each material like physical, chemical, biological, biomechanical and degradation properties. As a result of these demands, a wide range of natural or synthetic polymers capable of undergoing degradation by hydrolytic or enzymatic route are being investigated for biomedical applications. (Nair & Laurencin 2007).

There were a number of points considered for the selection of a polymer for this research project:

1. There should be a good deal of background information available on the material. One of the characteristics that the material will be tested on is the effects the Laser Welding process has on the degradation properties. One of the vital pieces of information needed for the degradation experiments is the chemical structure of the monomer. Information such as Glass transition temperature (T_g), melting points, physical characteristics are also needed in order to build up Baseline from which to compare experimental results.

2. The next point was that the polymer would have a wide scope from which laser welding would be used at some point in the manufacture of products made from the particular material in question. Also, that the material can absorb the energy supplied by the Laser, which in this case was Carbon Dioxide.

3. The final point was that the material would be widely available. Manufacturing polymers from the initial monomer was also considered, but it was thought that

the time needed to optimize these processes would be prohibitively expensive time-wise.

Biodegradable polymers offer further benefits due to the fact that they will degrade away naturally inside the body, eliminating the need for further surgery to remove the delivery vehicle at the end of its life. The goal for any drug delivery system is one where the drug is completely encapsulated at a microscopic level. This increases biological activity, improves therapeutic effect by controlling the release rate. The most common biodegradable polymers that are finding use in this area are polylactide, polyglycolide and Polycaprolactone. (Chen et al. 2000)

Poly(Lactic Acid)

Poly(lactic acid) (PLA) is a high strength and high modulus thermoplastic, which can be easily processed by conventional processing techniques used for thermoplastics like injection moulding, blow moulding, thermoforming and extrusion. Lactic acid is easily obtained by a biotechnological process (usually based on the strain of a lactobacillus) from inexpensive raw materials. A large number of investigations have been carried out on PLA and its copolymers in biomedical applications for resorbable medical implants in the shape of rod, plate, screw, fibre, sheet, rod, sponge, beads for bone and tissue engineering, microsphere for drug delivery system, films or foils for wound treatment and for applications in agriculture like mulch films, slow release of pesticides and fertilisers. This made it an excellent candidate, as its chemical structure and T_G is well known. PLA is used for orthopaedic and oral surgeries as fixation of augmentation devices. (Gupta & Kumar 2007) In these cases, Laser welding may well be used in the manufacture of the devices. It is also widely available in various forms, meaning no need for further time consuming processing.

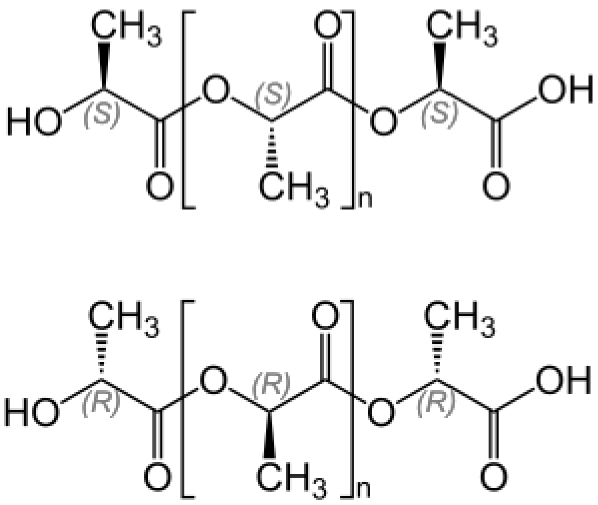


Figure 2 Chemical Structure of Poly(Lactic Acid) (Wikipedia 2014)

Poly(glycolic acid)

Poly(glycolic acid) (PGA) is the simplest linear, aliphatic polyester. PGA81–84 and poly(glycolic acid-co-lactic acid) (PGA/PL) are used as degradable and absorbable sutures. Their great advantage is their degradability by simple hydrolysis of the ester backbone in aqueous environments such as body fluids. Furthermore, the degradation products are ultimately metabolized to carbon dioxide and water or are excreted via the kidney. (Chandra & Rustgi 1998). PGA is also widely available, and because it is used in surgical sutures (classed as medical devices by most international regulators), it's background information is also well known. However, apart from their use as sutures, there did not seem to be much call for any laser welding in their applications and were ruled out as a result.

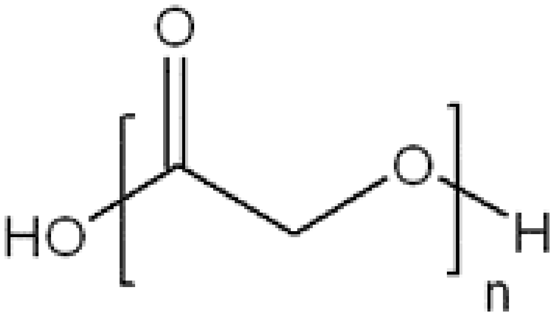


Figure 3 Structure of PGA (Sigma Aldritch 2014)

Poly(Propylene Fumarate)

This material was initially developed for orthopaedic applications, so laser welding could well have been need to be integrated into the manufacture of any products that would be built from this material. However, due to patenting issues, availability was proving to be a prohibiting factor.

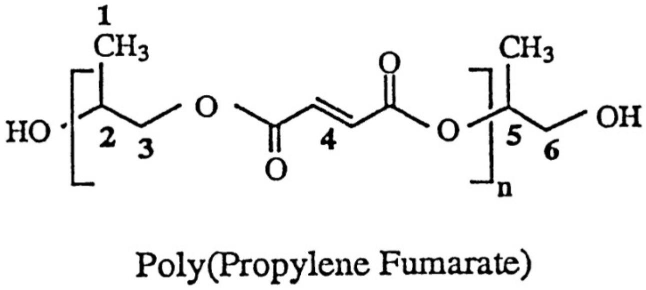


Figure 4 Chemical Structure of Poly(Propylene Fumarate) (Strut Patent.com Nov 2013).

Poly(Alkyl Cyanoacrylate)

This material is already being extensively used in biomedical applications, including drug delivery. It has a fast degradation time, so any experiments based on this material would have a reasonably short lifecycle compared to other biodegradable polymers. Unfortunately there was no real scope for the use of laser welding in any of its applications.

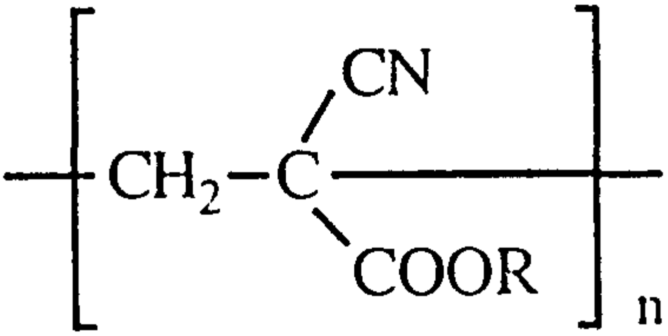


Figure 5 Chemical Structure of Poly(Alkyl Cyanoacrylate), (google images 2014)

Polyphosphazenes

This particular material could possibly have a large number of applications in various biomedical applications. However, in most of these cases, Polyphosphazenes are currently in clinical or even pre-clinical trials. Unfortunately the material is not on general release, so its supply would have been problematic and was not selected for this application.

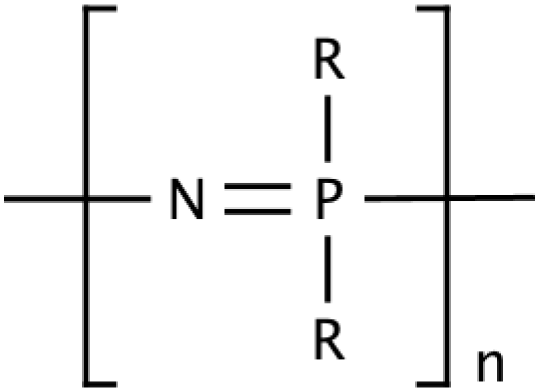


Figure 6 Chemical Structure of Polyphosphazenes, (Wikipedia Nov 2013)

Polyphosphoester

Polyphosphoester is currently in clinical trials for use as a drug delivery material. At the moment, there is no scope for using this material on its own in a laser welding capacity. However, due to its highly controllable degradation properties, it could well be used as a copolymer with other materials.

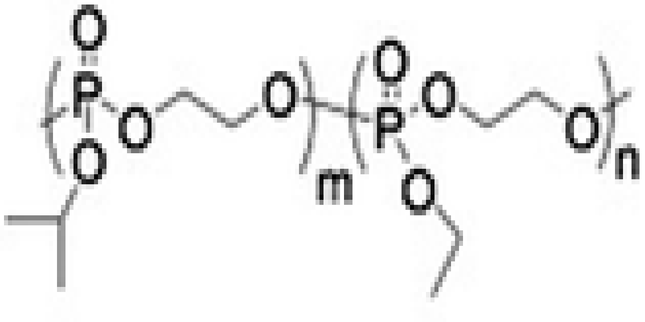


Figure 7 Chemical Structure of Polyphosphoester (Royal Society of Chemistry 2014)

Collagen

Collagen is a commonly used biodegradable material used in a diverse range of products from shields in ophthalmology to sponges and skin grafts for burns and wounds. It has also found uses in drug delivery in pellet and transdermal patch form. However, there were a number of disadvantages associated with this material, such as poor mechanical strength, difficulty in obtaining supplies fit for purpose. Most supplies that were available would have had to be purified on site, which would have meant extra time needed for processing samples fit for laser welding.(Lee et al. 2001)

Polycaprolactone

Polycaprolactone is a semi-crystalline linear aliphatic polyester. Historically it has been used to make resorbable sutures and drug delivery systems. It has lately seen a resurgence of interest due to the emerging field of tissue engineering. There have being a number of trials involving Polycaprolactone being used as a substitute for Bone Grafts. Polycaprolactone is compatible with a wide variety of other polymers which gives it a good range of applications.

Due to its slow degradation rates, it had also been trialled as a material for use in the manufacture of devices with long term activity such as contraception and hormone replacement treatment, orthopaedic applications and dentistry.(Woodruff & Hutmacher 2010) (Puppi et al. 2010)(Williams et al. 2005)

BIODEGRADABLE POLYMER APPLICATIONS

Tissue Engineering:

Tissue engineering is a relatively new area of research where attempts are made to either completely build an organ or tissues from scaffolds made out of biomaterial, or where repairs are made to an organ or tissue were damage has occurred, (also using biomaterials). There has been promising results in the use of polymers in a field of tissue engineering called Bone Tissue Regeneration. For example, In an experimental maxillary cleft model, a bioabsorbable composite membrane of ε-caprolactone and L-lactic acid 50/50 copolymer (PCL/LLA) film and mesh and poly 96L,4D-lactide

(PLA96) mesh were found to be suitable materials for guiding bone regeneration in the cleft defect area. (Minna Kellomaki, 2000)

Bone Tissue engineering encapsulates treatments in three distinct orthopaedic defects, Bone defects, cartilage defects and osteochondral defects. All of these treatments currently rely on harvesting living tissue from donors or in patient specific sites, for example iliac crest on the hip. In the last two decades, significant progress has been made in the development of surgical techniques for skeletal reconstruction. Beside them, tissue engineering is one of the most promising techniques to be used as alternative to the conventional bone harvesting or bone donation and cartilage transplants.

Under optimal conditions, cells harvested from donor tissues, including adult stem cells, can be expanded in culture and associated with resorbable biomaterials (scaffolds) of synthetic and/or natural origin and then implanted in the targeted site where the defect is regenerated by an optimal interaction between the graft and the host tissue. Treatments based on this technique would eliminate the problems of donor-site scarcity, adverse immune reaction and pathogen transfer. (Puppi et al. 2010)

Another goal of tissue engineering is grow organs in laboratory conditions to replace damaged organs and to transfer these organs directly into the patients. Current practices are overly dependent on donor organs which are not always successful due to the possibility of rejection in the receiver patient. Also, the availability of organs are so slight that it results in long waiting lists in which the patient who is need of the organ may die before one becomes suitable.

One of the difficulties with tissue engineering organs, was the ability to find a material that could expand and contract with an elasticity that could cope with the flow of blood through the particular organ. To cope with these variations, one study used major extracellular matrix components such as collagens, elastin, and glycosaminoglycans (GAGs). Each tissue/organ has its own unique set and content of these biomolecules. Type I collagen is an extracellular matrix protein that is widely used as scaffold material. It provides adhesive properties and tensile strength. Elastin provides elasticity to tissues/organs and is crucial for e.g. blood vessels in order to cope with variations in blood pressure. GAGs are negatively charged polysaccharides with biocharacteristics like hydration of the extracellular matrix and binding of effector molecules (e.g. growth factors and cytokines). (Daamen 2003)

Drug Delivery:

Currently used medicinal forms (tablets, injections, etc.) provide drug delivery with different amounts at variable times, often above the required dose. The constant drug level in blood or sustained drug release to avoid multiple doses and bypassing of the hepatic "first-pass" metabolism are the main challenges for every delivery system. In drug delivery applications the primary active agent is the drug. Degradable polymeric biomaterials can often enable the most effective use of the drug, and sometimes its only effective use, by routes which include:

1. Providing sustained effective systemic concentrations of the drug (i.e. avoiding the periodic potentially toxic over-dosing that can occur at the beginning of a dosing period and preventing the periodic ineffective under-dosing that can occur at the end of the dosing period)
2. Providing high concentrations of the drug only in the local vicinity of the drug-release depot, avoiding unwanted concentrations and effects of the .(Hubbell 1998)at locations far away from the disease treatment site; protecting the drug from the body's metabolism and clearance mechanisms as the drug is being released.
3. Targeting the drug to particular cells and sites within the body; and targeting the drug to particular organelles and sites within individual cells. (Hubbell 1998)

Medical Devices:

"Medical device" is an umbrella term used to describe devices that range from simple tongue depressors and bedpans to complex programmable pacemakers with micro-chip technology and laser surgical devices. Medical devices also include in vitro diagnostic products, such as general purpose lab equipment, reagents, and test kits, which may include monoclonal antibody technology. Certain electronic radiation emitting products with medical application and can also be covered under the definition of medical device. Examples include diagnostic ultrasound products, x-ray machines and medical lasers. (FDA 2012)

This term also includes devices that are implanted into the body to provide a therapeutic benefit for the patient. Medical devices may include Drug Eluting Stents, orthopaedic devices (e.g. replacement hip joints), catheters, syringes and other less common objects like Gastric Bands. There are many advantages to using biodegradable materials for medical devices over non-degradable or metallic materials, for example, bone fixing screws, biodegradable materials would transfer stress over time to the damaged area as it heals and there would be no need for a second surgery to remove the implanted devices, as they would be reabsorbed or excreted by the biological processes already present *in vivo*. (Tian et al. 2011).

Some of the most common polymers used in medical devices are prepared from glycolic acid and lactic acid have found a multitude of uses in the medical industry, beginning with biodegradable sutures first approved in the 1960 s. Since that time other medical devices, based on lactic and glycolic acid, as well as other materials, including poly(dioxanone), poly(trimethylene carbonate) copolymers, and polycaprolactone homopolymers and copolymers, have been accepted for use as medical devices. In addition to these approved devices, a great deal of research continues on poly-anhydrides, poly-orthoesters, and other materials. (Middleton & Tipton 2000)

As the understanding of biodegradable material increases, so to do the possible applications for such materials increase. The applications described above are just a small sample of what the industry is beginning to offer.

MECHANISMS OF BIODEGRADATION

There are many types of polymer degradation such as photo, thermal, chemical and mechanical degradation. All polymers share the property that they erode markedly under the influence of Ultraviolet (UV) light or gamma (γ) radiation. For polymer biomaterials, such effects are of minor importance unless they are submitted to γ sterilization, after which a significant loss of molecular weight can be observed. Thermal degradation plays a greater role for non-degradable polymers. Mechanical degradation affects those biodegradable polymers that are subject to mechanical stress such as non-degradable polymers or polymers that are used as fixtures or suture material. All biodegradable polymers contain hydrolysable bonds (chemical bonds that can be broken down in water). Their most important degradation mechanism therefore is chemical degradation via hydrolysis or enzyme catalysed hydrolysis. The latter effect is often referred to as biodegradation, meaning that the degradation is mediated at least partially by a biological system.(Göpferich 1996)

Thermal Degradation: This process occurs in all materials regardless of the nature of their compositions. Thermal degradation where biomaterials are concerned only becomes a factor during the production of the polymers concerned, or processing techniques involved in the manufacturing of devices etc. using the specific polymer. Thermal degradation of biomaterials usually occurs at elevated temperatures, exceeding the types of temperature ranges that are the focus here. However, due to the nature of the laser welding process used in this body of work, thermal degradation did become an issue during the welding process, but was easily controlled using the welding parameters and was not analysed to any great depth. More information on this issue can be found in Chapter 3.

Mechanical Degradation: The mechanical properties of biodegradable polymers and composites become crucial to the performance of devices made from them for support of healing bone, using stainless steel as a standard. The slowest-degrading unreinforced biodegradable polymers are poly(L-lactic acid) and poly(ortho ester). Biodegradable composites with carbon or inorganic fibers generally lose strength rapidly, with a slower loss of stiffness, suggesting the difficulty of fiber-matrix coupling in these systems. The strength of composites reinforced with (lower modulus) degradable polymeric fibers decrease more slowly. (Daniels et al. 1990) The temporary or permanent replacement of hard tissues in load bearing applications demands mechanically strong biocompatible materials. The attainment of such bone-matching mechanical performance depends on the technological ability to mimic the bone anisotropic character. Polymer based composites can, in principle, combine adequately stiffness and strength together with a clear anisotropic and viscoelastic character. (Sousa et al. 2003). It is important that the polymer retains its mechanical strength throughout the degradation process for as much time as is needed to enable the bones maintain the mechanical strain unaided. Because this body of work was chiefly concerned with the effects of laser welding on the chemical biodegradable properties of the material, little attention was paid to this mechanism of degradation.

Photo-Degradation: Photolysis (photo degradation) with UV light and the γ-ray irradiation of polymers generate radicals and/or ions that often lead to cleavage and crosslinking. Generally this changes the material's susceptibility to biodegradation. Initially, one expects the observed rate of degradation to increase until most of the fragmented polymer is consumed and a slower rate of degradation should follow for the crosslinked portion of the polymer. A study of the effects of UV irradiation on hydrolyzable polymers confirmed this. Similarly, photooxidation of polyalkenes promotes the biodegradation. The formation of carbonyl and ester groups is responsible for this change. Processes have been developed to prepare copolymers of alkenes containing carbonyl groups so they will be more susceptible to photolytic cleavage prior to degradation.

Chemical Degradation: Chemical degradation occurs when oxygen, water, or other reactive substances react with an active polymer layer. In hydrolysis for example, small amounts of oxygen and water can be absorbed in the different layers of the polymer. Oxygen is readily activated by UV illumination in the presence of sensitizers such as titanium oxide or organic molecules. The superoxide or hydrogen peroxide formed will then aggressively attack any organic substance present in the material, including the active polymers. (Jørgensen et al. 2008)

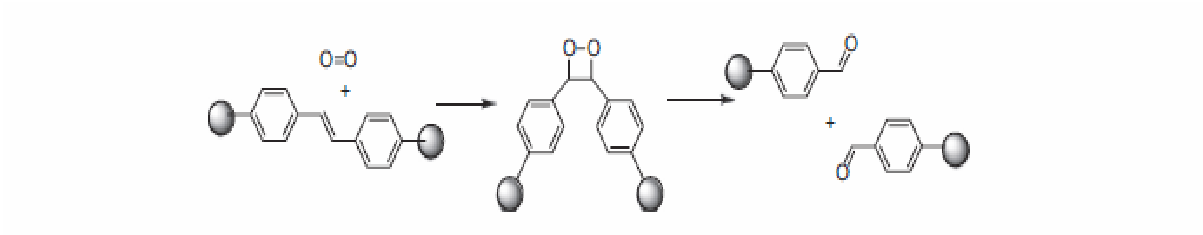


Figure 8 Initial reaction of a PPV polymer with singlet oxygen.

Singlet oxygen adds to the vinylene bond forming an intermediate dioxetane followed by chain scission. The aldehyde products shown can react further with oxygen.

There are several other factors within the chemical degradation mechanisms that affect the rate of degradation. These effects include polymer morphology, molecular weight and presence of oxygen or other free radicals within the polymer chain. Pre-treatment of the polymer may also affect the degradation rate.

Polymer morphology: Selective chemical degradation of semi-crystalline polymer samples shows certain characteristic changes. During degradation, the crystallinity of the sample increases rapidly at first, then levels off to a much slower rate as the crystallinity approaches 100%. This is attributed to the ongoing disappearance of the amorphous portions of the sample. This selectivity can be attributed to the less-ordered packing of amorphous regions, which permits easier access of the hydrolytic compounds into the poymer matrix.

Molecular weight: Low molecular weight hydrocarbons can be degraded by microbes. They are taken in by microbial cells, 'activated' by attachment to coenzyme-A, and converted to cellular metabolites within the microbial cell. However, these processes do not function well (if at all) in an extracellular environment, and the polymer molecules are too large to enter the cell. The molecular weight of the polymer also affects the degree of crystallinity in a semi-crystalline polymer, which has been discussed in polymer morphology.

Presence of Oxygen: Several enzymes can react directly with oxygen, the classical example being cytochromoxidase which is active in the respiratory chain. The presence of oxygen in the backbone of the polymer can act as point of breakage during the degradation process. Yet another type of biological oxidation exists, namely the process where the oxygen molecule is not actually incorporated into the substrate, but rather it functions as a hydrogen acceptor (i.e. electron acceptor). This can also lead to breakage of the chain and the formation of oligmers during degradation.

Basically, there are a number of different factors that contribute to polymer degradation. There are also some processes that can be carried out on the individual polymers to control the degradation rate. These processes can be used to either speed up or slow down the rate of degradation.

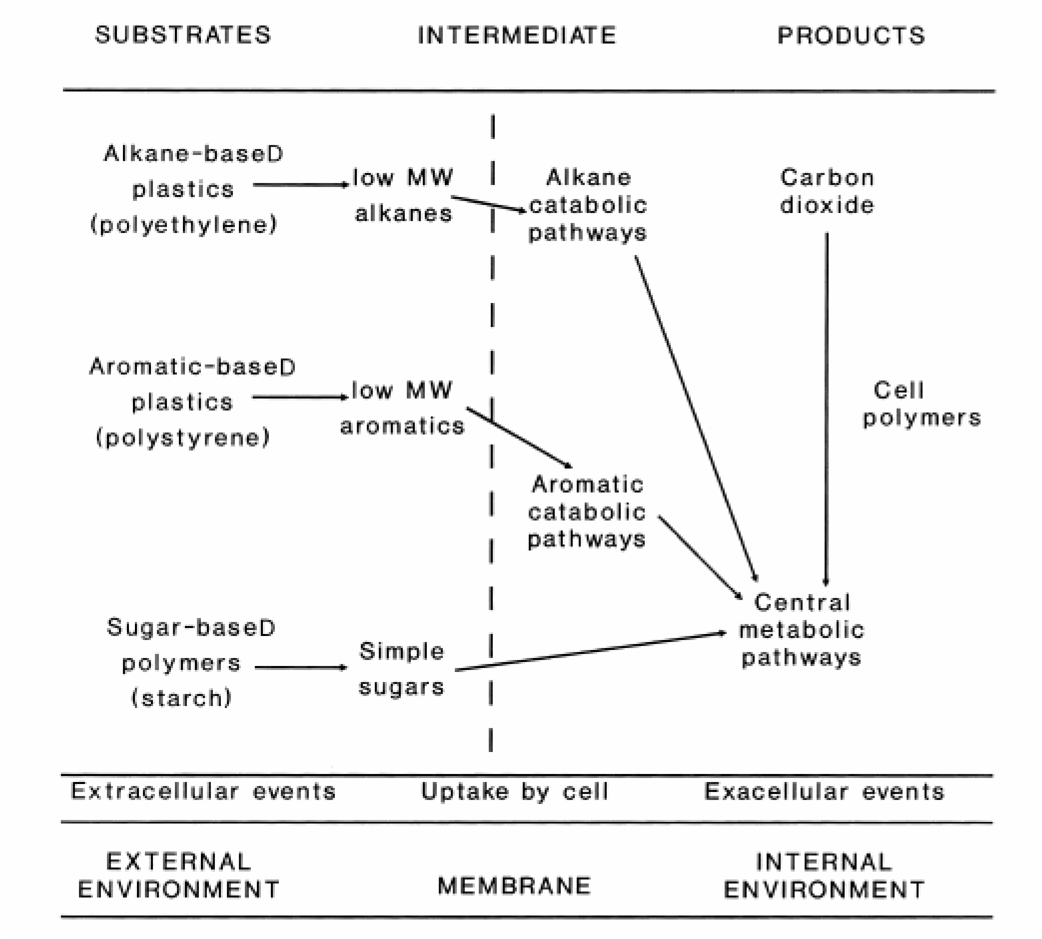


Figure 9 Cellular metabolic pathways for polymer biodegradation in microorganisms. (Chandra & Rustgi 1998)

LASER WELDING

The word laser is an acronym for the most significant feature of laser action: **L**ight **A**mplification by **S**timulated **E**mission **R**adiation. There are many different kinds of laser, but they all share a crucial element: Each contains material capable of amplifying radiation. The material is called the gain medium because radiation gains energy passing through it.(Milonni & Eberly.) Every laser needs four key elements in order for stimulated emission to occur:

1. A light signal of a controlled wavelength is pumped through a “cloud” of atoms or molecules (known as gain medium) stimulating their electrons into higher energy states.
2. The light signal is then reflected back through the “cloud” again, stimulating even more electrons.

3. As more electrons are stimulated, this has the effect of amplifying the signal. To sustain this amplification, more energy is pumped into the gain medium.
4. When the amplification hits a certain level, the beam signal is allowed to escape out of the cavity and into the material being lased.

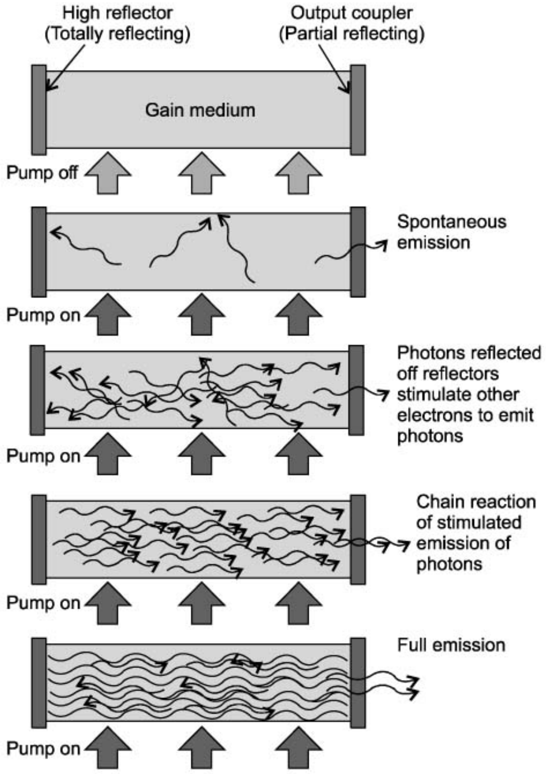


Figure 10 Light Amplification by Stimulated Emission Radiation courtesy of http://wjmh.org/ArticleImage/0074KJA

The advantages of laser welding are as follows:

1. It is a clean method of joining materials. Laser welding processing techniques offer many advantages over traditional fabrication techniques such as gluing, metallic welding or soldering. One of the main advantages is the fact that laser welding has no need of third part binding agents like in arc welding, soldering or gluing, thereby maintaining the purity of the material
2. Laser welding is also highly controllable and can deliver energy precisely where it is needed with an accuracy of micrometers. The flexibility of beam delivery also makes it an excellent option to weld hard to reach places

3. Laser welding provides concentrated thermal and photochemical energy to the joining area and rarely has a large heat affected zone around the particular weld you wish to obtain which is proving useful in the processing of many physical and chemical systems. (Duley & Mueller 1992).

Virtually all laser welding systems in commercial use are based on Nd:YAG or CO_2, (Duley 1998), However, other gain mediums, such as carbon monoxide and high powered semiconductor diode arrays are also beginning to find favour for certain applications.

The majority of laser welding applications occur in metallic specific materials, laser welding is slowly beginning to be used in no-metallic applications. One of these non-metallic applications is the routine use of laser welding in stent delivery systems. A stent delivery system is made up of a balloon attached to a catheter, both items manufactured from polymers. The stent to be used is then placed on this balloon. The stent is then applied by inserting the whole assembly through an artery, travelling through the artery to where the blockage is located. The balloon is then inflated, forcing the stent into the arterial wall. The stent delivery system is them removed in the same way as it was inserted. [US Patent 4,950,227, 1990]

One of the major risks associated with this application is the possibility that the balloon may become detached from the catheter during the operation.

To maintain the bond strength of the balloon to the catheter, the balloon is Laser welded onto the catheter. This provides a mechanically sound bond between the balloon and the catheter and avoids the introduction of further contaminants in the forms of metallic particulates (as in soldering) or potentially toxic bonding agents (as in gluing). A laser with a gain medium of Carbon dioxide is typically used for this process, which is similar to the type of laser used here.

The gold standard for hermetic encapsulation (complete seal) for implants is a titanium enclosure which is sealed using laser welding. But replacement of metals with polymers for encapsulation of active implantable medical devices is an area of interest for research and development. Advantages that polymers offer for this application include ease of fabrication, weight saving, flexibility, electrical and thermal insulation combined with electromagnetic transmission, as well as cost advantages. (Amanat et al. 2010)

Nd:Yag

This type of laser is the most common type being used in industry, especially for welding of metallic materials in the auto motive industry. The average power generated by Nd:Yag is between 0.3-3.0 kW and can be operated in three different modes, Q-switched mode, continuous mode and pulsed pumping. The laser welding system is made up from several laser rods pumped in a single resonator, making the pumping and the energy extraction more efficient. However, the input to output power ratio of the Nd:Yag is very low, making the efficiency of the laser very low overall. The main advantage of this laser is the fact that the laser radiation generated in the cavity can be delivered via a fibre optic cable, allowing laser welding to be completed in hard to reach areas, for example the inside of door frames in cars. The operating wavelength for Nd:Yag laser is at 1064nm, but the absorption coefficients of organic polymers are much smaller than they are at 10.6 µm, where the majority of organic materials are strongly absorbent. In the case of the Nd:Yag, the bulk heating is spread out over a larger volume and poor conversion of incident laser radiation to heat result, without the aid of material additives. (Duley 1998)

Carbon Dioxide

Initially reported in 1972 by Ruffler and Gurs, Duley and Gonsalves, Carbon Dioxide lasers are the second most common type of laser used in industry. The Carbon Dioxide laser directly excites vibrational modes in organic solids, which generate heat in different ways than other types of lasers described here. Carbon Dioxide lasers do not directly transfer heat to the surface of a film via photons, but actually excite the molecules in the bulk of the film to such an extent as to generate heat as a bi-product. The operating wavelength of the CO_2 laser is at 10.6µm making it ideal for polymer welding because many organic materials are strongly absorbing at this wavelength. The main advantages of CO_2 welding are as follows:

- Good Penetration at low laser power.
- Fast processing speeds.
- Small heat affected zone.

- Fit up not too critical.
- Non contact process.
- Can be used with many, but not all polymers. (Duley & Mueller 1992)

Semi-conductor Diode Array

Traditionally used in the communications sector, semi-conductor diode arrays are beginning to find use in Laser welding applications. There are many characteristics to these systems that make them attractive in laser processing techniques such as their small size, low power consumption, high reliability and wide tunability. They operate in wavelengths of between 940 to 1000nm making them well suited in polymer welding processes.

As well there are many different types of laser; there are also numerous ways of configuring the films in order to weld them. The most important aspect of the join is that both films are placed close enough together so that they fuse as the laser passes over them. There also needs to be sufficient distance across both sides of the weld pool to provide a mechanical strength comparable to the films on their own. (Duley & Mueller 1992)

Butt Weld

A butt weld is a simple joint configuration where the ends of both films are pushed against each other and the laser path runs down the middle of the joint. However, the small amount of material available in the fusion zone during the welding makes butt welding of thin sheet susceptible to pinhole formation. This can be aggravated by the presence of any gap between the sheets. The sheets also have a tendency to misalign during the welding due to thermal stresses and distortion, making clamping hugely important. (Duley 1998)

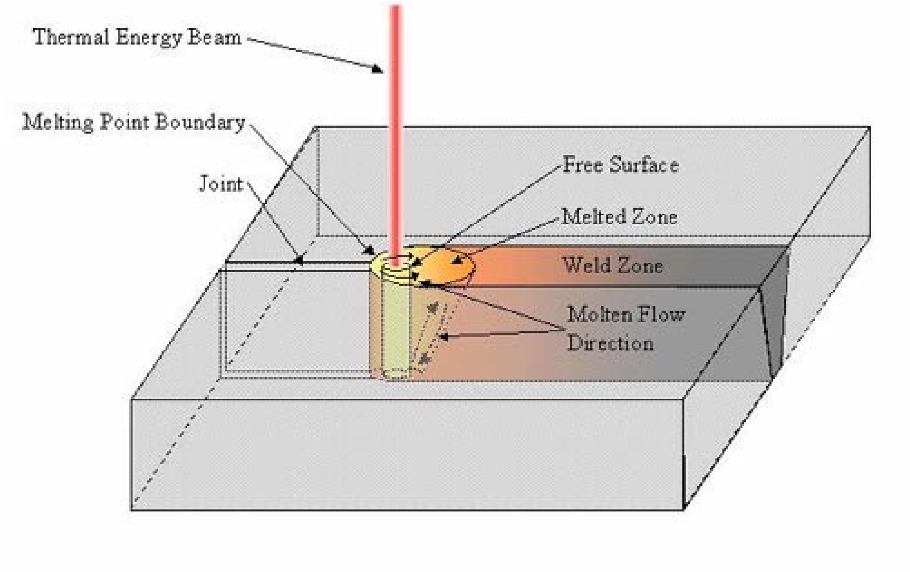


Figure 11 But Weld Laser joint (Joining Tech 2014)

Lap Weld

Lap welds are commonly used in applications involving thin films. In a lap weld, one film is placed on top of the other and clamped into position. The laser beam is fired through the top layer, which then due to transmission of heat, also melts the surface of the bottom layer. These joints are always involved in through transmission welding, where the beam is absorbed more strongly in the bottom layer, causing the surface of the top layer to melt. Clamping is important here also, however to obtain good bonding at the interface between the sheets, this clamping must include provision for a fine gap when lap welding galvanized steels or other coated materials with continuous wave laser radiation. (Duley 1998).

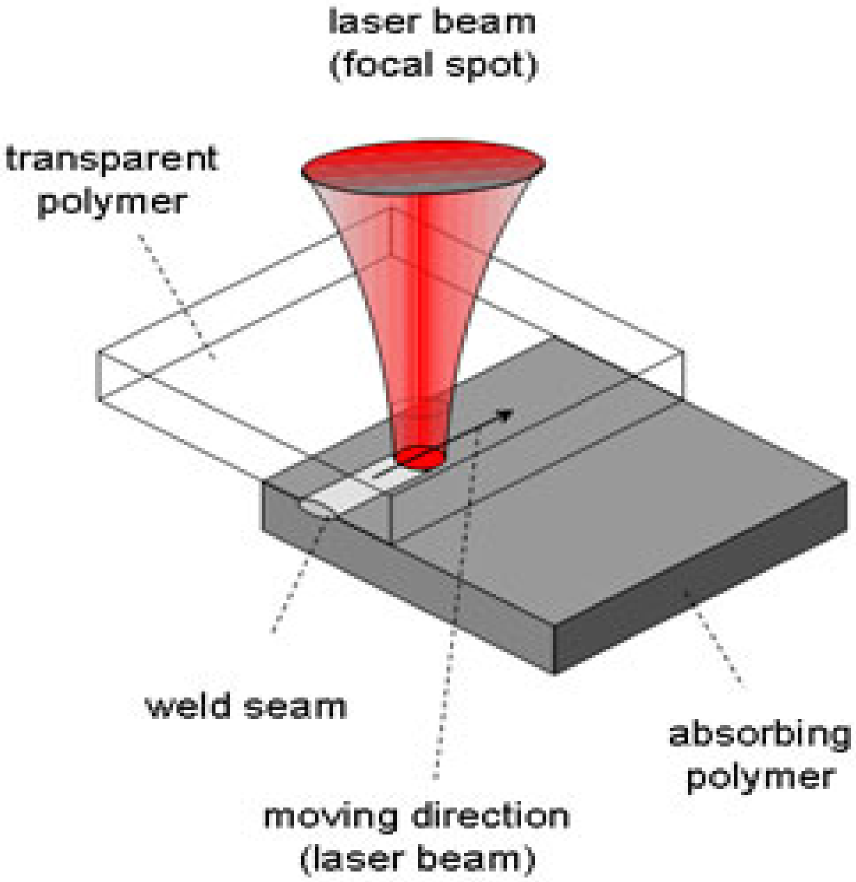


Figure 12 Lap Weld Laser joint (Rofin 2014)

Edge Weld

Similar in application to Butt weld, the two films been welded together are pushed against each other and where the edges of the films meet is becomes the path for the laser beam. As with the butt weld, a good fit-up is still necessary.

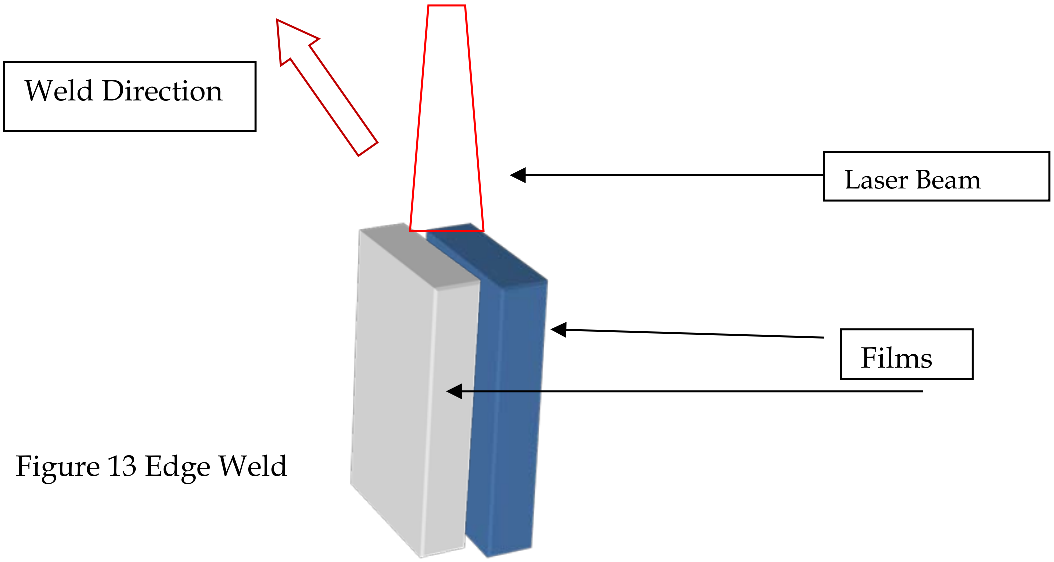


Figure 13 Edge Weld

SUMMARY

Biomaterials are extensively used in healthcare today in such applications as orthopaedics, drug delivery, contraceptives, medical implants and other therapeutic applications such as aortic valve replacements and stent applications. Biomaterials can come in polymer, metallic or ceramic forms. However, future trends suggest that polymers are increasingly being used to replace their metallic due to the latter's shortcomings which were explained above. Metallic materials usually need subsequent surgeries to remove them from patients once they reach the end of their therapeutic lifecycles, putting patients at further risk of adverse effects. One of the main advantages that polymers have over their metallic counterparts is the fact that once they provide the therapeutic function, they can degrade away naturally in the body, removing the need for secondary surgical interventions.

Biodegradable polymers come in natural and synthetic forms, but the focus in this body of work is centred around synthetic polymers. Synthetic polymers can be engineered to have specific degradation times, mechanical, chemical or thermal properties are readily available and can be processed in highly pure forms. Natural polymers availability is highly dependent on the organisms that produce them and also may need secondary processing to remove them as in for example in the processing of collagen.

Laser welding is a clean and pure form of joining materials together. It is extensively used in highly automated joining processes in the automotive and electronic industries. Laser welding is highly controllable and can be readily be adapted to join materials in hard to reach places. Laser welding using carbon dioxide as a gain medium is extremely suited to weld together polymer materials due to the way the energy transfer vibrational nodes in organic polymers, which in turn can generate an adequate amount of heat to melt the polymer in a weld pool.

With the growing popularity of the use biodegradable materials in the field of medicine, and with the excellent suitability of the use of the laser welding to join biodegradable polymers, it is the intention of this body of work to explore how the laser welding process effects the biodegradation properties of a particular polymer.

Chapter 2 Material Processing and Film Formation

This chapter will discuss the material selected and how the films were manufactured. It will also discuss the initial experiments to the current best practice batch manufacture process that was developed in the current body of work. The film itself had to be easily formed, thin enough to be welded and strong enough to be handled. Because the films were to be used in degradation experiments as part of the overall project this chapter discusses the impact of Statistical Process Control had on the quality of the films produced in order to have enough films in stock to complete the degradation experiments.

INTRODUCTION

Synthetic polymers are ubiquitous in modern day living and are found in many applications, from clothing to the automotive industry. The branch of synthetic polymers that are of interest in this body of work are biodegradable, specifically polymers that have found use in the pharmaceutical and medical device industry. Biodegradation is a natural process by which organic chemicals in the environment are converted to simpler compounds, mineralized and redistributed through elemental cycles such as the carbon, nitrogen and sulphur cycles. Polymers may degrade in many ways within the physiological environment due to hydrolysis of the polymer backbone or through enzymatic degradation of the whole molecule. There are several diverse biodegradable polymers being considered for potential roles in medical applications at present. The common ones used would be Poly(Lactic Acid), Poly(glycolic acid), Poly(caprolactone) and their co-polymers. (Chandra & Rustgi 1998).

Polycaprolactone (PCL) was the polymer of choice for experimentation in this body of work because it is readily available in a relatively pure form, had a workable degradation time (up to two years) which could be accelerated in a controlled fashion using reagents available to the researcher at the time (Phosphate buffered saline and lipase. More information on the degradation process can be found in chapter 4). PCL is a semi-crystalline polymer PCL can be prepared by ring opening polymerization of a cyclic monomer called ε-caprolactone. It can also be manufactured using free radical ring-opening polymerization of 2-methylene-1-3-dioxepane. A diagram is provided below.

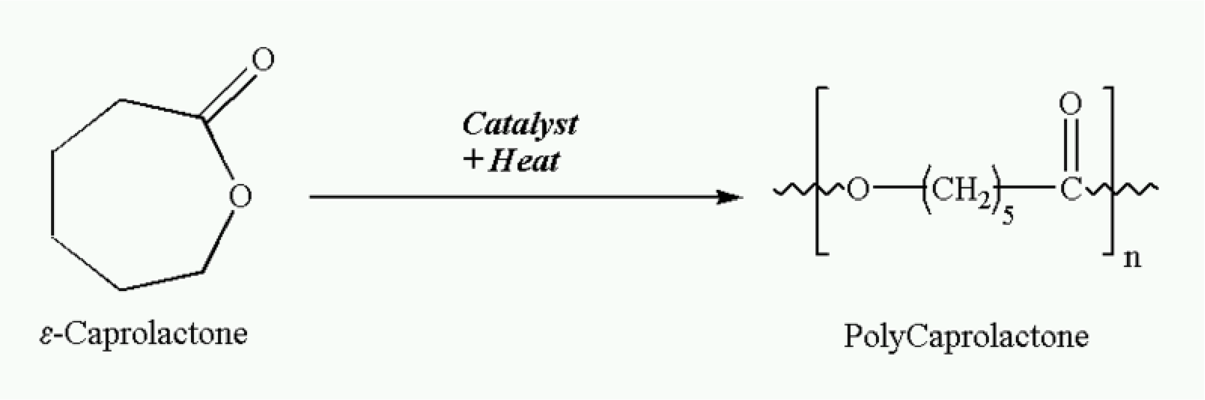


Figure 14 Ring Opening process step of ε-Caprolactone to generate Poly-caprolactone. (Wikipedia 2014)

Catalysts such as stannous octoate are used to catalyze the polymerization and low molecular weight alcohols can be used to control the molecular weight of the polymer.

The crystallinity tends to decrease with increasing molecular weight. It has a melting temperature of between 59 and 64 ^{0}C and a glass transition temperature of -60 ^{0}C. The IR-spectra of PCL molecular weight of 8200 Da is shown in Fig. 5.

It has a maximum tensile strength of 14.2MPa. PCL undergoes two types of degradation, Hydrolytic and Enzymatic.

PCL was difficult to source as a film suitable for the needs of the project. After some consideration it was decided to buy in Polycaprolactone granules and process them into suitable films In-house.

The films to be used for experiment where to have required to meet certain standards, as defined by the researcher. The basic user requirements were:

1. The films were easily formed, thin enough to be welded and strong enough to be handled.

2. The film formation process itself would have to be robust enough to be able to manufacture sizeable quantities with a good level of consistency.
3. The system process would also need to have a minimum financial investment initially until a method was deemed fit for purpose. Some of the processes considered are described briefly below.

FILM FORMATION TECHNIQUES

Compression Moulding

A compression mould consists of the required mould positioned on a hydraulic press and heated to the required temperature needed to melt the polymer. A specific ‘dose’ of the material, known as a charge is placed in the heated cavity and becomes soft and plastic. The mould is then closed and subjects the charge to high pressures which forces the charge to take up the shape of the mould. The mould remains closed until the part hardens, or ‘cures’. The mould then opens and the part is removed. (Poli 2001) This process would have easily dealt with quantity aspect in number 2 and would have had good control over the physical aspects as laid out in number 1 above. However, a financial investment would have been needed to buy in equipment or to outsource the process elsewhere for a fee.

Extrusion

Extrusion is a process involving material pellets being placed into a hopper which feeds into a long cylinder containing a rotating screw. The screw transports the pellets into a heated portion of the cylinder where the pellets are melted and mixed to form a uniform melt. The melt is then forced through a die hole in the required shape to form long parts of uniform cross sections such as sheets, rods, tubes and other regular or irregular profiles. (Poli 2001) This particular process also needed an investment in equipment or services.

Electrospinning

The process of electrospinning was first patented in 1934 by Anton Formhals. The process involved producing polymer filaments from solution using electrostatic force. In its simplest form, the set up consists of a pipette, which is used to hold the solution, to electrodes and a DC voltage supply. The polymer drop from the tip of the pipette is drawn into a fibre due to the high voltage. The jet then becomes electrically charged and the charge causes the fibres to bend in such a way that every time the polymer fibre looped, its diameter would be reduced. The fibre would then be collected as a web of fibres on the surface of a target that was connected to ground.(Ramakrishna. 2005) Though the equipment that was needed for this process was available at the institution, it was not pursued due to the time it needed to develop the process further.

Thin layer deposition

First developed in the second half of the 19th Century, and growing rapidly in the 1960's due to the early development of microelectronics, thin layer deposition involves passing an organic gas through an electric discharge. (Biederman 2004). A surface containing Benzene molecule as a substrate, get bombarded by high energy particles from the electric discharge. The fragments from the gas, in the form of positive ions and electrons, react with the benzene molecules and each other and a plasma polymer film grows on the surface. This was not pursued on the grounds that there may have been some interference with the results from the substrate.

Solvent Cast Method

In the manufacture of polymeric films by the solvent evaporation process, (solvent cast method), the polymeric material, with or without plasticiser, is dissolved in a solvent or solvent mixture and into this the active constituent is dissolved or dispersed. This solution is then cast onto a suitable substrate and the solvent allowed to evaporate leaving a solid polymeric film containing drug substance. (Jones & Medlicott, 1995)

Solvent Cast method described here involved dissolving a known amount of Polycaprolactone granules (as the "drug substance") in a specific volume of solvent. A known volume of solution was then cast into a mould and left until the solvent had evaporated, leaving behind a film of Polycaprolactone. (Centre et al. 1995), (Jones et al. 2002). It was decided to use this particular method as the set up costs were low, and did not require too much investment of time to learn the intricacies of the method.

A number of different versions of the method were researched in order to obtain suitable films that were to be used in this project. But a version described in (Jones et al. 2002)was used as a guide for the purposes of this body of work. The choice of solvent was also an issue. From various other publications, it was found the PCL dissolves quite readily in a number of organic solvents, for example Acetone and Ethanol. Dichloromethane was chosen, primarily because of its hydrophobic nature, so that any water present in the granules would not trigger any premature degradation while the films were being formed. As Reported in (Middleton & Tipton 2000)"The additional complication during processing is the potential for molecular weight decrease due to the hydrolytic sensitivity of the polymer bonds. The presence of moisture during processing can reduce the molecular weight and alter the final polymer properties." It was hoped that by using Dichloromethane in the processing of the films, the risk of hydrolytic sensitivity would be lessened because (Centre et al. 1995) found that "There will be poor penetration of solvent (distilled water) into dichloromethane cast polymeric films due to the dense polymer network, a slow rate of dissolution and hence slow release of chlorhexidine into the dissolution medium."

It was believed the solvent cast method could also offer a direct and simple way to control the thickness of the films being produced. Either by controlling the concentration of the Polycaprolactone in solution, or by possibly applying multiple layers of one particular solution concentration. Also, solvent cast method offered a comparatively low cost and fast set up solution compared to the other methods mentioned above.

MANUFACTURE OF POLYCAPROLACTONE FILMS

Initial Film Manufacture

The initial experiment was run using the small amount of Polycaprolactone that was available at the time. A small amount of PCL was placed in the flask and was then re-weighed. Using the micropipette, small additions of Dichloromethane were added to the flask until the Polycaprolactone was completely dissolved, leaving a solution that had an approximate concentration of 0.1g/ml.

Using the micropipette, the resulting solution was spread out over the microscope slide on top until its surface was completely covered. The lid of the glass tank was then replaced and left the fume hood.

After an hour had passed, the lid was removed and the film was inspected. It was observed that a film was beginning to appear on the surface. The lid was then replaced, and tank left for a period of greater than 14 hours.

When the period 14 hours had elapsed, the tank was inspected again, and it appeared that all the solvent had evaporated off. The lid was once again replaced and left for another period greater 14 hours. After this period, the tank was inspected and there were no observable differences. The resulting film was extremely thin, almost like cling film which was not suitable for the laser welding set up in house.

Effects of Concentration on Film Thickness

A second batch was attempted, whereby a stock solution was to be made up initially, at 10% $^{w}/_{v}$ and then the respective 8% and 4% solutions were to then be created. This was to investigate two possibilities, whether the thickness of the film could be adequately controlled by varying the concentration of the solutions and to investigate which concentration would yield suitable films for laser welding and degradation tests. The results of the experiment showed that the 10% $^{w}/_{v}$ offered the balance of thickness and handling. The 8% films were very flaccid and it was envisaged that these films would be much harder to clamp in place for welding. The 4% film had a consistency described above which broke very easily.

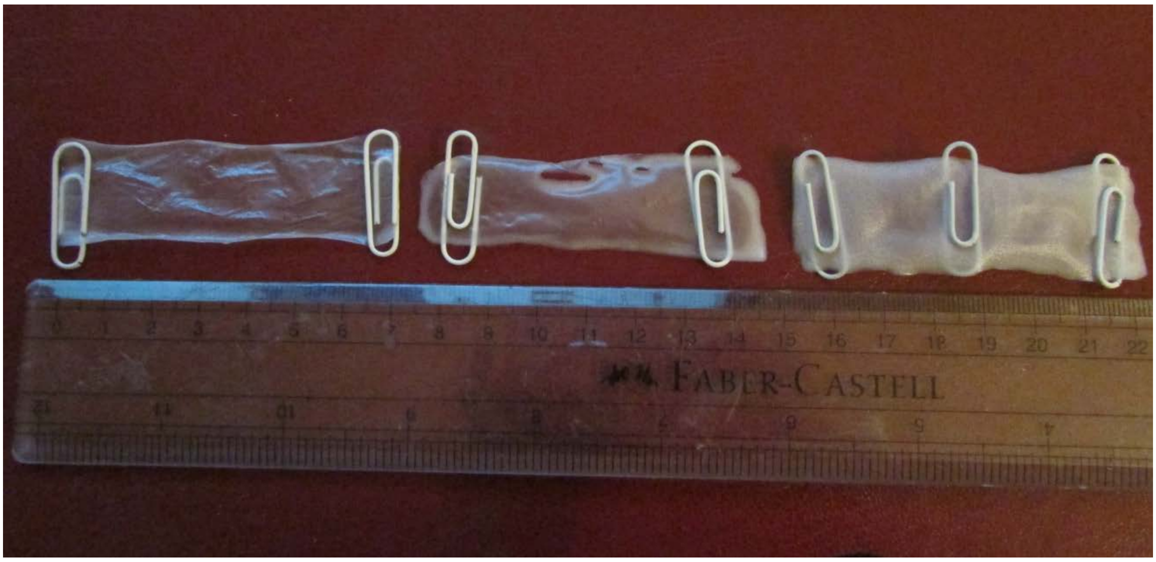


Figure 15 Left to Right; a visual representation of polycaprolactone films manufactured through solvent cast method from 4%, 8% and 10% $^{w}/_{v}$ concentrated solutions

Film Formation in Layers

In the next experiment, an attempt was made to control the thickness of the films by using a technique where each film would be built up in layers.

A 1-1.5ml volume of stock solution was applied to the surface of a microscope slide and placed in a glass tank. The glass lid was replaced and left for more than 14 hours in the fume hood. A second layer of stock solution was applied on top of the film that was left behind from this period and left to dry once again for more than 14 hours. A third layer was applied in the same fashion as before on the next work day. After the third layer was added, the 2 layer film dissolved instantaneously on contact with the solution. Control of the application of the solution could not be maintained, as it spilled out over the edges of the microscope slide. When the film was observed again, a change in the physical properties was not expected, but there was an observable difference in the "Stiffness" of the film, but no real observable differences in the thickness. Due to the difficulties occurring in the control of the application of film layers, this method was abandoned in favour of concentration based process.

Film formation process and SEM analysis

The initial stages of film formation are associated with loss of solvent, leading to a touch dry film that will contain significant quantities of moisture. Subsequent drying leads to collapse of the voided structure initially formed to create a densely packed structure. This indicates that film formation occurs over a number of stages.

1. The film solution dries out due to evaporation at a set rate. This leaves a film that is dry to the touch, but may still have some solution left inside. The loss of this solvent also leaves behind microvoids in the structure of the films. These microvoids can be detected using an SEM microscope.
2. The second stage occurs when the film is completely dry. This causes the microvoids in the structure to collapse in on themselves, giving the film a smoother appearance under the SEM microscope.

In latex film formation there is evidence that a drying front first creates micro voids in the loosely packed film structure. Evaporation rates are retarded in a latex that is well above its T_g [glass transition temperature] probably as a result of the reduced surface area of water caused by extensive particle deformation. It has been suggested that there are two important stages in the process of film formation: evaporation of the aqueous solvent and deformation/compaction of particles leading to void closure". (Pethrick, 1999) The temperature that the evaporation occurs at may also have an effect on the formation of voids. The T_g of PCL is -60^0 so the films were left to dry at room temperature. When a film exists at a temperature that is higher than its MFFT [Minimum Film Formation Temperature] its resistance to deformation is slight (Pethrick, 1999). From these statements it was assumed that drying the films at room temperature for a short time (24 hours), there was an increased risk that voids will form the top layers, while drying at or near the T_g for the same period, will reduce void formation. However, because the T_g of PCL is so low, it became impractical to dry the films at this temperature with the instrumentation available at the time. But, evidence shown by looking at the SEM images then perhaps drying at room temperature for a longer period would also have decreased the risk of void formations.

All the films manufactured were touch dry after 24hrs, however, SEM analysis was carried out on films in an attempt to determine the best minimum length of time that the films should be evaporating for. The samples shown here were cut from the centre of the film using a standard kitchen scissors. Samples were then placed on a double side, self adhesive Carbon tab. All of the images were manipulated using the visual software that came with the SEM.

The first sample observed in the SEM was of the film that was left to evaporate for more than 14 hours. At the lower magnification (x 150) the films had shown numerous micro voids of around 500 - 1000μm across. The images obtained were from the topside of the film (the bottom side would have been in direct contact with the microslide). The surface shown here was typical of the surfaces at various positions of the sample. (See Figure 17)

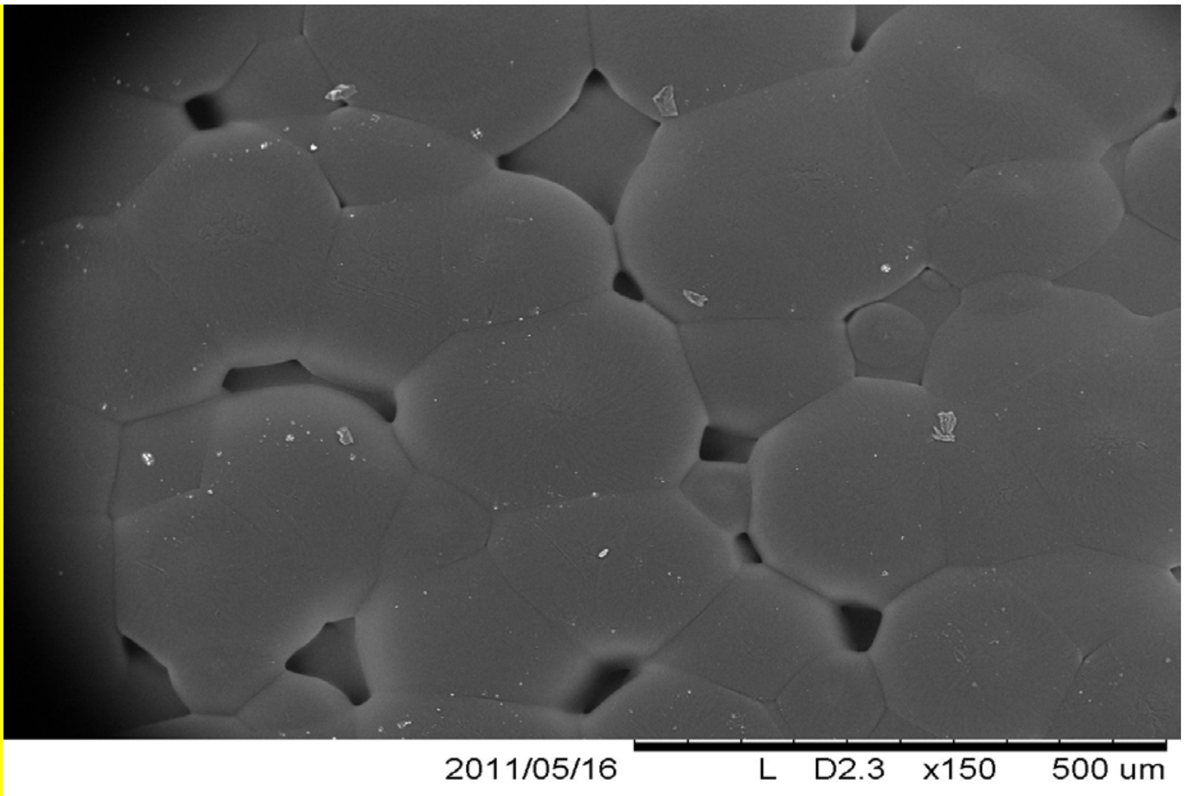


Figure 16 SEM image of the top side of the sample 1 after been left to dry for more than 14 hours. The bottom side of the sample appeared a lot smoother at the same magnification. (see figure 17)

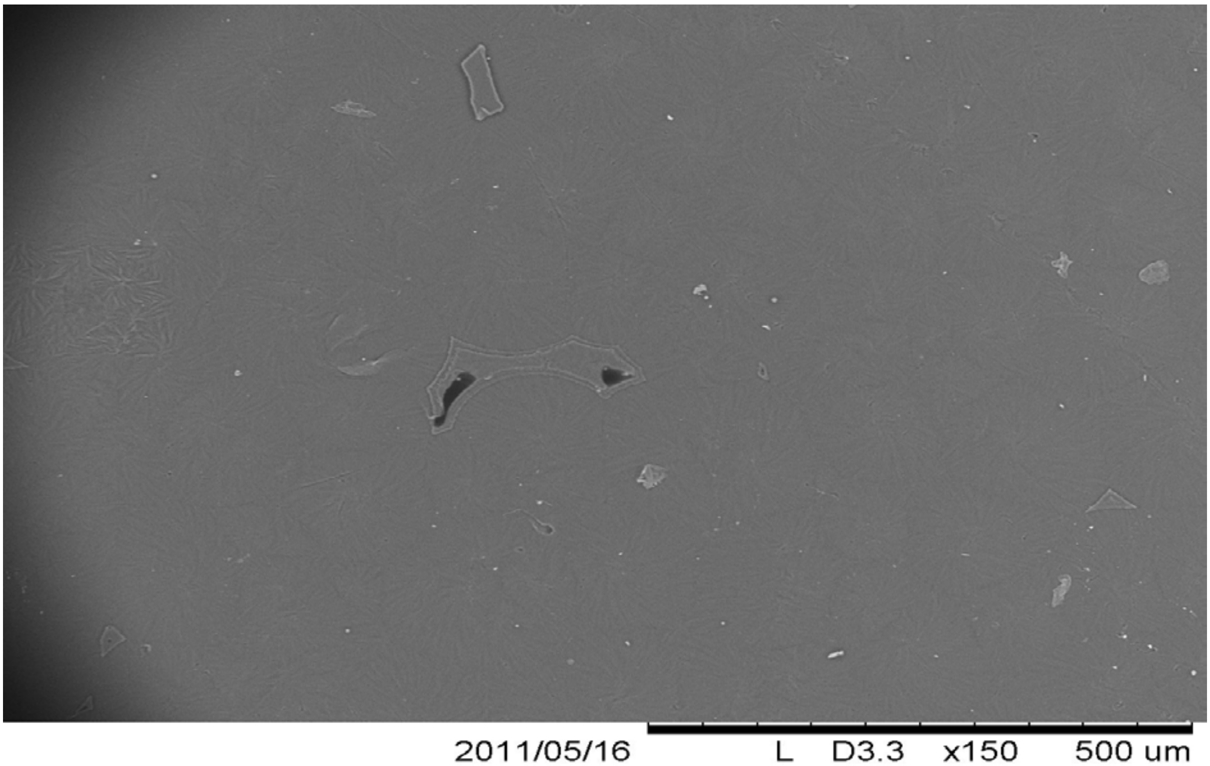


Figure 17 SEM of the bottom side of sample 1 after been left to dry for more than 14 hours(x150 Mag).

This trend was seen in almost all samples scanned, the top having micro voids and the bottom being comparatively smooth.

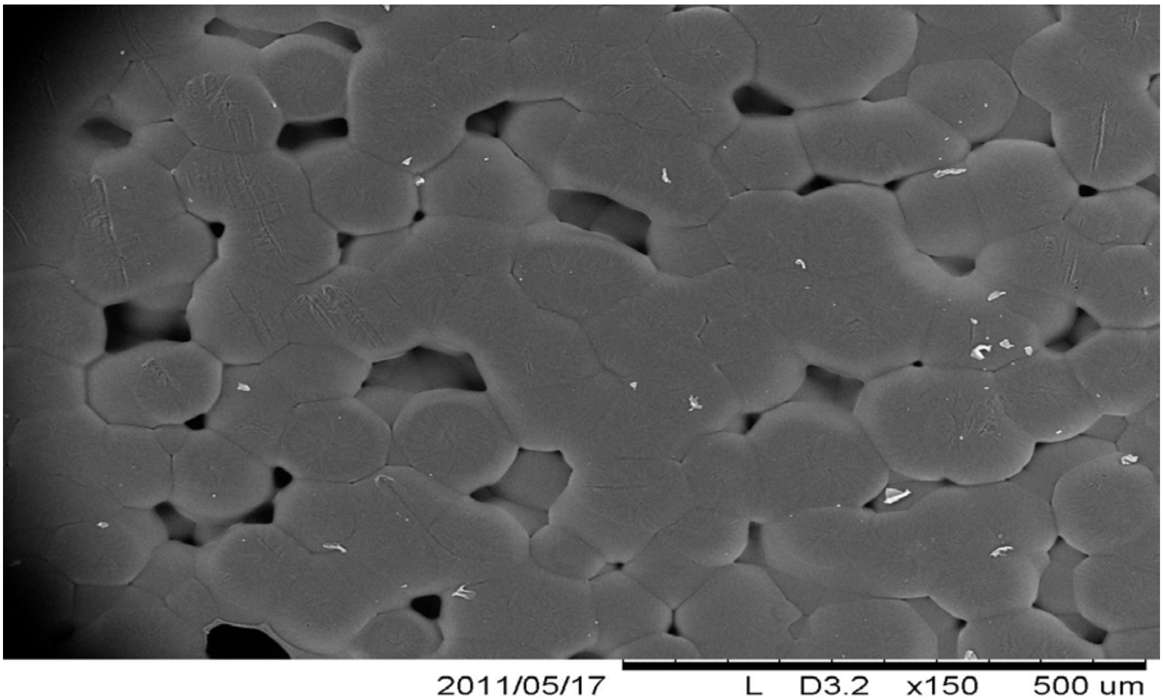


Figure 18 SEM image Sample 2 Topside

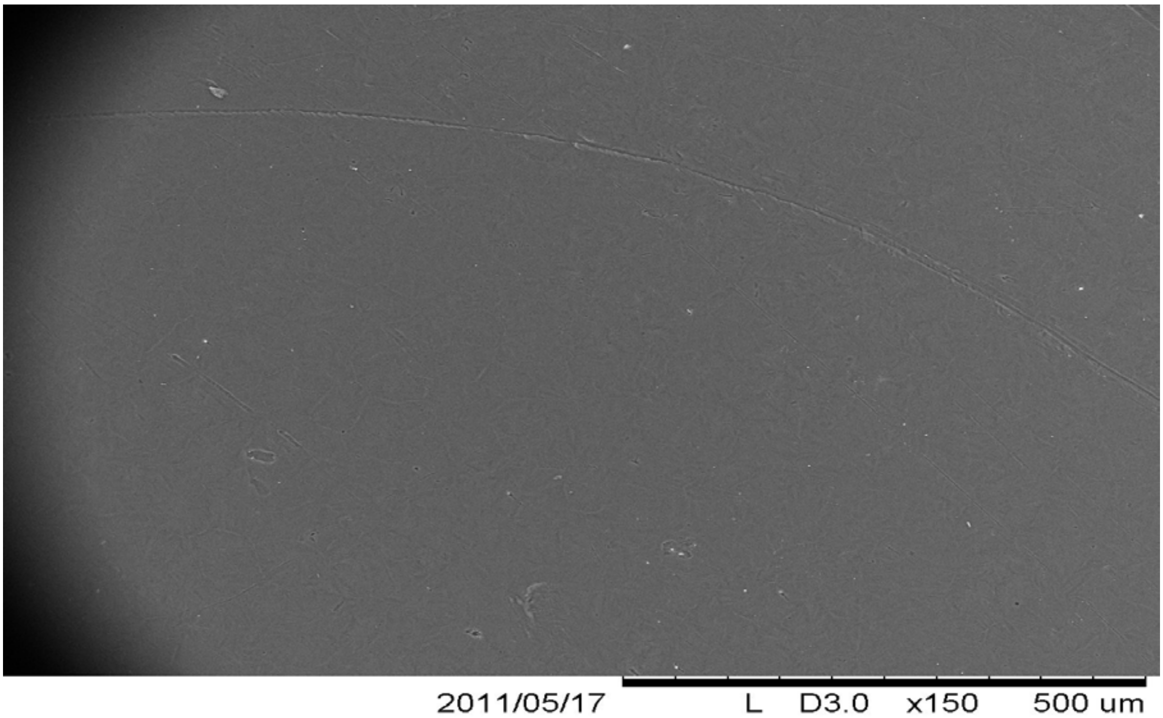


Figure 19 SEM image Sample 2 Bottom side

The occurrence of micro voids seem to have disappeared entirely from the samples that were left to evaporate for more than 24 hours (see Figure 21 below)

The images seem to show that films formation is an active process after the first 24 hours even if the films themselves appear to have dried out.

BATCH MANUFACTURING AND PROCESS CONTROL

Calculating Concentration

Previous experiments described above had found that the ideal concentration of PCL to dichloromethane needed for suitable films was 10%. For batch manufacturing purposes it was decided to make up a standard stock solution from which individual aliquots of polymer solution would be removed and placed into the special glass containers that were used for evaporation. 25g of Polycaprolactone particles were dissolved in 250ml of Dichloromethane and used as the standard stock solution.

The next stage of the process involved calculating the volume of the aliquot removed from the stock solution and placed into the glass container. For this calculation it was assumed that the film which would be left behind in the evaporation dish would be a cylinder, so the formula for calculating volume of a cylinder was used;

$V=\pi R^2 h$

This volume of the aliquot was calculated to be 32 ml. The target thickness of the film was approximately 0.2 mm. In order to have tighter control on the environment in which the films were drying out in, the container was then covered with a glass dish and left in the fumehood. After a period of 7 days, parts of the film was removed from the glass lid and cut up using a surgical blade into sections. These sections were removed and viewed under the SEM.

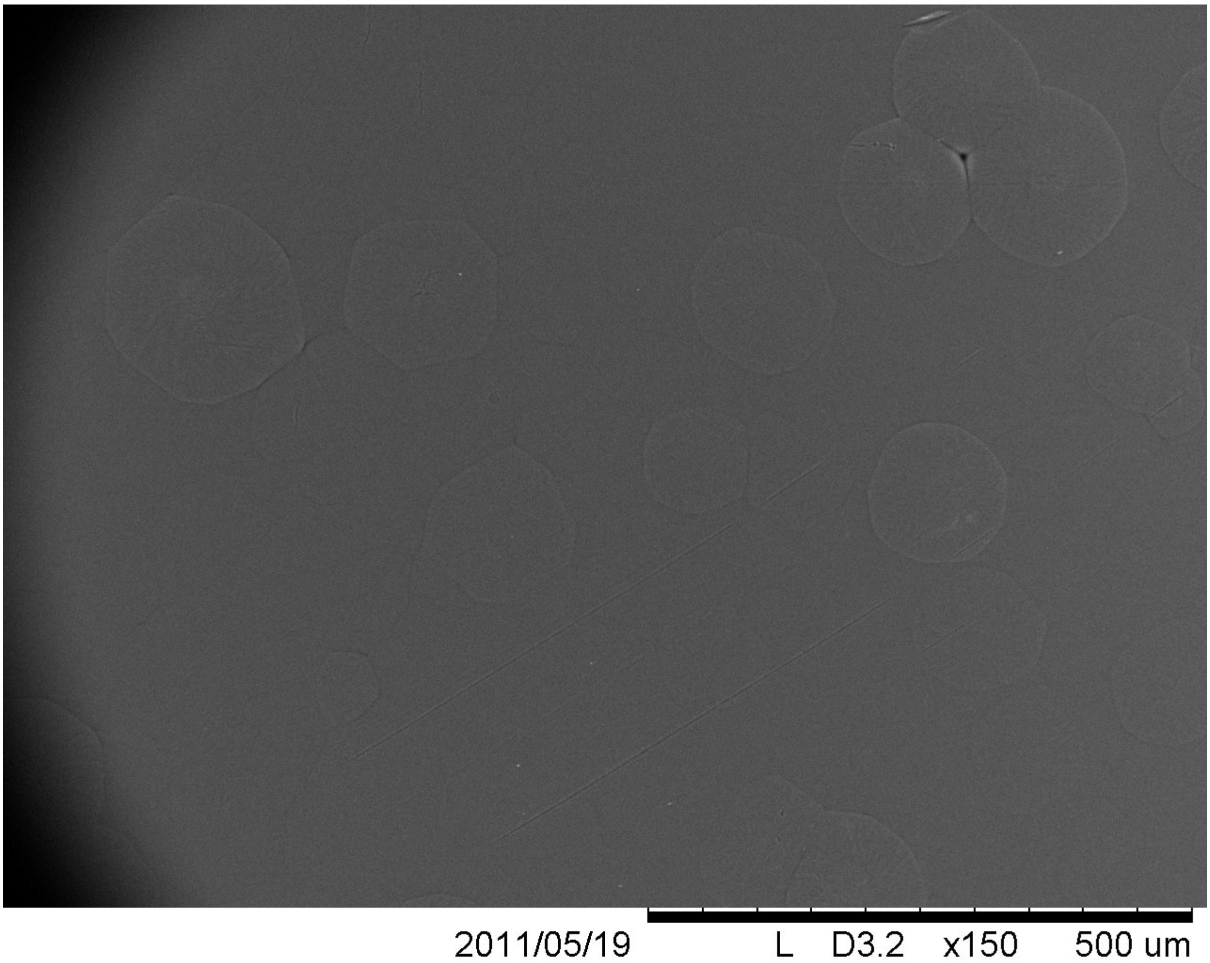


Figure 20 SEM image of a portion of the surface of a batch of PCL films that were left to dry 7 days

An interesting problem with this method started to appear during the manufacture of the second batch of films. In these cases, the films had an unusual consistency. The surface appeared wrinkly and inconsistent. This was traced back to the way the glass dish was placed over the film as it was drying out. The dish that covered the film was concave/convex, and when the dish was placed concave (see fig 21) the film appeared as described above. But when it was placed Convex, (see fig 22) the film surface appeared homogenous.

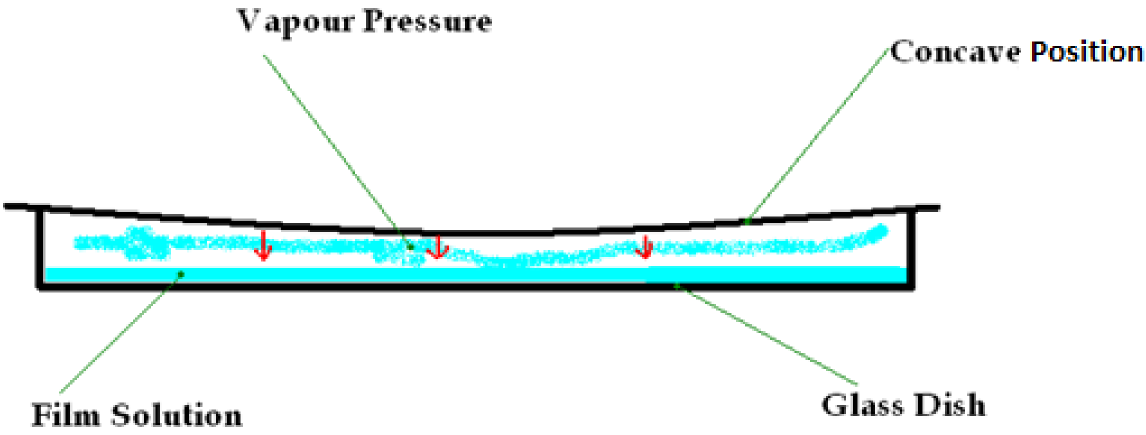


Figure 21 Pictorial representation of glass dish placed concave over the solvent tank

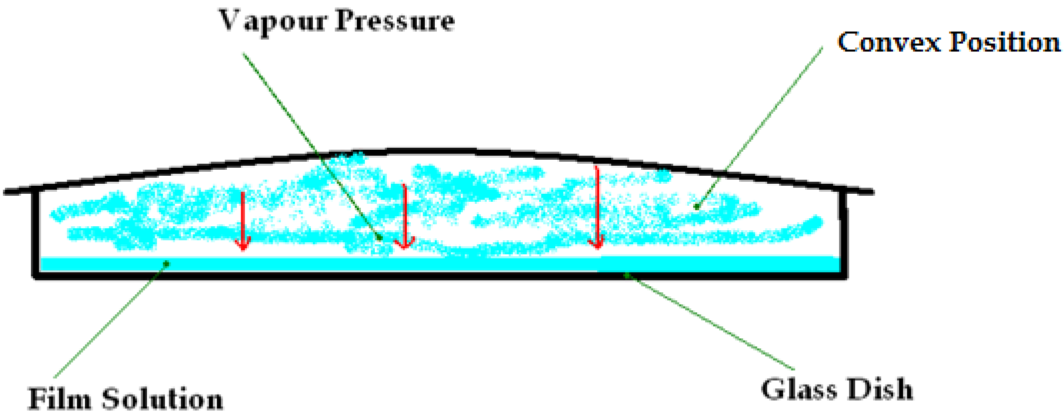


Figure 22Pictorial representation of glass dish placed convex over the solvent tank

Cursory glance suggests that vapour pressure during the evaporation process plays a major role in creating a homogenous solvent cast film. Why this happens or what exactly the effect is out beyond the scope of this body of work.

STATISTICAL PROCESS CONTROL FOR POLYMER FILM MANUFACTURE

Once the method of batch manufacture was selected, it was important to be able to manufacture polymer films that would have certain physical properties that were consistent in order to design a welding process that was optimised to fit those properties. For this reason Statistic Process Control (SPC) would need to be applied to the batch manufacturing process in order to provide films that were consistent over the entire process and were capable of been laser welded using the same welding process parameters. The end goal of the process was to provide welded film samples that were as uniform as possible so that any variation that appeared in the degradation results were due as much as possible to the laser welding process only. This reduced the risk of unknown or uncontrolled variables from interfering the experimental results, for example, different welding parameters or physical differences in the polymer films themselves.

Process Control

Statistical Process Control is a specific standard methodology for measuring and controlling quality during a particular manufacturing process. Quality data is obtained from product or process measurements during real-time manufacturing. All of this data is then plotted on a graph within specific control limits that are determined by the capability of the process.

Process Capability

Process capability describes the variability of the process over a long period of time, where all likely external influences are present. Variability can occur due to many factors including methods, materials or operators and machines.

Process capability is determined by comparing the spread of the process to the width of the specification limits. Process capability can be used to verify if a product can be produced within specification of the process or if the specifications can be tightened using the same process. The specification limits are usually determined by customer needs. In this case, the specification limits were determined by the range of weights of the films that could be satisfactorily welded using an optimised Laser welding process.

Control Charts

Control Charts are an excellent tool in distinguishing problems in the process due to Special Cause or Common Cause variation. Special cause variation occurs when once off factor is responsible for samples or a particular batch to fall outside a specified set of control limits. For example, in the film formation process described here, the average weights in some of the batches were either too heavy or too light. This is an indication that there is a root cause that can be assigned to these failures. Common cause variation is an indication of chance variation which is inherent in all processes. A process that has common cause variation is said to be in statistical control when there is no presence of any non-random variation, i.e. no trends occurring in the mean or variation points of the graphs. (Harris D.C 2003.)

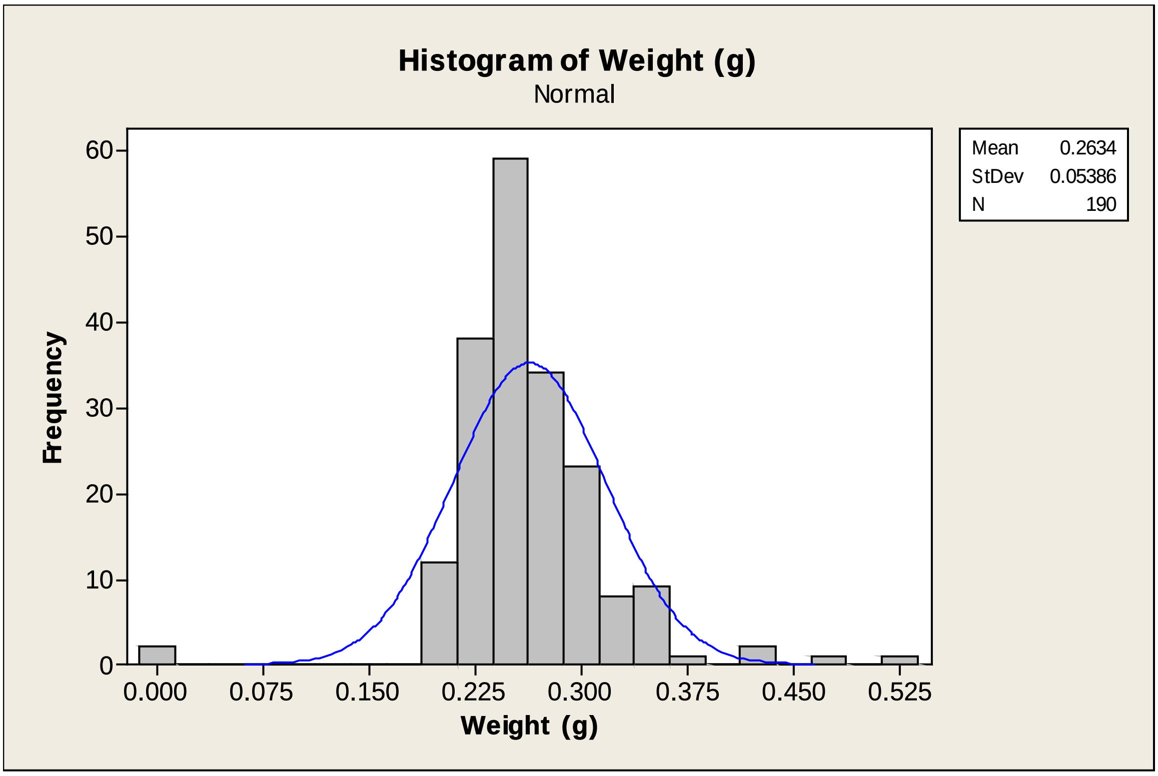


Figure 23 Distribution of individual weights in Single Layer Batch Formation

Figure 24 above is a histogram developed from every single film that was produced for the laser welding process using the single layer batch process. The histogram shows that the distribution of the weights is approximately Normal. This is an important fact because the upper and lower limits for the process can only be determined if the selected quality characteristic is Normally Distributed. As described earlier in the chapter, 32ml of dissolved PLC was pipette onto two flat dishes, covered with another dish and left to evaporate for a week. The films were then cut using a surgical blade around a glass microslide template and were then weighed to 4 decimal places. At the end of each week of manufacture, the process yielded 10 samples; each sample was weighed on an analytical balance. The weights were recorded in separate tables and each batch was given an individual identifying number. Over the course of the research 19 batches were manufactured, two batches however only had a total of 9 samples. The missing samples were given a weight of 0.000g in order to keep each batch size the same. The graph shows that the majority of the sample weights fall within 3σ from the centre value. It also showed that there were a number of samples that fell outside the "normal" weights produced by the solvent cast method. The fact that the data was normally distributed also aided the setting of Upper and Lower control limits which was later used to aid selection of films for laser welding as discussed in Chapter 3.

As well as setting upper and lower process control limits, control charts were used to construct charts to use as an aid in capturing the natural variation of the Single Layer Batch manufacture process. They were also used to look for unusual trends or patterns, and to see if the process was in control.

The quality characteristic of interest for the solvent cast method was weight, as this became an important factor in selecting films for laser welding and for measuring the effects of degradation (sees chapters 3 and 4).

At the end of the manufacturing period, the recorded weights were placed in a table with their respective batch numbers and the data was manipulated using Minitab™ statistical software.

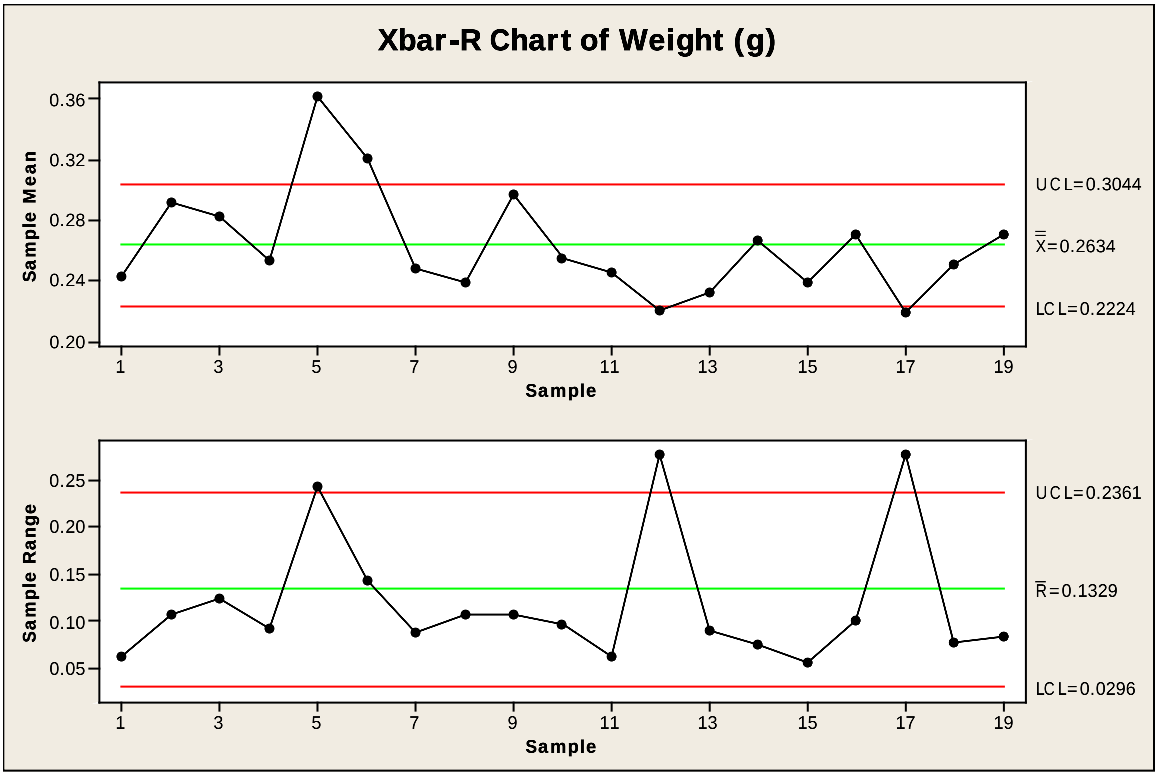


Figure 24 Control Chart for the Solvent Cast method (all Batches)

The process was then tested for stability to check to see if there were any special causes for variation in the solvent cast method. The data was assessed using Xbar and R charts. Xbar and R charts are the most commonly used charts to monitor process control. The Xbar chart (top graph in fig. 24) tracks changes in the process average or mean weight over time. The R chart (bottom graph in fig. 24) monitors changes in variability of the process in the short term. Both graphs showed that the process was not in control because some batches contained samples that were outside of the control limits. These errors were attributed to batches that were manufactured with a stock solution that had slightly higher concentrations of PCL to Dichloromethane. Reasons for this will be discussed later in the chapter. Once these erroneous batches were traced and removed from the data set, another control chart was generated using data from 5 randomly chosen film samples per batch. (5 being a common sample size for use in Xbar and R charts). The results are shown in fig 25 below.

Capability for this process was measured by using the same 5 random samples that were used in the Xbar and R charts above and using the Control limits established for the entire process using data from batches as laid out in fig 26. The results are shown below in fig 26.

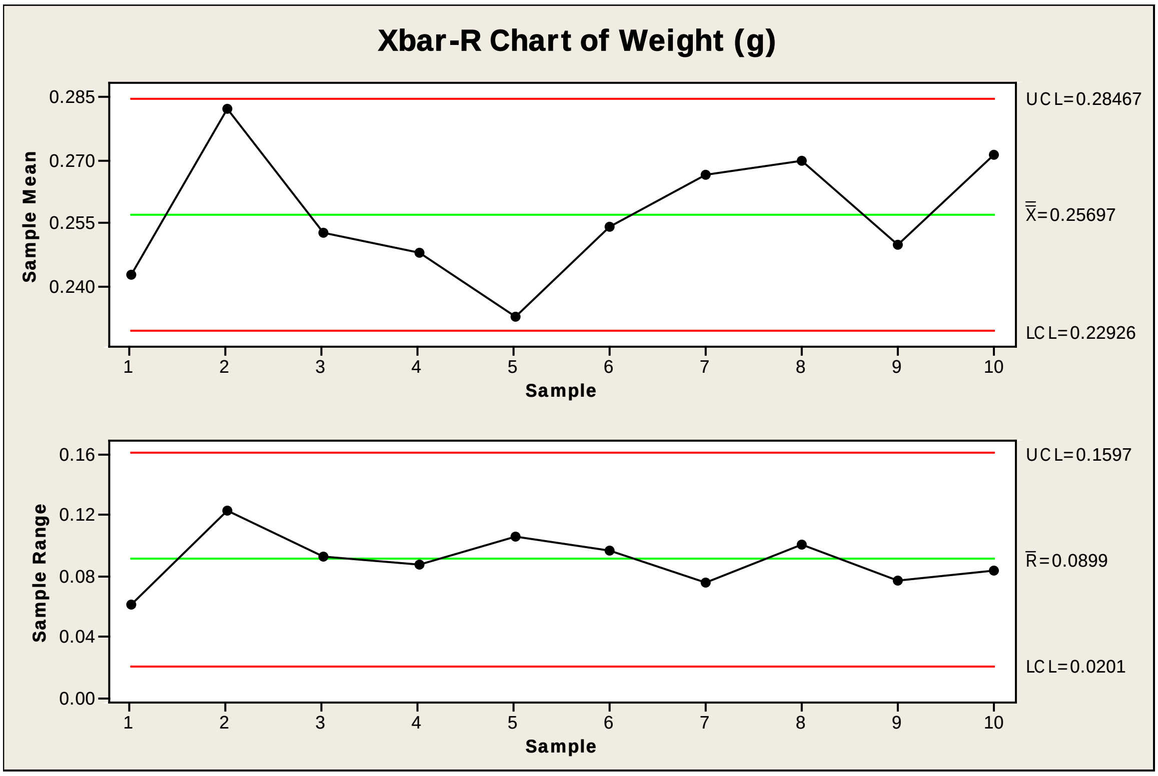


Figure 25 Control chart for (Revised Control Limits)

Both graphs in fig. 26 show a process that is in statistical control as there are no points outside the control limits, no unusual patterns or trends within the control limits (no non-random patterns). The graphs also generated revised control limits that were used to determine which films minimum and maximum standards for films on which to base the laser welding process parameters that were laid out in Chapter 3.

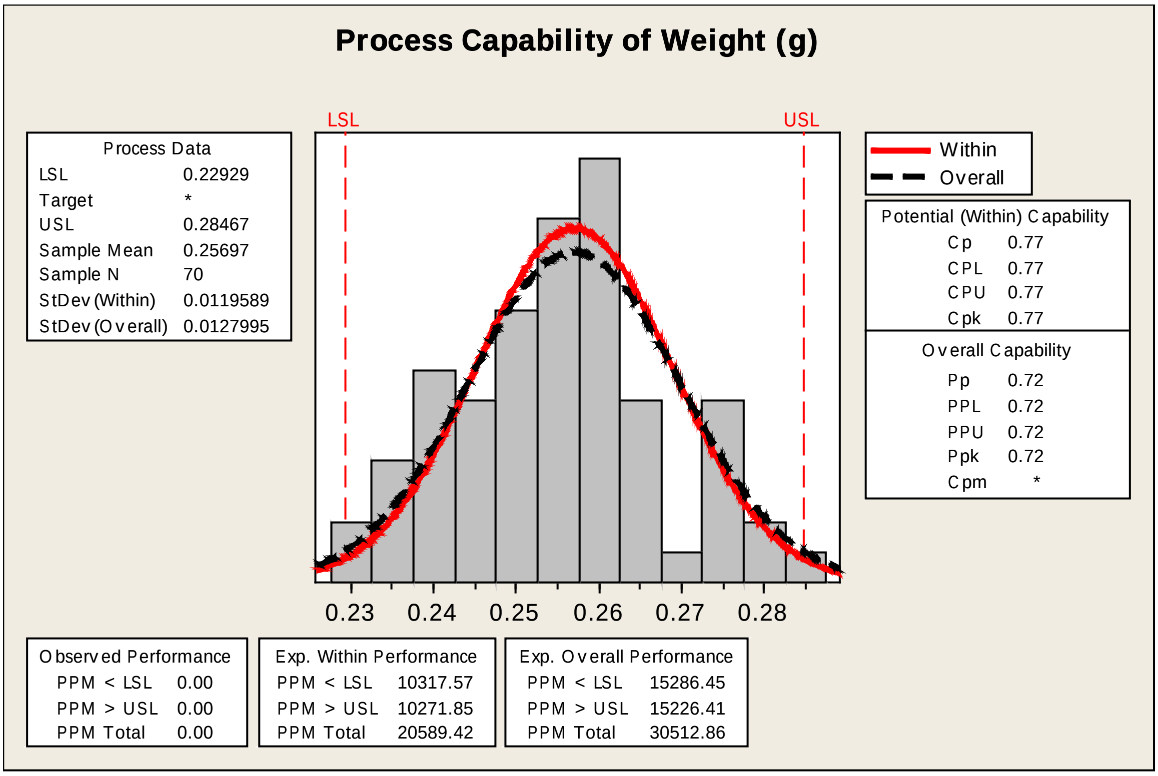


Figure 26 Process capability original control limits

As mentioned before, there were a number of batches that fell outside the control limits, skewing the results of the experiments. As seen in fig 24 the batch numbers concerned were batch 5, 6, 12 and 17. Investigations into batches 5 and 6 yielded the root cause to be a loss of solvent through natural evaporation to an extent that when the required volume of stock solution was removed from its primary container and placed into the casting dishes, the stock solution concentration was more than the required 10% PCL in Dichloromethane. The primary container in this case was the volumetric flask that was used to make up the stock solution at 10%.It was discovered from the laboratory notes at the time these batches were made that there was a significant time difference between the extraction of solution for batch 4, and the extraction of solution for batches 5 and 6 which caused the increase in concentration. The solutions to this would be:

1. To increase the number of casting dishes, so more stock solution can be removed from its primary container at the start of the process and if possible, to empty the primary container initially. This would cut out any loss of solvent over time, maintaining the 10% concentration for each batch.

2. Using the current number of casting dishes, ensure that the primary container is emptied within 3 weeks.

3. Use smaller volumetric flasks to create the stock solutions for all the batches.

For batches 12 and 17, no discernible root cause was evident in the note books for why the batches were too light. It is suspected that the cause may be due to operator error in extracting the volumes of stock solution for these particular batches. (The volumes were extracted using a pipette, it maybe just that the operator extracted smaller volumes than normal for these batches).

The process capability results show a Cp of 0.72 and a Cpk also of 0.72. As a general rule of thumb, a value of 1 indicates the process variation exactly equals the tolerance, values of less than 1 indicate the allowable variation (the tolerance) is less than the process variation and values of more than 1 indicate that the process variation is less than the tolerance. Values greater than 1 are most desirable, and many quality organisations recommend values of 1.33 or greater. This allows a margin of error in case a process shift occurs that is not immediately detected. Because the results here are low, there is scope for more improvements to be carried out to the process in order to tighten the process variation. This could be obtained in a number of ways:

1. Controlling the temperature of the environment in which the process occurs in, as the evaporation process occurred at room temperature, the rate of evaporation could be adversely affected by variable room temperature in which it was occurring.
2. Ensure that the casting dishes were kept level at all times, carrying out periodic checks to ensure this. (Calibration)
3. Use a different process technique.

The overall aim of the process control was to ensure that films that were created for the research met a minimum specification and ensure that any variation between the degradation rates of the welded films versus the un-welded films was due to the Laser welding process only.

SUMMARY

The material chosen for experimentation in this body of work was Polycaprolactone. Polycaprolactone was chosen for its wide availability, manageable degradation rate and the fact that it could be accelerated if needed by using a combination of Phosphate Buffered Saline and lipase. The Polycaprolactone granules were processed into films using the Solvent cast method which was selected for its low setup costs. From the experiments in the process control parameters for these films, it was found that using a stock solution with a concentration of 10% $^{w}/_{v}$ of Polycaprolactone in dichloromethane provided the most suitable, tactile films for laser welding. Statistical process control was carried out on the manufacturing process in order to achieve a higher degree of control over the selection of Polycaprolactone films for the laser welding process. This type of SPC cut down on the amount of time spent in optimising the welding process by providing an empirical method for providing a steady stream of consistent quality films. Further discussion of the how these quality methods impacted on the laser welding optimization process can be found in the next chapter.

Chapter 3 Laser Welding

In this chapter, the process of the laser welding of the polymer films is discussed. Also in this chapter, the various problems associated with welding films are also explored in some detail. There were two types of welding experiments carried out for this chapter. The first was the attempt to obtain a good weld, the second was the attempt to weld as much of the surface area of the films as possible in order to investigate any effects the laser welding process had on the degradation properties of the material

INTRODUCTION

As discussed in the introduction, the gain medium for the laser used in these experiments was Carbon Dioxide. The laser had an operating wavelength of 10.6µm. The laser was manufactured by Synrad, model number J48-1W. There were no lenses used to manipulate the beam, which had a beam width of approximately 5mm. The only control used for the beam was the laser power setting. The laser itself was generated in a continuous pulse wave. The laser set up was used as is, the only addition been an Acrylic enclosure that was designed to enclose the whole beam path, from the radiation source to the surface for the polymer films. The setup also had a diode laser, which was used as a guide to set the laser beam for automation.

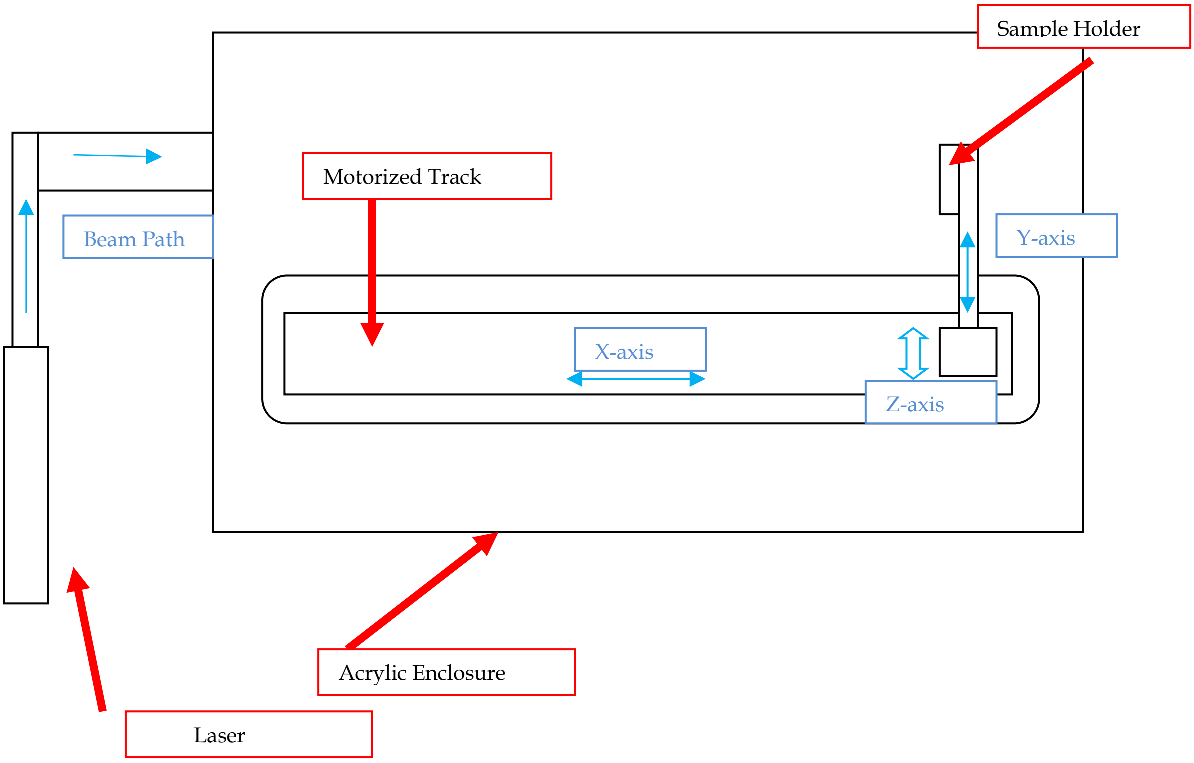


Figure 27 Plan view of the laser setup.

Initial tests on the laser were carried out to obtain just one good solid weld seam on the films and then using the welding parameter to further optimise the parameters of the final welding process used to generate test samples for the degradation experiments (see table 1). Once the parameters were narrowed down, the process was further optimised to give a weld across the whole surface of the films (see table 2). As the degradation process for Polycaprolactone occurs in a combination of surface and bulk erosion (which is not limited to specific areas of the films), it was decided to attempt a complete surface weld in order to achieve relevant experimental results. This was expected to give a good correlation of results between non-welded and welded films. See chapter 4 for further details.

THE LASER WELDING PROCESS

Laser Welding can occur only when the heating effect of the laser radiation extends well into the joint to be welded. Penetration of laser welds in polymers occur over a wavelength range of 9.12μm to 11μm.There is a narrow temperature band where the polymer melts and the polymer decomposes. Control of the temperature in the melt pool is critical. (Duley 1998). Treading the border between polymer decomposition due to thermal degradation and generating just enough heat to melt the films enough to achieve a weld pool constitutes the main difficulty with welding polymers. The temperature that this occurs at is so very close to the optimum temperature at which the polymers melts to form the weld pool. For PCL this temperature is relatively low, at around 60^0C which made the whole laser welding process into a delicate balancing act in order to control the welding process environment.

With this in mind, initial welding experiments were started at 50% laser power setting and a sample movement rate of 30 ms^{-1}. However, the heat generated at these settings was enough to burn a hole right through the PCL films. There were two options that presented themselves at which this could have been controlled:

1. The actual amount of laser power applied to the surface.
2. The speed at which the sample moved to create the weld seams between the films.

In the welding process used for these experiments, the welding process occurs in three stages:

1. The radiation delivered by the CO_2 laser was absorbed by the PCL film on the top layer.
2. The energy absorbed excites the Carbon bonds inside the film causing it to heat up.
3. The heat was then transferred to the film on the bottom layer, inducing both films to melt at the point of absorbance and generating the weld pool.

Another problem that arose while welding the films was the occurrence of holes between the weld pools. This was caused by surface tension building up between the rapid heating and cooling actions on the same surface in different areas. Special welding patterns were put in place to limit these defects, more of which are explained later in this chapter.

Clamping

Clamping is very important in laser welding, especially important in the welding that was carried out in these experiments. However, even though the clamping is important, the clamping mechanisms themselves need not be complicated. What matters most in the sample clamping is that both films to be welded are held as close to each other as possible and as firm as possible, especially in conduction mode lap welding that was used here. Conduction mode lap welding is where one film is laid over the other and the laser applied. The energy transfer from the laser to the film occurred by heat generated from the molecular vibrations inside the top layer, transferring to the bottom layer and causing the two surfaces to melt into one another.

If the films were not clamped together correctly, what tends to happen is that the resulting welds are incomplete or that a distortion occurs near the area that does not have sufficient clamping force. The distortion is easily spotted, but incomplete welds were not as obvious, as the weld pool itself may not have sufficiently bonded in the interior of the films which creates weaknesses to the weld strength.

Weld strength was of lesser importance here, because this body of work is focused more with the effects of the welding itself on the degradation properties rather than the strength of the welding bond. But clamping was still important to obtaining decent weld pools.

The clamping mode was limited by the setup of the laser apparatus. The film had to be attached in some way to the aluminium "Arm" that was in turn attached to the automotive movement table. (See fig 28)

This arm consisted of a number of aluminium plates bolted together to form an "elbow" on to which a film holder could be attached. Two separate bespoke clamping methods were created for the two stages of the process development.

In the first stage of development a clamp was created to hold the films in close contact with each other in order to explore the best laser welding parameters to be used to create a single weld seam. The clamping method used for this particular weld was made up of a glass rod stuck onto the middle of the surface of a microscope slide. The two films were pressed together and draped across the glass rod and held together at both ends of the microscope slide with sticky tape. The idea behind draping the films over the glass rod was that both films would be forced close together at the point where the two films cross the glass rod. This point created an excellent fit up and it was along this point that the film was exposed to the laser. The whole clamping mechanism, along the films to be welded were then held in place on the "elbow" of the film holder using "bluetac^{tm}"

For the multiple seam welds, a slightly different setup was designed in order to achieve good 'fit ups' for both films across the entire surface of the films. Also the clamps themselves had to be placed in such a way as to expose the maximum surface area of the films to the laser itself. This design consisted of a single microscope slide and four separate bobby pins to apply the forces needed to keep the films pressed together in order to achieve a solid weld. Two pins were placed on the slide by sliding them length ways in parallel with each other. The films that were to be welded were then draped over the bumpy side of the pins and then both films were clamped onto the microscope slide using the second pair of pins. The crest of the bumps on the bobby pins provided excellent points of force application which spread evenly across the entire surface are of the films. The microscope slide itself was held into position on the film holder again using "bluetac^{tm}"

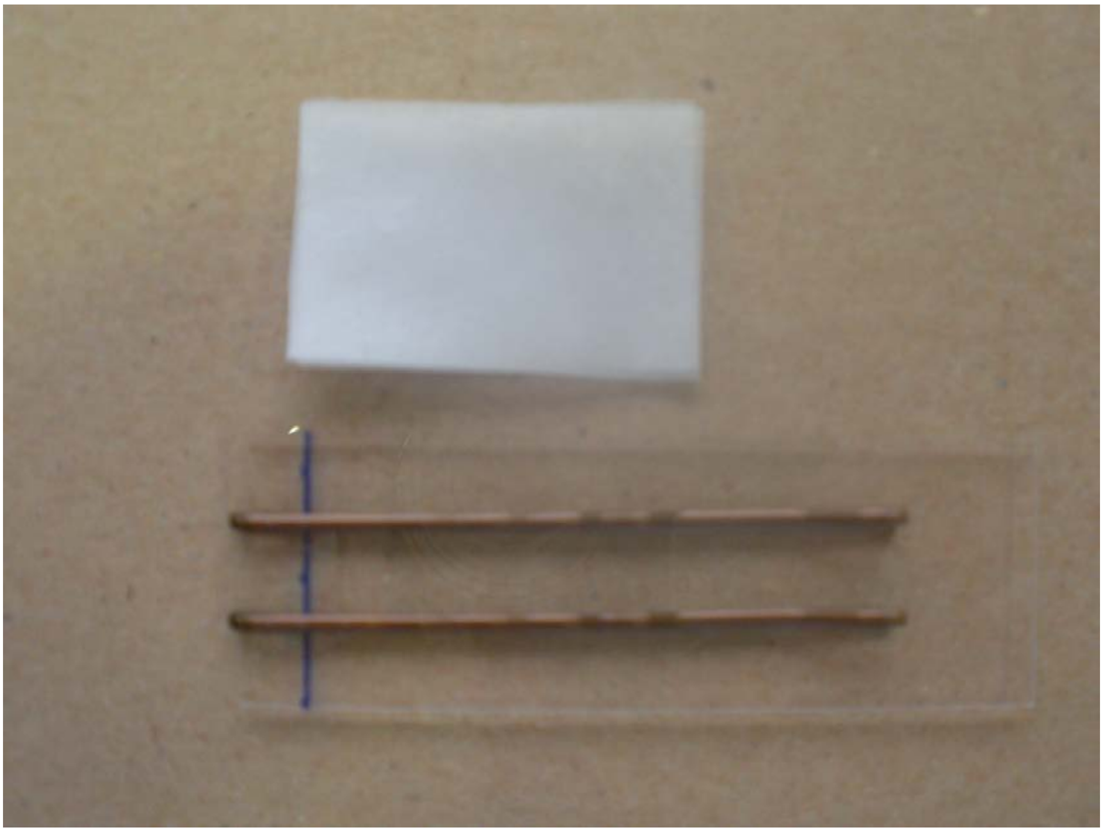


Figure 28 Sample Clamping, two bobby pins (for this purpose, termed “foundation Pins”) are fixed to the microslide and are held on under the tension generated by the bobby pins on the glass surface

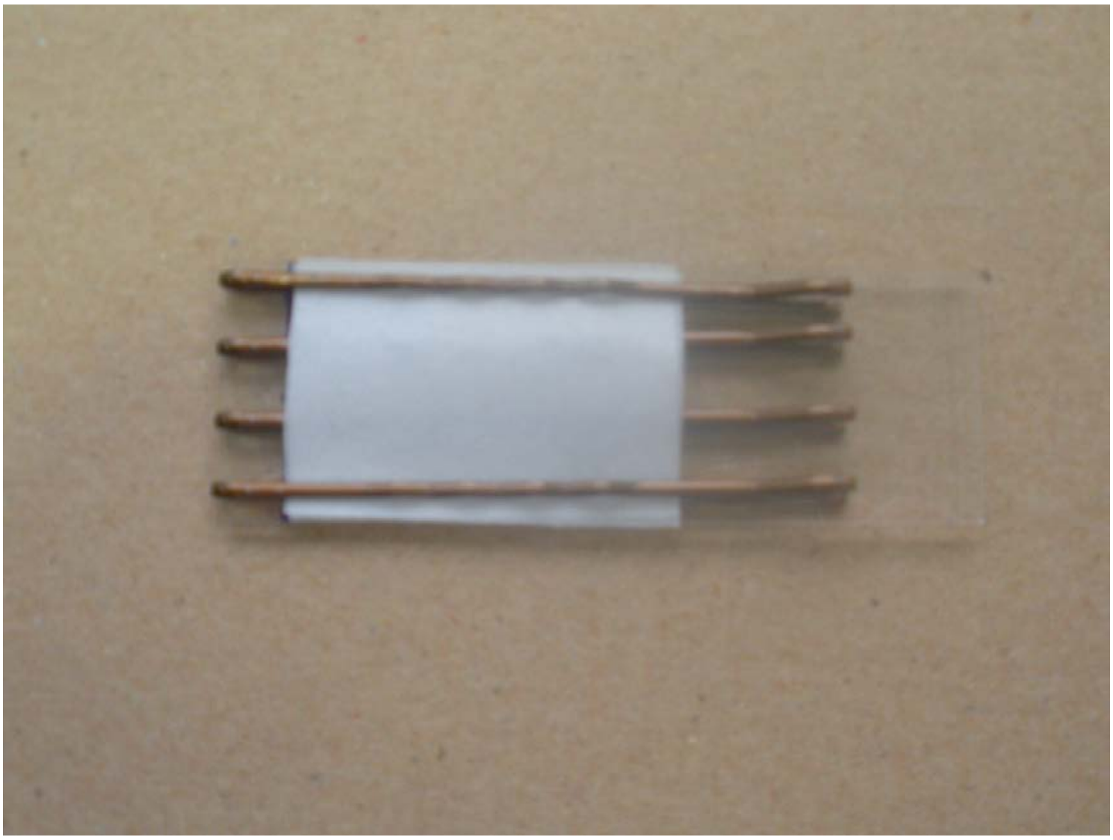


Figure 29 Sample Clamping 2, the sample to be welded is then placed over the Foundation pins. Two more pins are placed near the edges of the weld samples, therefor fixing the samples on tight to the slide. This particular set up generates two separate clamping forces onto the weld sample. The first is the downward pressure provided by the pins on the edge, fixing the sample in position. The second force is generated by the "bumps" on the foundation pins which keep the film pressed firmly together in the centre.

Film Sample Movement

The setup of the laser welding apparatus kept the laser in a fixed position and allowed the film to be welded to move through 3 axis, X, Y & Z. The sample movement was controlled us a DS (Dynamic Systems) controller. Motion control was programmed using the Super SEL programming language and connected to the central processing unit (CPU) via an RS232 cable connection. The system velocity could be set in 1mm/sec increments, and allowed different velocities to be set for each position change. The maximum stroke length along the X axis was 500mm, Y and Z axis were both 50mm.

The actuator had two different levels of repeatability, ±0.05 mm and ±0.02on the X axis. The movement was driven by an AC servo motor and ball screw for multiple positioning. A magnetic brake was installed on the Z axis to prevent the arm from dropping in the event of power loss.

The controller that was used to control the movement itself was a 32 bit RISC CPU that used Windows NT software. The CPU was used in Program mode, and parallel processed signals coming from the Laser unit, external warning light and a guide diode laser used for programming the position of the weld seams. A PC was used to interface with the programs used to control the welding process parameters.

Programming

Each position for the sample movement had to be programmed individually through the SEL programming language as described above. The position of the film holder was programmed in three axis, X,Y and Z. The values for these positions were retained in a separate file to the main program called a position file and had its own *.PNT extension. The velocity of the actuator was also stored in this particular program. The main program itself, governed the timing of the sequences and the activation of each of the inputs, for example, turning on and off the laser, the warning light and the diode laser that was used as a guide for the welding process. These values were stored in the program with the file extension of *.PRG. For the complete program used in the both single and multi seam welds, please see Appendix A.

Parameter Selection

There were only two parameters that could have been manipulated in this setup in order to control this welding process. The first was laser power which could be adjusted manually through a dial control and the second was the movement speed of the film to be welded relative to the lasing source, which was fixed. The laser power could be adjusted in increments of 0.5% of total laser power and the movement speed was controlled by the manipulating the control software called SEL.

The movement speed of the film was in fact an important parameter to control, because the movement speed dictated the laser contact time with the samples to be welded (the longer the laser contact time, the greater the amount of heat generated in the films).

The contact time indirectly depended on the programming parameters that were programmed in the SEL programming software. By adjusting these parameters, and by adequately controlling the clamping conditions as explained above, a plan was devised to select the best parameters to use in welding of the samples.

The first laser firing was carried out at 50% laser power on a sheet of paper. The reason for this was two-fold, first, it gave an indication of the position of the weld spot in relation to the film holder and second, it gave an indication on the diameter of the weld spot, (which turned out to be approximately 5mm). Once the position and size of the weld was determined, two full sized PCL films were placed together in a clamping device which was based on the single weld seam discussed previously and placed in the film holder. The program was run and the weld quality was assessed after, based on the whether the weld pool had fused both films together at the seam.

This was the exploratory phase of the experiments. The goal of this phase was to pin point the starting parameter selections, i.e. laser power and movement and from here process could be optimized further to give consistently good welds. Each of the films was selected using the criteria laid out in previously in Chapter two under the process control section. Both films were placed together in the clamping set up (for single welds) and the lasing program was run. If the weld seam was not satisfactory, a second pair of films was selected and the process was adjusted before running the program again. A table was created using the results of this phase and can be viewed in Table 1 below.

% Laser Power	**Film Holder Speed ms^{-1}**	**Result**
50	30	Both layers degraded.
45	30	Top layer degraded, burned holes in second layer.
40	30	Top layer degraded, second layer seems untouched.
35	30	Weld pool created, but with holes burned through.

% Laser Power	**Film Holder Speed ms^{-1}**	**Result**
30	30	Weld pool generated in both layers, hardly any burn holes, but the surface seems warped.
25	30	No weld pool generated. Faint outlines of the laser exposure on the surface of the top layer.

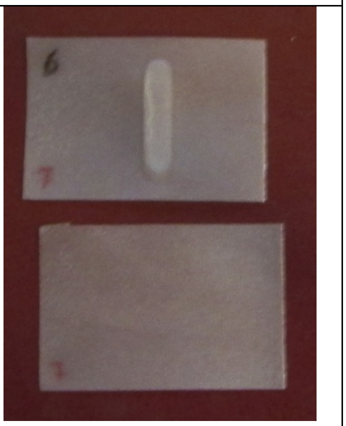
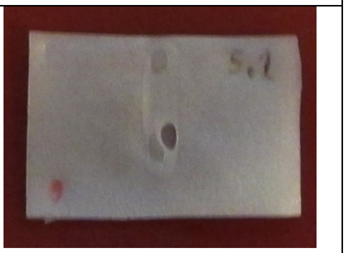
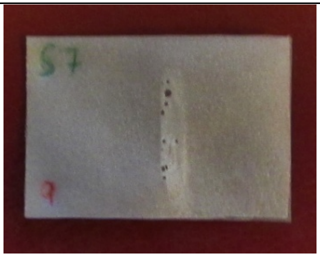
Table 1 Stage one of Laser Process Parameter Selection

From the results of this phase of experimentation, it was found that a parameter combination of laser power 30% and sample speed of 30 ms^{-1} achieved the most satisfactory weld seam. The next phase was designed to fine tune the parameters using this as a starting point in order to produce even better quality welds. The aim of this phase of the experiment was to see if the selected parameters produced a consistently good weld on new films that had been selected based on the criteria mentioned in chapter two. There were some other adjustments made to the process and films also in order to achieve the results. It was decided at this point that in order to preserve similar environments for the welded and non-welded films during the degradation experiments, both sets of samples should have similar weights. This would preserve the polymer mass to volume of degradation solution ratio in the experiment, the importance of which is further discussed in chapter four.

PROCESS OPTIMIZATION

In this phase, a film sample was selected, folded in half and then cut along the centre line, creating a film sample that was the same weight as the non-welded films. The new films were then placed in the single weld seam clamping device and the lasing program was run. This process was repeated four more times using different films. This was to test if the samples could be welded consistently using the same parameters. The description of the results obtained in table 2 below were a summary of the majority of what was evident from each 5 sample batch used in the optimisation process.

% Laser Power	Sample Speed ms^{-1}	Result	Image
30	30	Partial mixed weld pool top and bottom. (heat was not transferred adequately to bottom layer).	
32	30	Good weld pool formation. Top layer damaged in some areas with burn marks.	
29	20	Several burn holes through both layers.	
28	20	Several burn holes through both layers.	
27	20	Partial weld pool formed. Few burn marks. (heat not transferred to bottom layer)	

% Laser Power	Sample Speed ms^{-1}	Result	Image
26	25	Good melt pool formed. Holes in top layer	
26	20	No weld pool formation. No heat transfer to bottom layer.	
27	10	Good melt pool formed. Holes in top layer	
27	12	Melt pool formed, but not all the way through second layer. Holes in top layer	

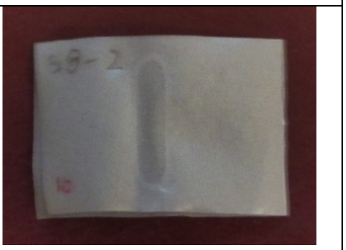
% Laser Power	Sample Speed ms^{-1}	Result	Image
27.5	12.5	Good weld pool formed. Good transfer to both layers	

Table 2 Stage two, Laser Process Optimization

Once stage 2 had been completed and the parameters were pinned down for single seam welding, the program was adjusted accordingly to cope with running multiple weld seams across the surface of the samples welding the films together. The use of multiple welds required some further process optimization. These optimizations took the form of slight changes to the speed of the sample movement, and built-in time delays to the programming to allow for the seams to cool and solidify before the next seam was produced. The reasons for this are described below in the results section. As in stage two, the films were welded in batches of five and pooled together in order to have a good number of samples available to the researcher for selection for the degradation experiments as laid out in chapter four.

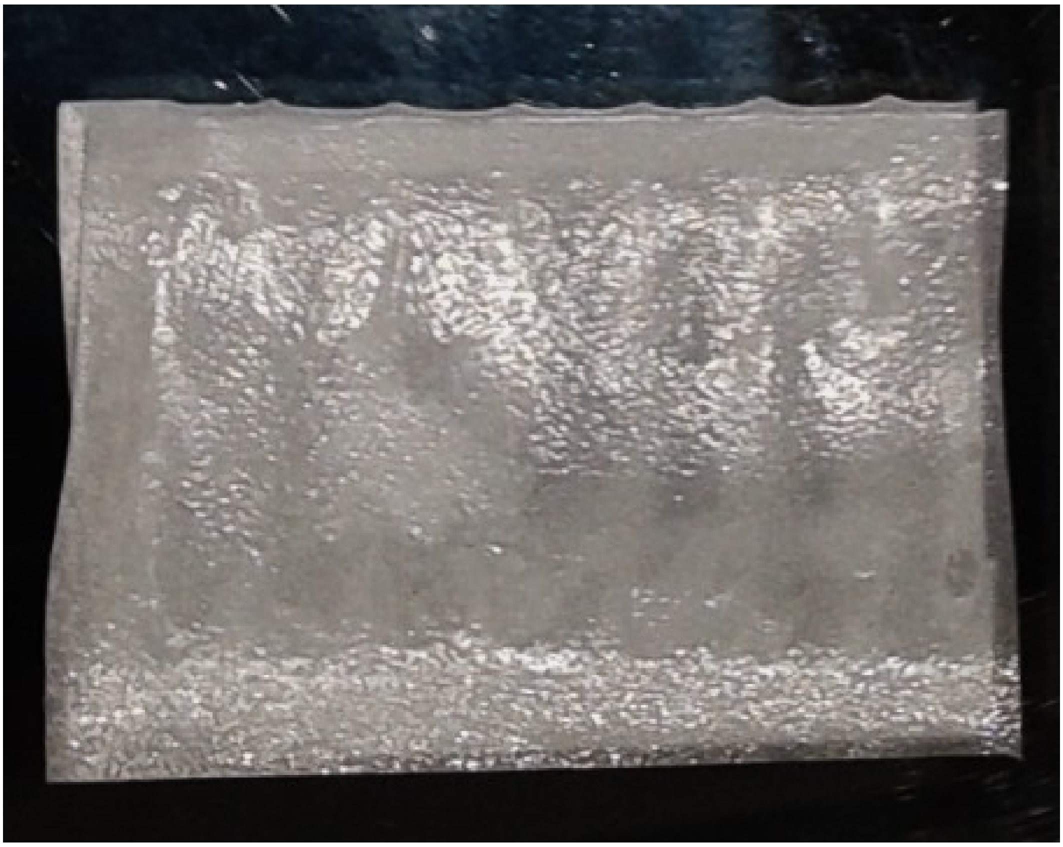


Figure 30 Sample of a multiple seam weld

RESULTS OF OPTIMIZATION PROCESS EXPERIMENTS

Initial tests showed that there were six main factors affecting the quality of the weld pools.

1. The obvious one was the percentage laser power used in the weld, the higher the percentage, the more likely the films would go into thermal degradation.
2. The exposure time the film surface had to the laser, the longer the surface was exposed, the more radiation that part of the film received.
3. Cooling time of the weld seams. This did not have as much of an effect on the single welds as it did on the multiple welds however.
4. Inherent deficiencies present in the films themselves. Despite every effort to maintain a homogenous film thickness, in some cases this did not occur, and resulted in differences in the rate thermal degradation in individual films.
5. Clamping.
6. Mechanical forces within the welded films occurring due to the cooling of material in the weld pool.

Percentage Laser Power: As discussed in the parameter selection section above, the laser power was manually controlled via a dial on the laser unit. When the films were welded at this setting however, they were almost completely degraded on initial exposure. Using 50% as a starting level, subsequent welds were carried out on films, with the level decreased by 5% for each run. At 30% weld power, the top samples were not as badly degraded and there was decent mixing of the two layers in the weld pool.

Laser Exposure Time: The time that the films were exposed to the laser was governed by the speed at which the sample was moved in front of the laser. The slower the speed, the longer the surface was subjected to the Laser radiation. The default speed of the sample holder was at 30 ms^{-1} and was used initially to get a decent weld, without too much thermal degradation on the top film. When this was achieved, the speed of the sample movement was adjusted during the process optimization stage. The optimized speed for acceptable weld pools was found to be 12.5 ms^{-1}

Film Thickness/weak spots: Occasionally, some films would be obliterated by the same parameters that were used to successfully weld other films. This could be traced in the majority of cases to the fact the film that was been welded weighed less than the average films. Concurrently, films that weighed more than the average did not generate sufficient melt between the two layers. Weight was an indication of the thickness of the films, and any films that did not have sufficient weld pools were discarded. This waste was lessened by only selecting films that met certain weight restrictions. Through experimental methods, the ideal weight was found to be 0.2570 $^{+}$- 0.0900.

Cooling Time: This came more of an issue for the multiple weld seams. Problems were occurring when a second weld seam was started before the first one had cooled. As the border of the first seam cooled, it shrunk, placing a mechanical strain on the second seam which resulted in the surface between the seams being pulled apart. This was corrected by changing the order and position of individual weld pools as shown in the diagram below.

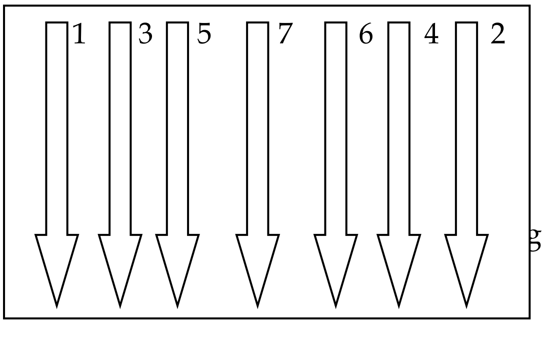


Figure 31 Direction and position of individual weld seams in multi welded films

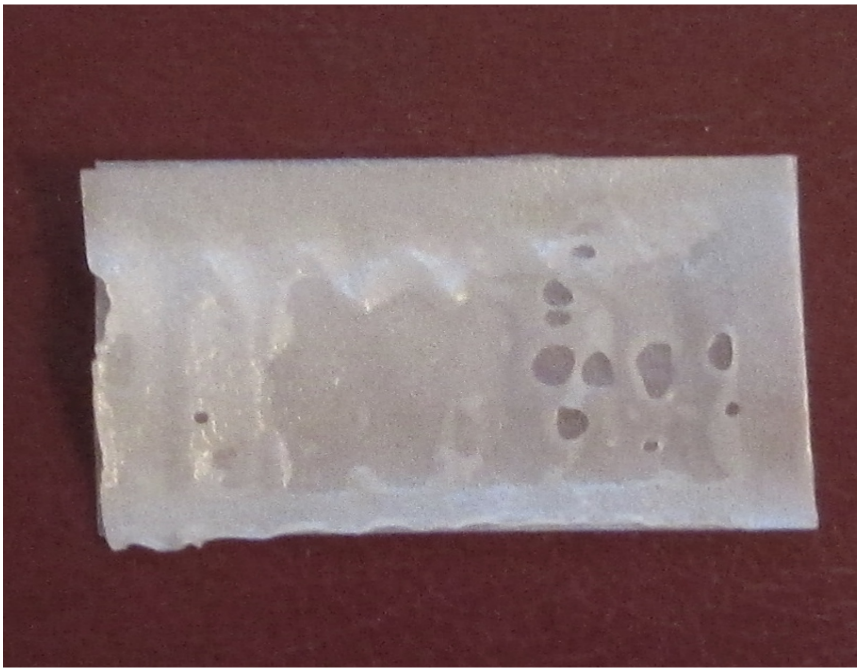


Figure 32 Defects on sample due to Insufficient cooling time

Clamping: As discussed previously, it was of vital importance that the two samples were kept in close contact throughout the welding process. It is shown in the picture below; the samples took on a warped appearance if the clamping mechanism was not spreading sufficient clamping force in that area. In the example below, the warpage was caused when insufficient clamping force failed to hold the two films together adequately at point A. This introduced a void, or bubble which warped the surface in the surrounding area.

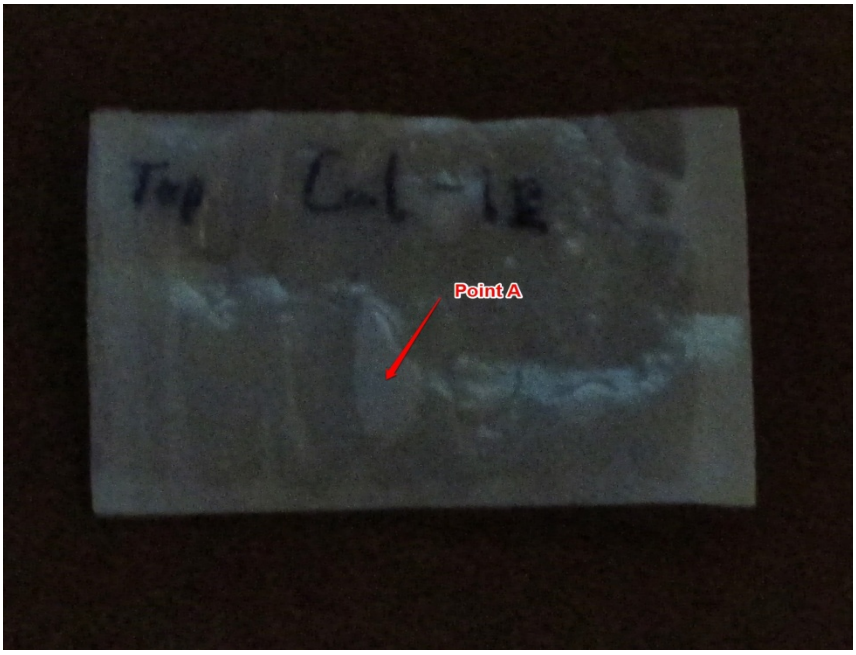


Figure 33 Example defective welds due to poor clamping

Thermally Generated Mechanical Strain: Similar defects occurred in this way as they did in the section discussed in Cooling time. They almost always occurred in films that had multiple weld seams. They differed slightly in the fact that the films were well within the weight tolerances discussed in the film thickness section. The defects were lessened by alternating weld pools and also slightly increasing the cooling time, especially in sections were the weld seams were close together. Thermally Generated Mechanical strain occurs when a force deferential appears between two sections of the same surface of the samples being welded. This force differential can be destructive when one section cools faster than the other section, with the contraction force due to the cooling creating an increase in surface tension, pulling the two sections apart.

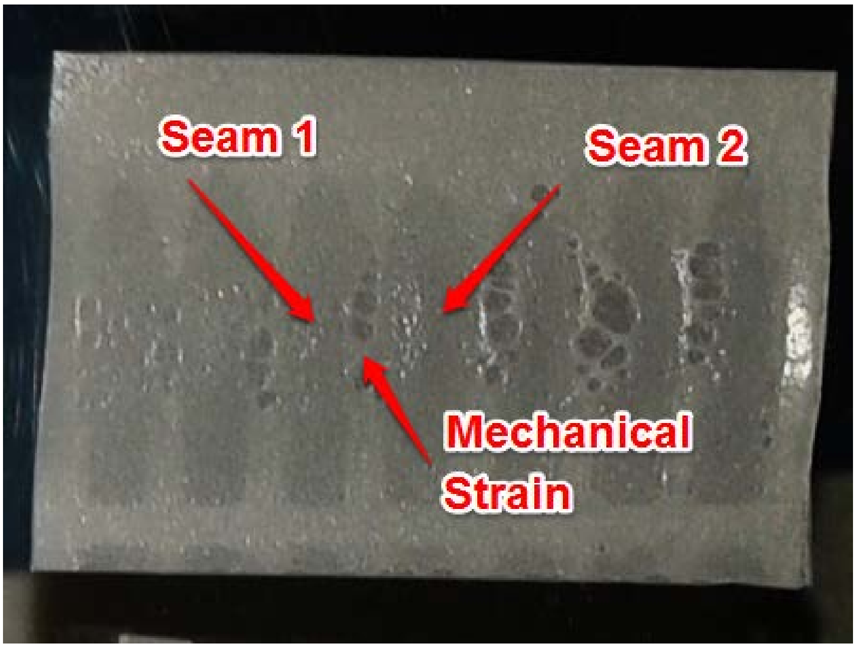


Figure 34 Examples of defective welds due to Thermally Generated Mechanical Strain.

SUMMARY

The aim of this chapter was to describe the process involved in achieving consistently good quality welds on the polymer films. It also described in detail the good and bad affects that clamping, laser radiation exposure time, and the quality of the films that were welded using specific welding process parameters. The welding process went through three distinct phases at the development stage. The phases were as follows:

1. The exploratory phase where roughly estimated parameter selections were used to generate a single acceptable weld pool.
2. Optimization phase where the selected parameters discovered in the exploratory phase above were used on five consecutive films to verify that these parameters provided a consistently good quality weld seam for each film.
3. Parameters used in the optimization phase were then applied to weld films with multiple seams, ready for the degradation part of the experiments.

At the end of the three stages of optimization, the end result was a stable process that welded large quantities of films together with the minimum input from the user at the start of each batch. The process took into account the thin line between the attainment of a good weld seam and the total thermal degradation of the polymer that was to be welded. It also kept wastage to a minimum through following of a selection process of films laid out in chapter two and fine tuning the welding process parameters around this sample selection process. It also maximised the amount of samples available to continue on with Degradation testing itself which is discussed in greater detail in Chapter four.

Chapter 4 Degradation Testing

In this chapter the Degradation Mechanisms of the biomaterial are discussed along with the effects the Laser welding had on the rate and structures of the material itself. The degradation was split into two phases, Phase 1 where untreated samples were degraded for 18 weeks in Phosphate Buffered Saline (PBS) and PBS containing 1 mg/L of Porcine Lipase. Degradation was characterized using weight loss, pH and HPLC testing. Degraded samples were also viewed with a Scanning Electron Microscope at different stages of the Degradation Process. Phase 2 consisted of the same tests on biodegradable films that were either treated by laser or actually welded together. Comparative analysis was then completed on both sets of data.

INTRODUCTION

All polymers degrade eventually, over time spans ranging from six minutes (poly-anhydrides) to 83,000 years (poly-amides). For the purposes of medical devices, drug delivery or Tissue engineering, most materials require a degradation time of between several weeks and up to 2 years. (Göpferich 1996)

Degradation for most semi-crystalline polymers typically happens in two stages. In the first stage, degradation preferentially occurs in amorphous regions as some of the water from the PBS penetrates the bulk of the film through the cavities between the amorphous regions of the polymer. The remaining polymer chains then start to align in a more crystalline structure. As more amorphous material is lost through degradation, the crystalline portions of the polymer get shorter and are open to hydrolytic and enzymatic degradation, increasing the rates of degradation for that portion of the process. (Middleton & Tipton 2000)

As part of the Laser Welding project, it was decided to carry out some degradation studies on the biodegradable material to see if any changes were evident once the material was Laser welded. Samples were initially degraded before the laser welding process was applied in order to obtain baseline data onto which we could work from.

METHOD

Films of PCL measuring on average 26x76x0.2 mm were degraded in 25 ml of Phosphate buffered saline (PBS) and PBS 1mg/l Lipase at 37^0 C for 16 weeks. A set of three samples were removed every 2 weeks and analysed under Scanning Electron microscope (SEM). The dry weights were measured and results were tabulated in an Excel spreadsheet. The PBS and PBS/Lipase was renewed twice a week and pH measurements were taken at each change over (PBS samples only). The PBS came in tablets and was sourced from Sigma Aldritch. Each tablet generated 200ml of solution at pH of 7.3. The Lipase (porcine) was as also sourced from Sigma Aldritch and came in powder form.

SEM

For the SEM analysis, samples were cut using a blade from the samples that seemed to have had the highest mass loss. These samples were cut to approximately 5 mm square, usually cut from an area in the centre of the film and in some cases, areas that included the edge of the original sample. The samples were attached to Carbon Tabs of 12 mm diameter and then placed on aluminium stubs. The entire film surface was first viewed at a lower magnification of 150. The field of view was then moved from right to left, then down along the edge, left to right, up along the other edge, and back across to the opposite side. Any typical images were taken and saved at magnifications of 150, 500, 1000, 1500, 5000 and in some cases 10000. The SEM was a Hitachi TM-1000 table top microscope. The Working Distance was 6440 µm and the Emission Current was 57900 A. The acceleration voltage used to obtain the images was 15kV.

pH

For the pH analysis a Thermo Scientific, Orion Star meter was used in conjunction with a VWR International, gel filled glass probe. Readings were taken twice a week during the buffer change. The meter was calibrated prior to use, (At least twice a week), using three buffer solutions purchased from Acros Organics: phthalate buffer solution pH 4.01, phosphate buffer solution pH 7.00 and borate buffer solution pH 10.01.The pH was then recorded in an Excel spreadsheet, where the differences in measurements were graphed. The data for this table was obtained by measuring the pH of the buffer before it was placed in the petri dishes with sample and then measured again at the next buffer changeover. The differences were then plotted on a graph to verify chemical changes if any were occurring during the degradation process.

The PBS was sourced from SigmaAldritch and came in tablet form. Each Tablet was dissolved in 200ml of Ultrapure water obtained on site. This solution was measured and had an average pH of 7.3

Weight Loss

Before the samples were placed in the petri dishes for degradation studies, each one was individually measured and weighed using a standard300mm rule for the lengths and an analytical balance that had the capability to weigh down to 0.0001g. . The weights were then recorded on the lid of the petri dishes for future reference. There were three samples representing each of the time intervals of the degradation process. The Time intervals were split into 8 different segments, each segment representing 2 weeks of degradation time. The interval samples were placed in the incubator every 2 weeks. The samples were then washed with distilled water, placed in the incubator over night to remove the bulk of the water. The samples were then placed in a desiccating tank for a week to remove the rest of the water content. Samples were then taken out of the desiccating tank and weighed on an analytical balance. From which the weight was the recorded to 4 decimal places in grams.

The mass loss was calculated by subtracting the weights of the film after the 16 week degradation process from the initial weights recorded prior to immersion in the degradation solution. The percentage weight loss was then calculated from these figures, with the average % weight loss plotted in a graph. (See fig. 37)

Liquid Chromatography

Liquid chromatography testing was carried out on the supernatant that was removed from the film samples at each changeover (PBS only). Samples were tested in triplicate on a Varians ProStar 335 HPLC with a C18 column and a combined UV-PDA detector. The detector was set up to analyze the ssamples for traces of Caproic acid as an indicator of how the degradation was progressing. 20µl of the sample was injected onto the column which had Water / Acetonitrile Mobile phase pumped through on various isocratic and gradient flow rates. The pH of the Mobile phase was controlled to pH of 4 using Hydrochloric acid. The chromatographs were analysed using the software that was provided with the instrument and was called “Star Driver”. The column was at room temperature.

RESULTS

Weight Loss

The samples that were used in the weight loss experiments measured 76x26x0.2 mm and had an average weight of 0.2570g. They were placed in individual petri dishes and degraded in 25ml of 1g/litre porcine lipase in PBS. The reason this was chosen was because it has been shown previously that lipase accelerates the degradation of the family of polymers know as Poly-ortho-esters to which Polycaprolactone belongs to. (Chen et al. 2000)

The graph below shows a comparison of the degradation rates of films immersed in the PBS only and in the PBS lipase.

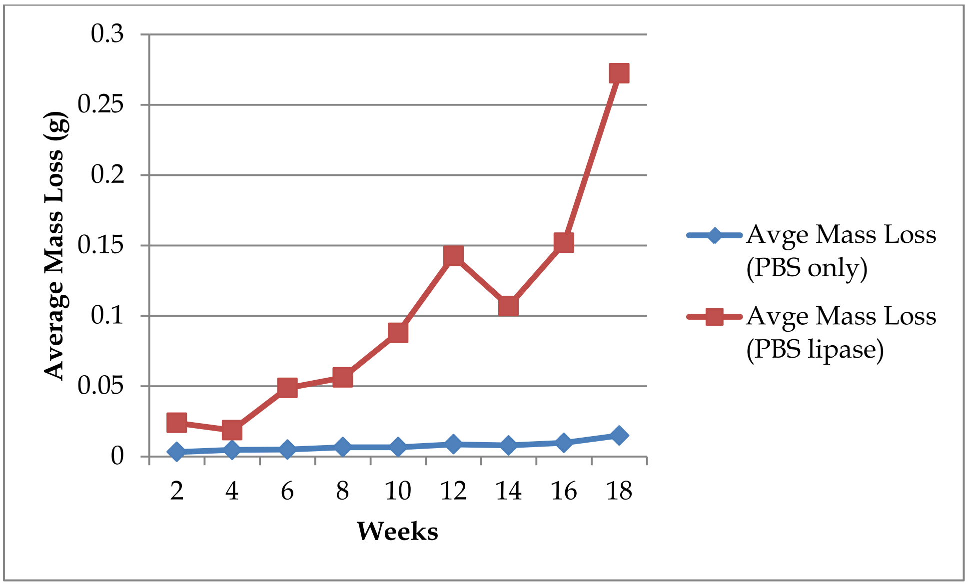


Figure 35 Weight loss comparisons between PBS, and PBS/Lipase solutions

Data gathered from this experiment showed that the degradation rated of films submerged in PBS/lipase solution was significantly increased and was chosen as the preferred method for gathering data on the weight loss experiments.

Welded samples were placed in PBS/Lipase solutions and allowed to degrade for 16 weeks. The results are reported in the graph below.

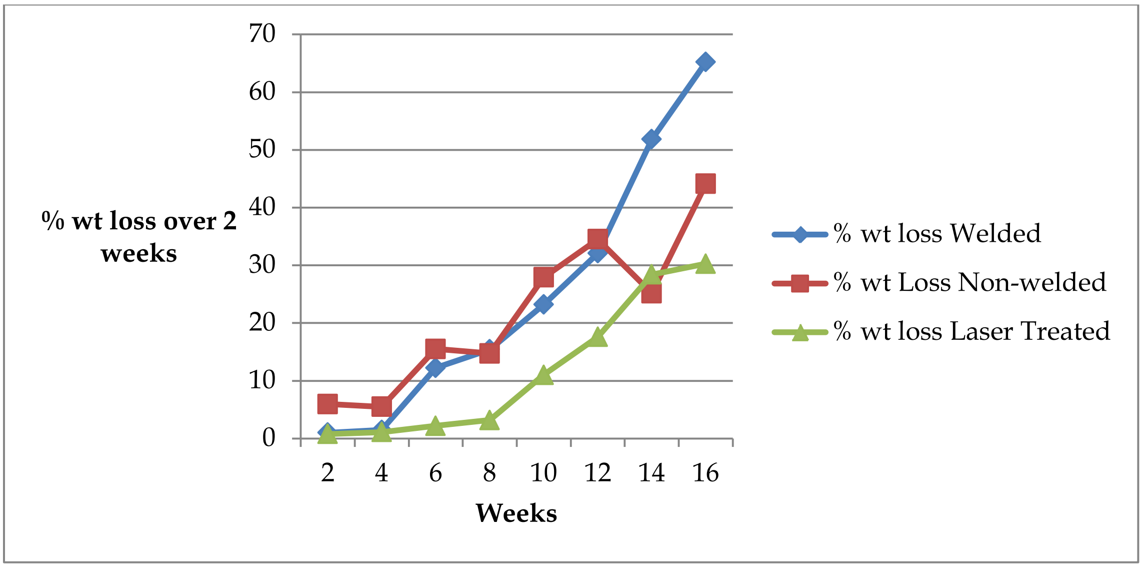


Figure 36 Comparisons of Average % Weight Loss, welded, non-welded and treated samples

Each time interval represented 2 weeks of degradation. As in the pH experiments, the PBS/lipase solution was changed twice a week. The graph shows that the average percentage weight loss was similar between the welded and non-welded films up until Interval 6 (12 weeks degrading), where the average weight loss of the welded films was greater than the non-welded films. Selective chemical degradation of semi-crystalline polymer samples shows certain characteristic changes. During degradation, the crystallinity of the sample increases rapidly at first, then levels off to a much slower rate as the crystallinity approaches 100%. This is attributed to the eventual disappearance of the amorphous portions of the sample. (Chandra & Rustgi 1998). This is the reason why there is a drop in the % weight loss for the non-welded films at interval 6, after 12 weeks the majority of the remaining material is crystalline in nature and has started to slow. On the other hand, in the welded films, because the laser welding process has changed the ratio of amorphous to crystalline material, even at 16 weeks, the film is still appears to be more amorphous in nature and continues to lose mass. Further evidence of the importance of the polymorphisim on the degradation rates is illustrated in the SEM section, in images figs. 39 to 58.

pH

Previous publications, (Bosworth & Downes 2010)(Vey et al. 2011), have stated that as the film degrades, it releases acidic compounds into the surrounding PBS liquid that it is degrading in, thereby effecting its overall pH. It was thought at the time that this characteristic could be used as a secondary measure of the degradation rates and the results from controls and welded samples could be compared. It was assumed that as the film degrades, so would the size of the pH drop throughout the process. This assumption was also based on experimental results obtained by diluting set volumes of Caproic Acid into PBS and building up a standard curve. The results of this experiment are in fig. 37 below.

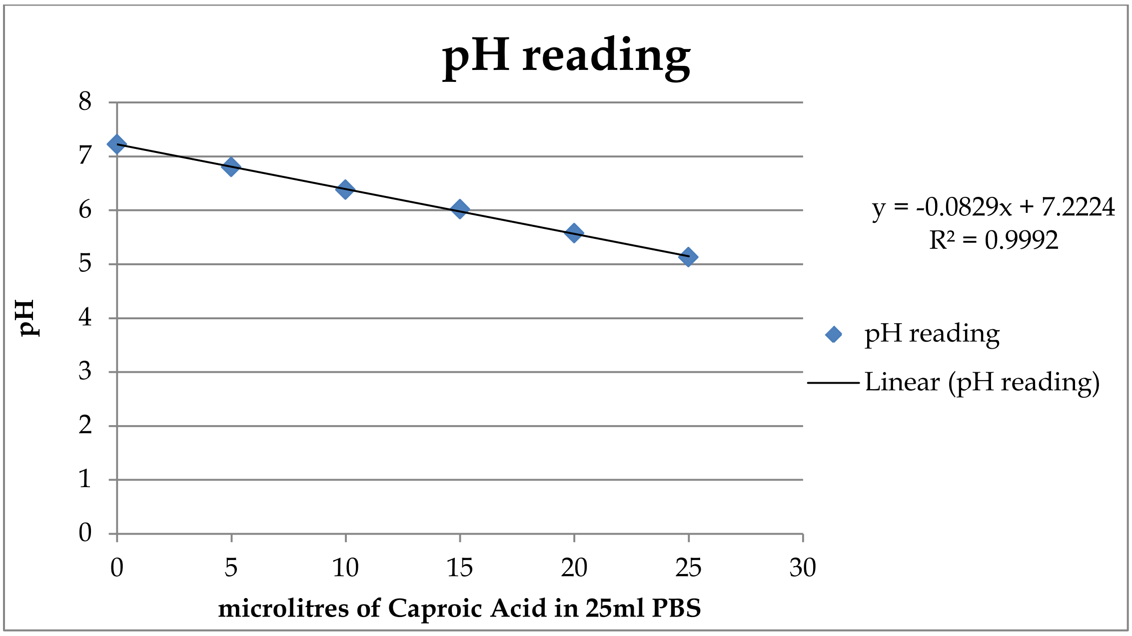


Figure 37 Standard Curve pH vs Volume of Caproic acid added

On average, the pH dropped by 0.42 for every 5µl of caproic acid added to PBS. However, over the course of the degradation experiments on the films themselves, the largest pH drop was 0.2 for the welded samples, and 0.15 for the non-welded samples. The total average pH drop for welded samples over the 18 weeks was 0.89 and the total average drop for the non-welded samples was 0.73.

Initially, the pH readings varied throughout the test process, with no trends evident from the table of results. A number of specific reasons for this presented themselves, but the most likely cause, is due to the difference in polymer mass to volume of degradation medium ratio used. The samples from the initial readings were taken from samples that were $^1/_3$ the size of subsequent degradation tests. A similar phenomena was reported by (Vey et al. 2011) when they investigated the in vitro degradation of poly(lactic-co-glycolic) acid copolymer with different lactic to glycolic ratio.

The pH results reported here were rerun with full size films (76mm x 26mm x 0.2mm average) for another 18 weeks in PBS solutions. pH readings were obtained every two weeks as per initial method. Each pH difference was noted and placed in an Excel spreadsheet. Each reading corresponding to the particular time interval was averaged and the results were then plotted on a graph with pH difference on the Y-Axis and the number of weeks on the X-axis, see fig. 38 below.

For the welded samples, the same test was carried out. The welded films were placed in PBS solutions and allowed to degrade for 18 weeks. The results are plotted in the graph below.

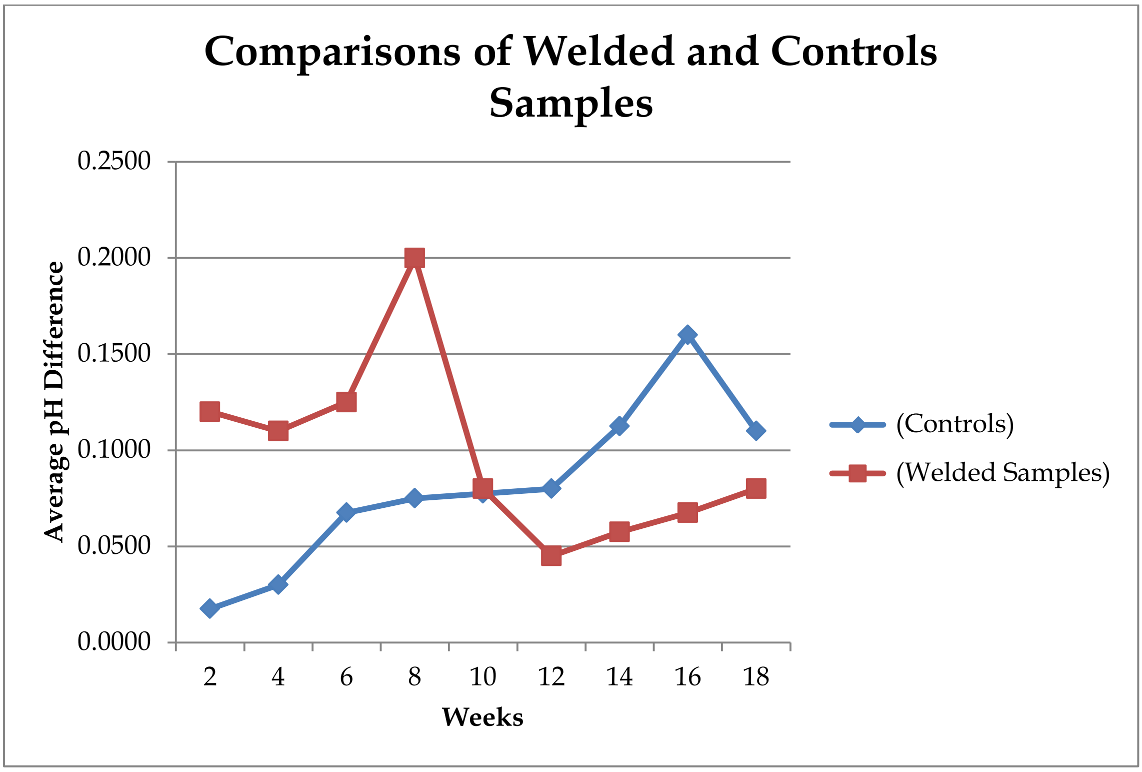


Figure 38 Welded and Controls, a pH comparison

It can be seen from the graph in fig. 38 that the pH drop did not increase incrementally like the % weight loss results did. Taken out of context, it would appear that as a measure of degradation, it shows that the films degrade at different rates (speeding up, then inexplicably slowing down half way through the process). As it turns out, when observed in context with the SEM images, the results actually point out the points in the process where the material composition changes from mostly amorphous to mostly crystalline, pointing to the presence of the two step degradation process that has been discussed here previously in the introduction. (Middleton & Tipton 2000)

SEM

SEM images were taken at various positions of the surface of the films for each interval. Positions of interest were saved as JPEG images and the images of both welded and non- welded films were compared to each other at set magnifications.

150 times Magnification

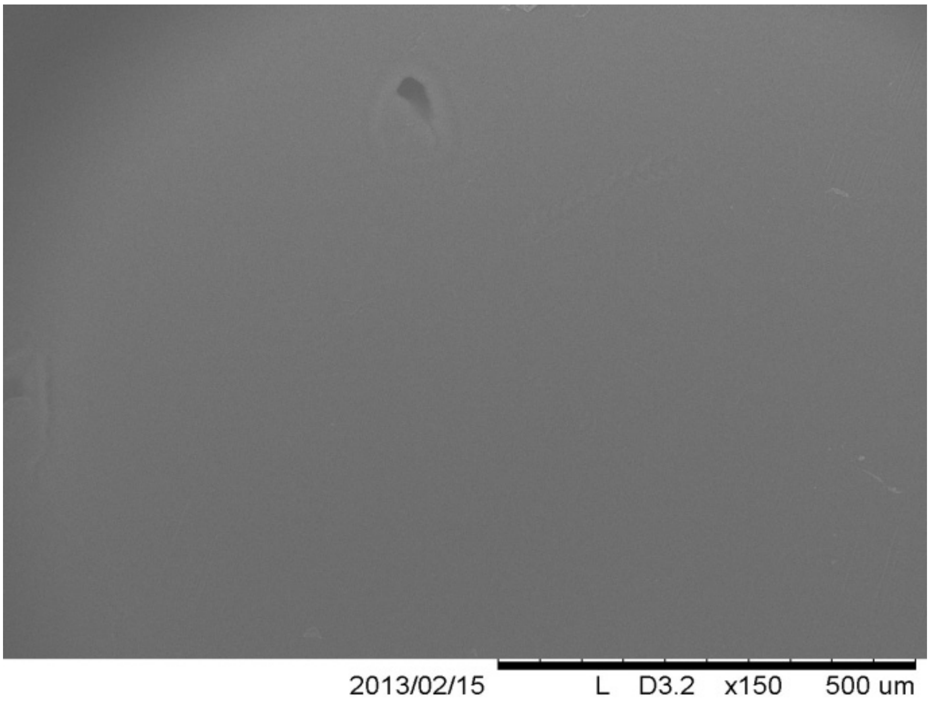


Figure 39 No Degradation, Welded

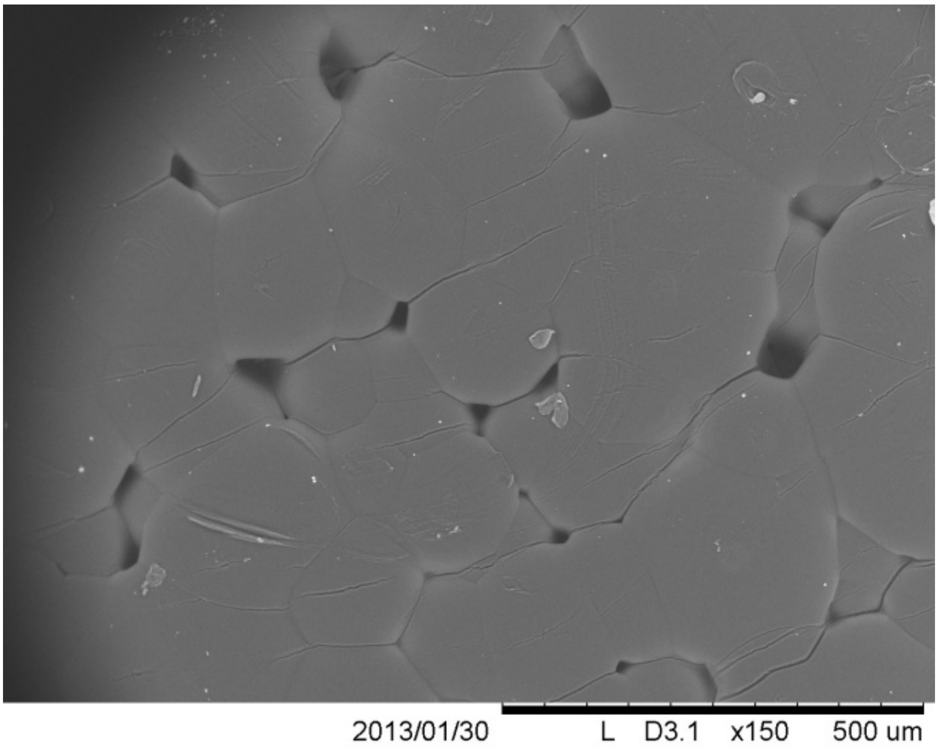


Figure 40 No Degradation Non-welded

No Degradation: Initial appearances show very little difference in the structure of the films. The non-welded sample (Fig. 41) looks "bumpier". This is to be expected as the laser welding action smoothes things out in the weld pool. However, at higher magnifications, the non-welded sample does start out slightly more crystalline as will be shown below.

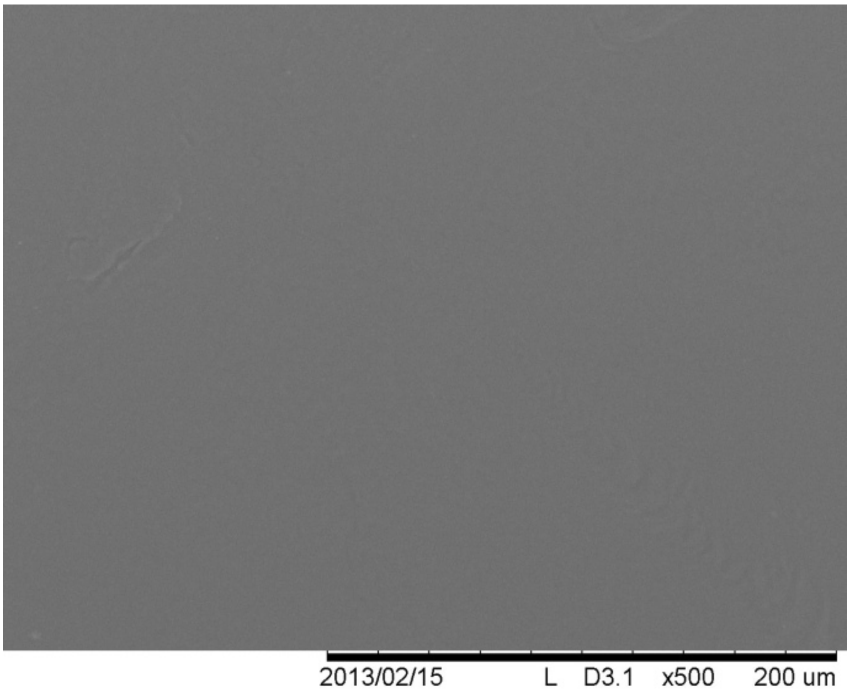


Figure 41 Welded film, x500 Magnification

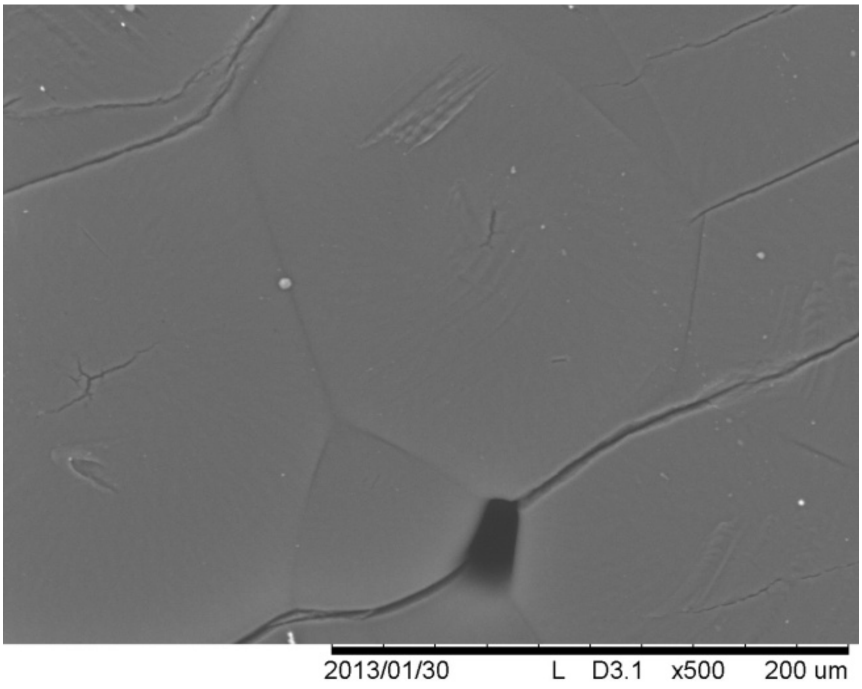


Figure 42 Non-welded film, x500 Magnification

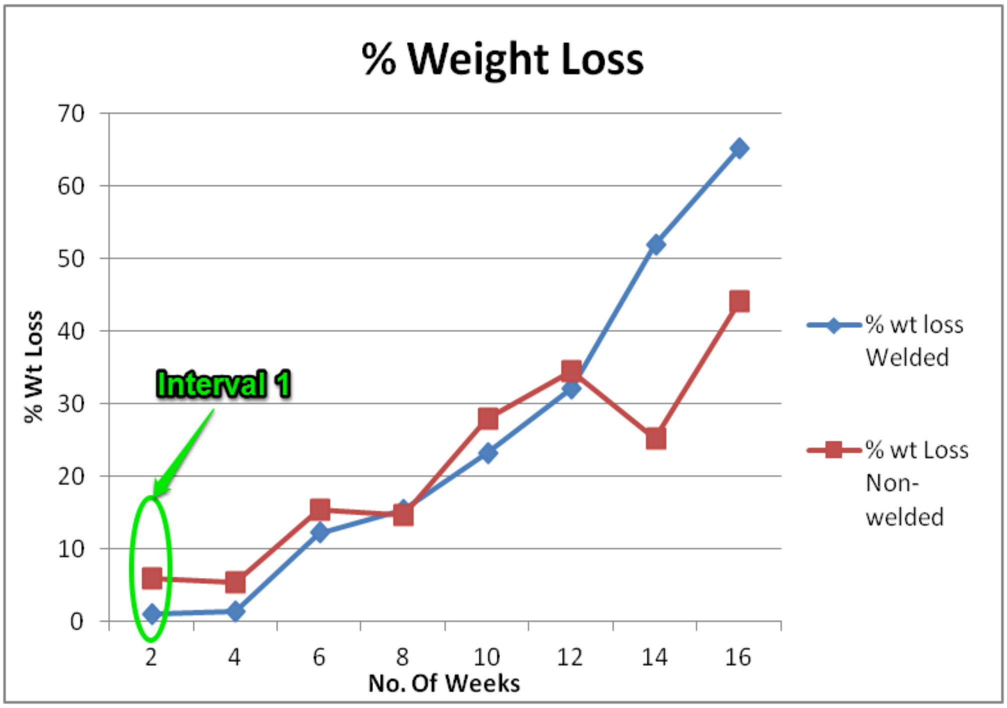
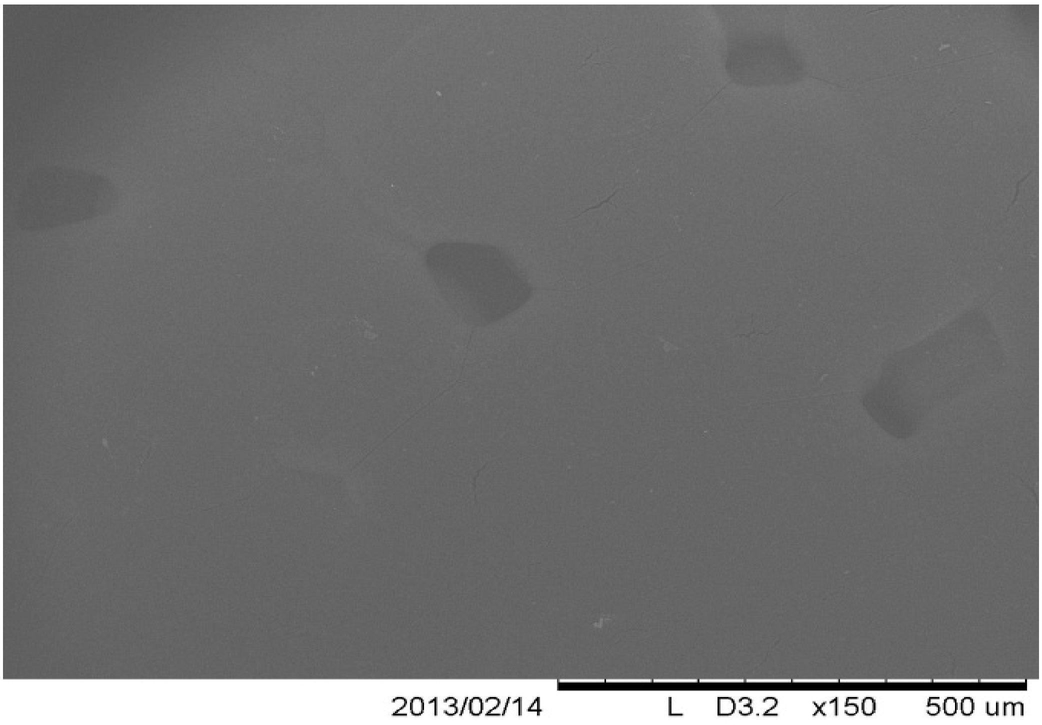


Figure 43 Interval 1, Welded



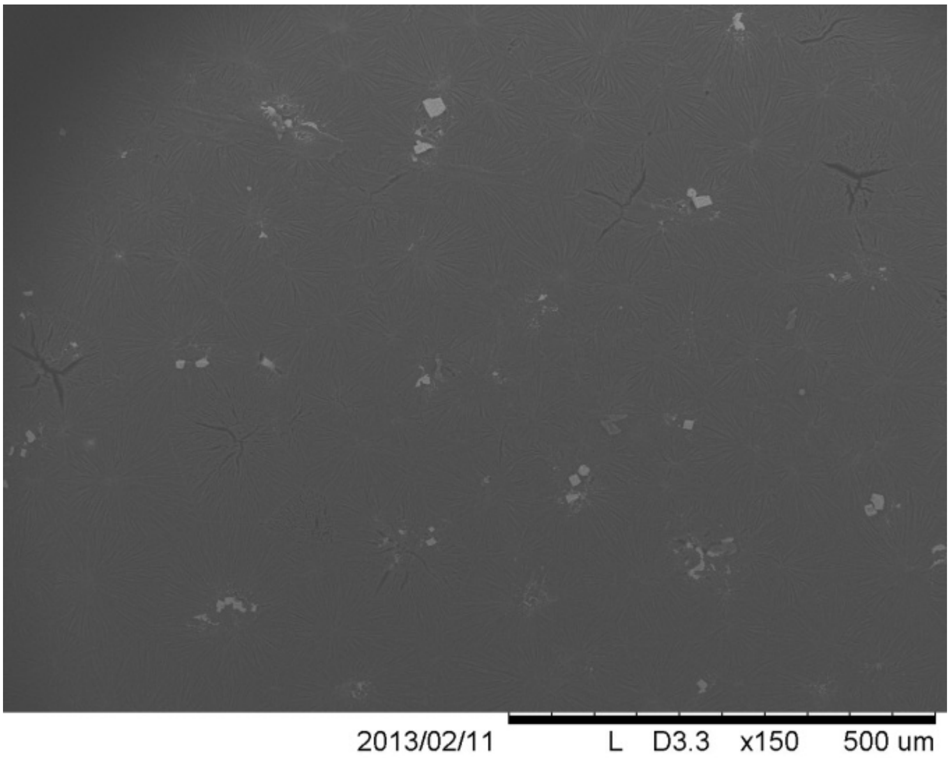
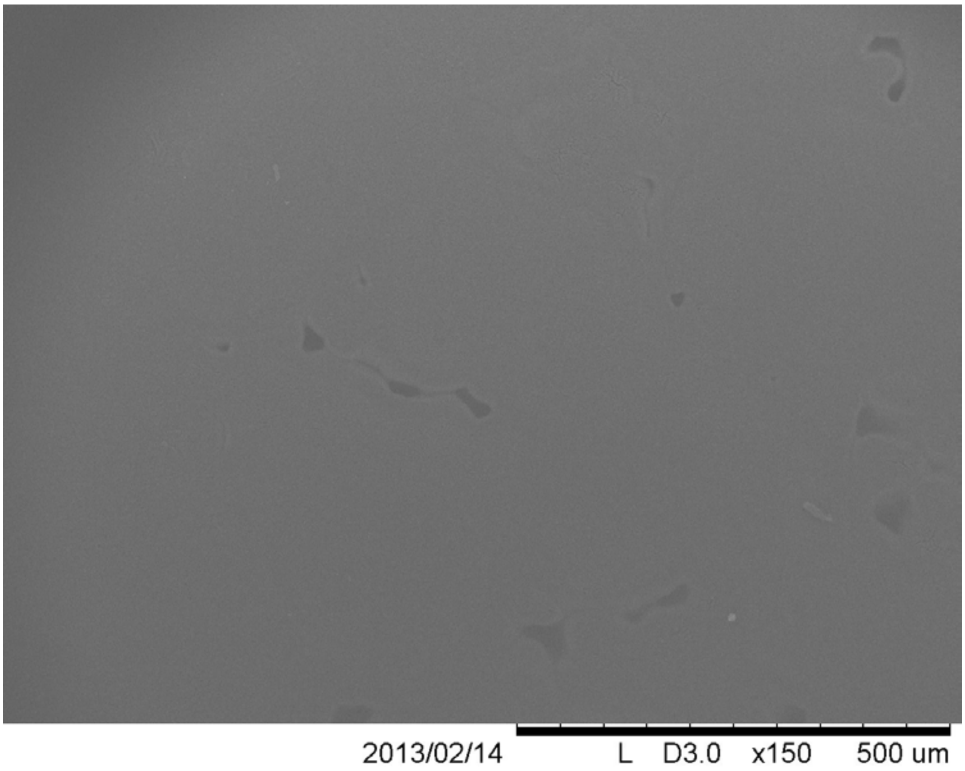


Figure 44 SEM image of the Non-welded Film surface after 2 weeks,

Interval 1: The welded sample shown in fig. 44 had a more porous appearance which may be due to the faster release of amorphous material into the supernatant. This can be seen in an increase in pH at the earlier stages of degradation. The non-welded sample in fig. 45 is becoming increasingly crystalline as shown by the growth in spherulite formation. It has been documented in previous publications that spherulites are usually crystalline and intermediate and non-spherulites are amorphous. (Gupta 2010). However, the % weight loss for both films appear to be at similar rates to each other.

Figure 45 SEM Image of the Welded film surface after 4 weeks.



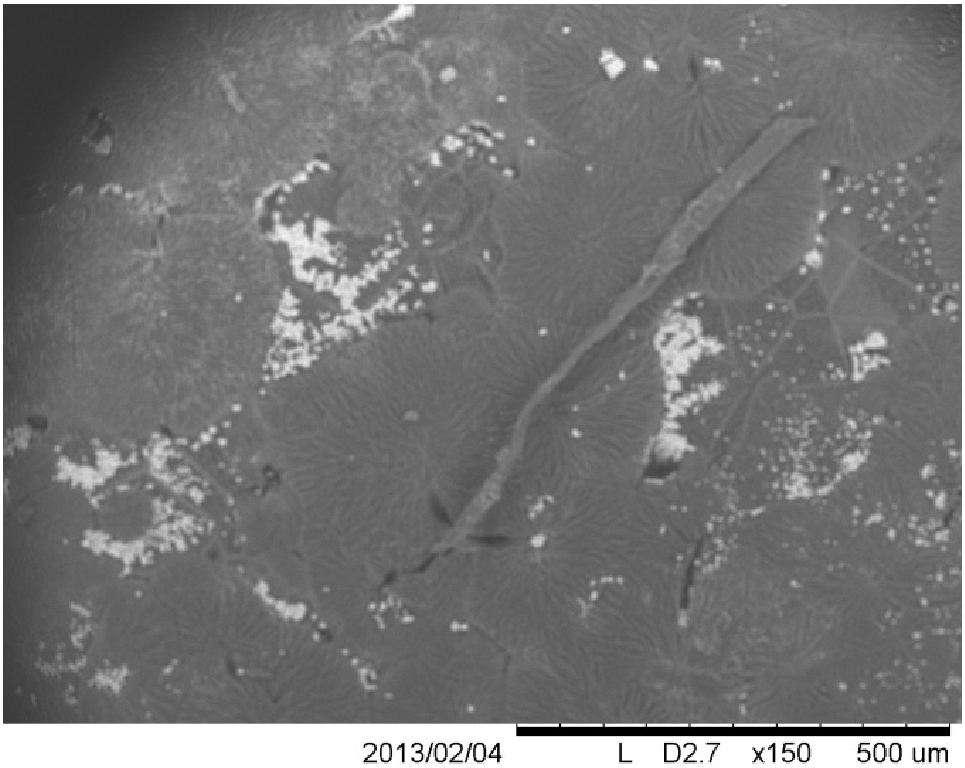


Figure 46 SEM image of a Non-Welded film surface after 2 weeks.

Interval 2: The welded films are retaining their amorphous appearance where as the surface of the non-welded samples is almost completely covered in spherulites. The lighter coloured “blobs” were also analysed using the Energy Dispersive X-ray Spectrometer that came with the microscope and show traces of Carbon (the majority), Oxygen, Nitrogen, Chlorine and Sodium. See related information in Appendix B. As before, the % weight losses for both films have similar trends.

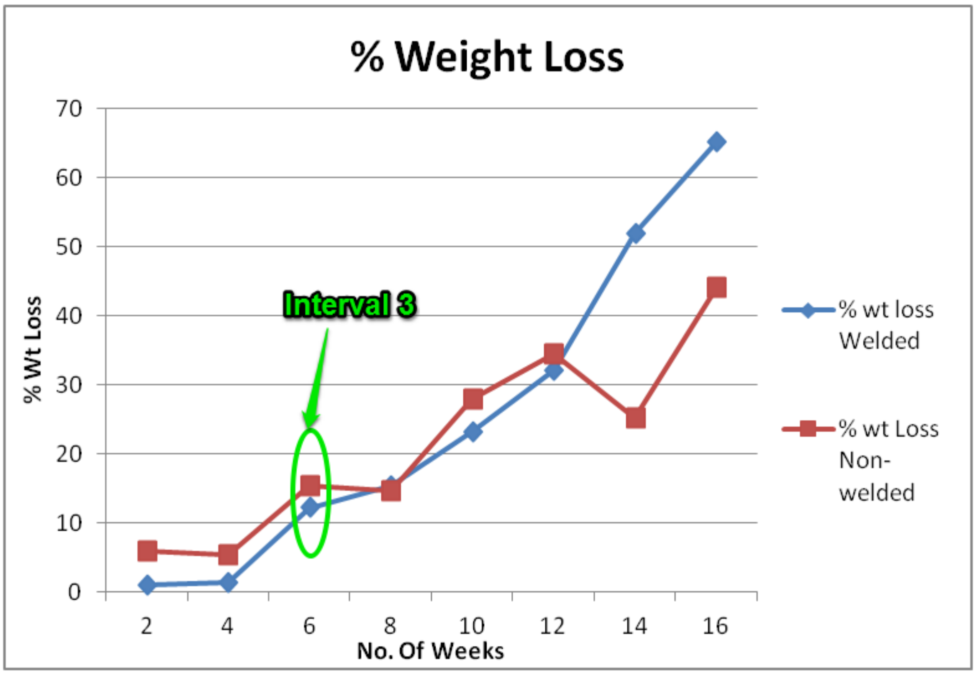
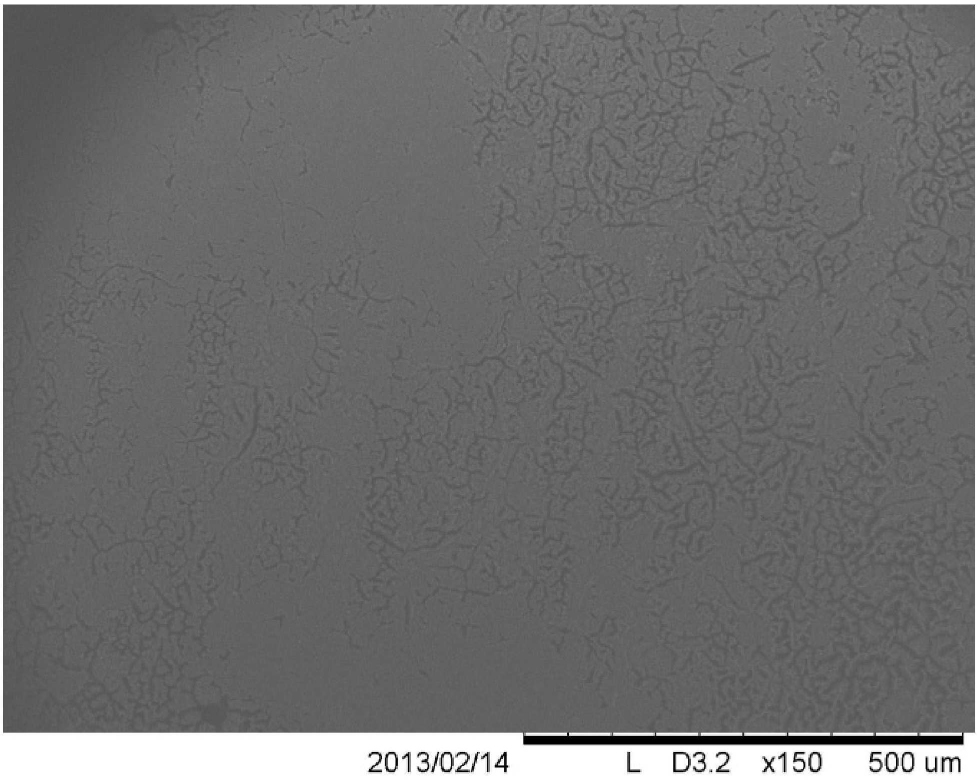


Figure 47 SEM image of a Welded film surface after 6 weeks



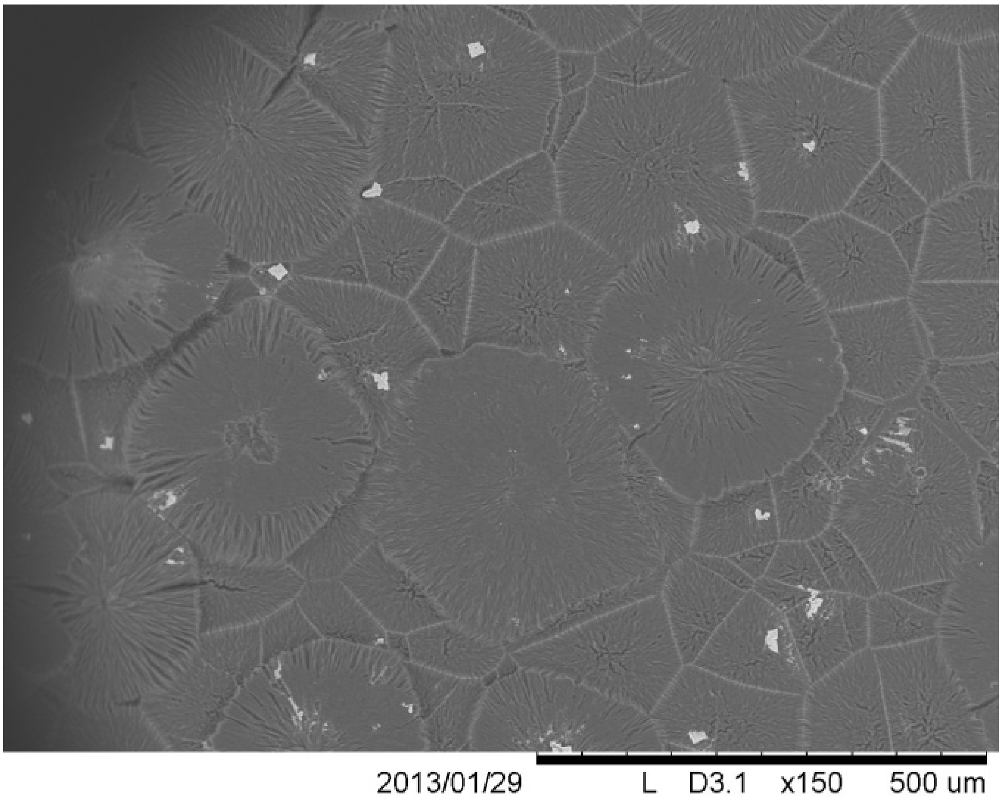
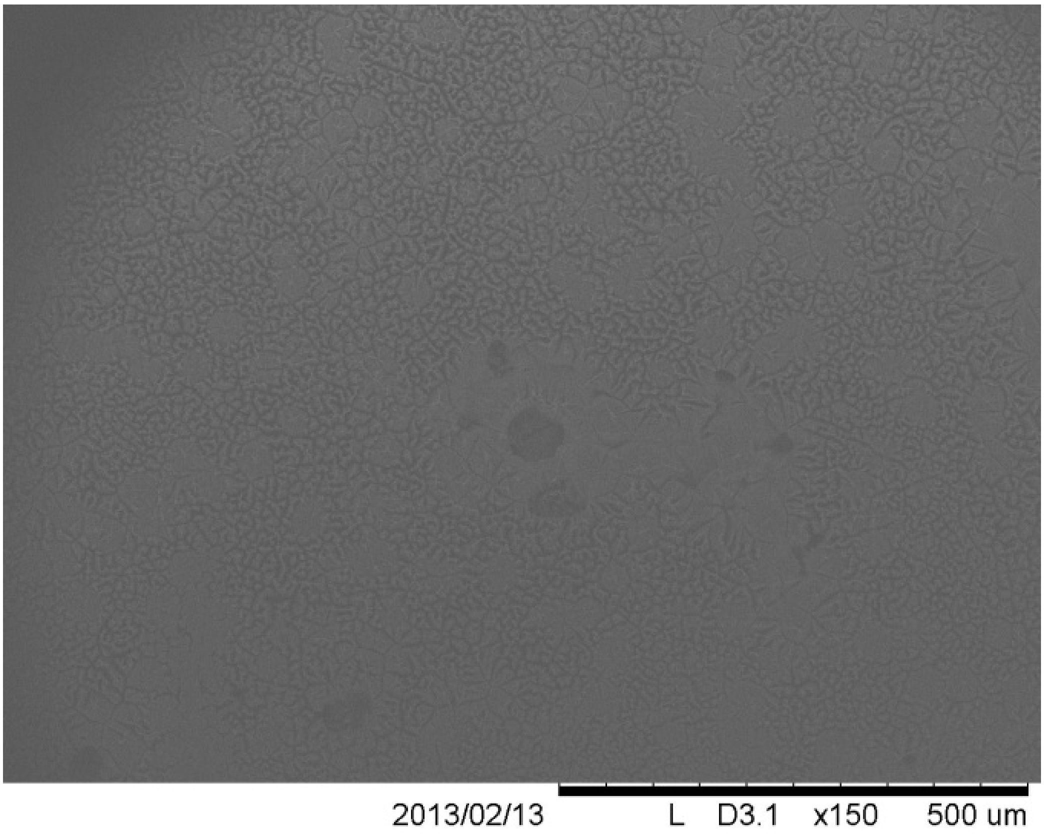


Figure 48 SEM image of a Non-welded film surface after 6 weeks.

Interval 3: The welded films are starting to become more porous as more material is being lost into the supernatant.. The weight loss for both type of films are the same at this point. The non-welded sample, in fig. 49 instead of becoming porous seems to becoming more crystalline in nature. The bright lines around the boundaries of the spherulites are an amalgamation of lamellae from the surrounding crystals beginning to grow into the non-crystallized areas. This happens when the lamellae from both crystals extend across their respective boundaries into any un-crystallised material.(Gupta 2010)

Figure 49 SEM Image of a Welded film surface after 8 weeks.



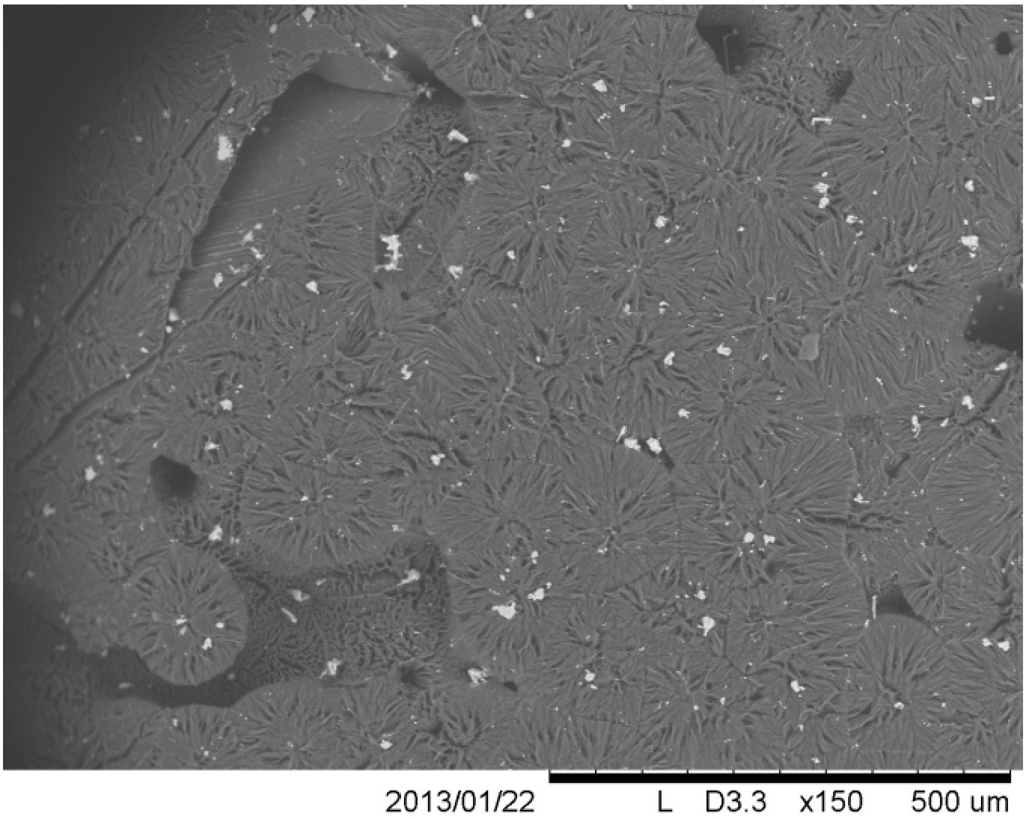


Figure 50 SEM image of the surface of Non-welded film after 8 weeks.

Interval 4: Small spherulites are starting to form on the surface of the welded films, with small percentage material loss in the predominantly amorphous regions. The non-welded film on the other hand is still contains majority crystalline material. Also, some material is beginning to degrade away from the lamellae that make up the spherulites. According to the weight loss graph, at 8 weeks degradation it appears that both welded and non-welded films have the same % weight loss. It is clear however that the causes of the weight loss in both films are different. The SEM image shows that the welded films still retain a larger amorphous ratio of material and the weight loss is happening in the first stage of degradation. The SEM images for the non-welded films show that the material has a larger ratio of crystalline material, and all weight loss is occurring in the second stage of degradation. The weight loss that occurs in the second stage is due to the lipase starting to attack the smaller, more crystalline oligimers, which are not as acidic as the oligmers that are entering the supernatant from material that is predominantly amorphous in nature.

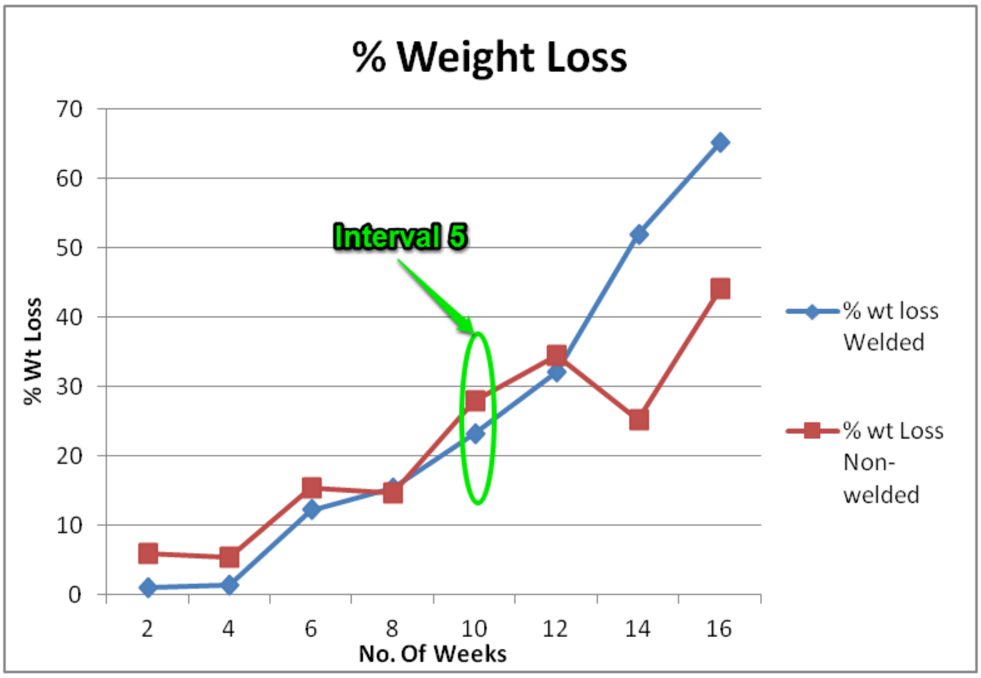
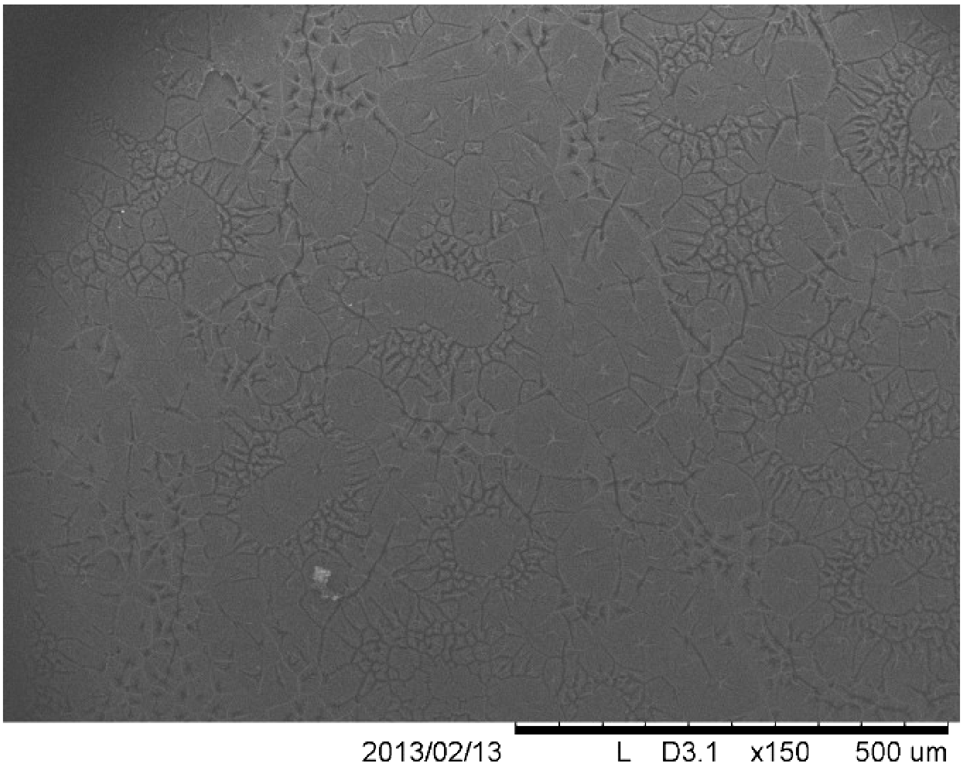


Figure 51 SEM image of the surface of a Welded film after 10 weeks



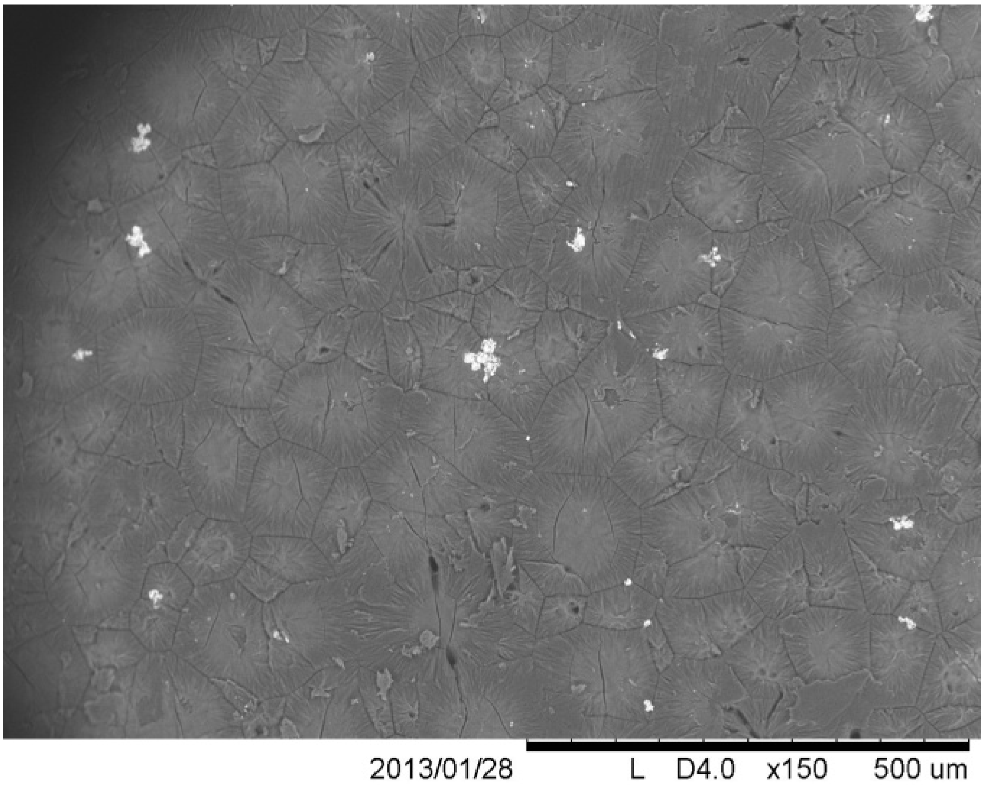


Figure 52 SEM image of the surface of a Non-welded film after 10 weeks.

Interval 5: Spherullites in both welded (fig. 51) and non-welded (fig. 52) are similar in size, however, there is more uncrystallised material between the spherulites in the welded films than in the non-welded films. There also seems to be more material degraded from the surface of the welded samples that in the non-welded samples. Some degradation is happening though, as the weight loss is still increasing. It is also evident from the SEM pictures, as it appears that there is some amorphous type material left. There does not appear to be too much degradation happening in the non-welded films however but this is to be expected because the material is near totally crystalline, making it harder for the lipase to attack the molecules.

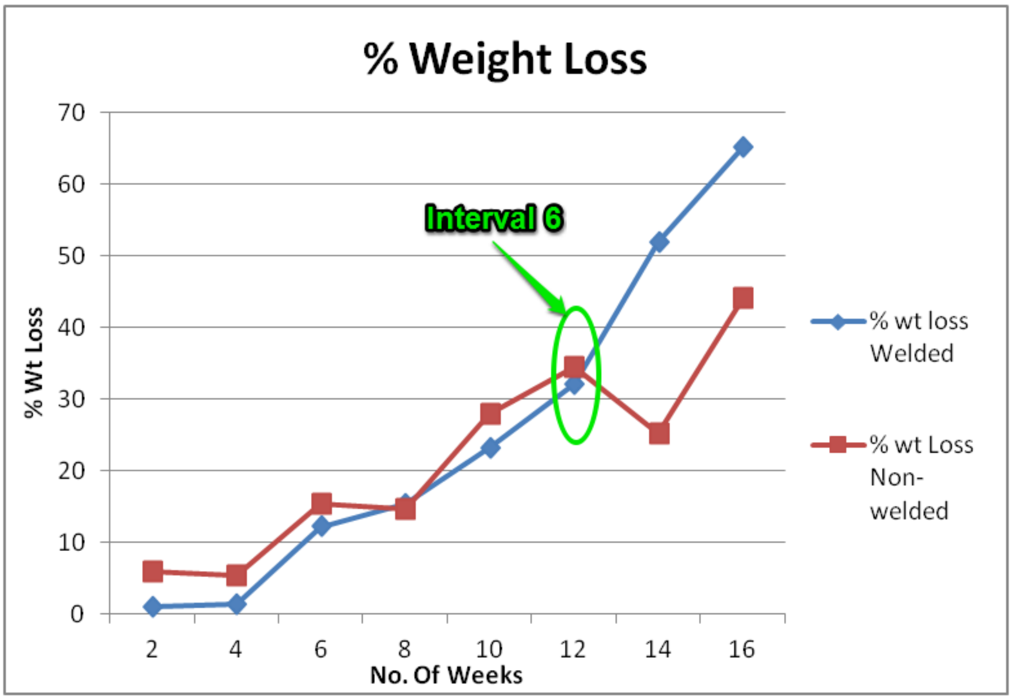
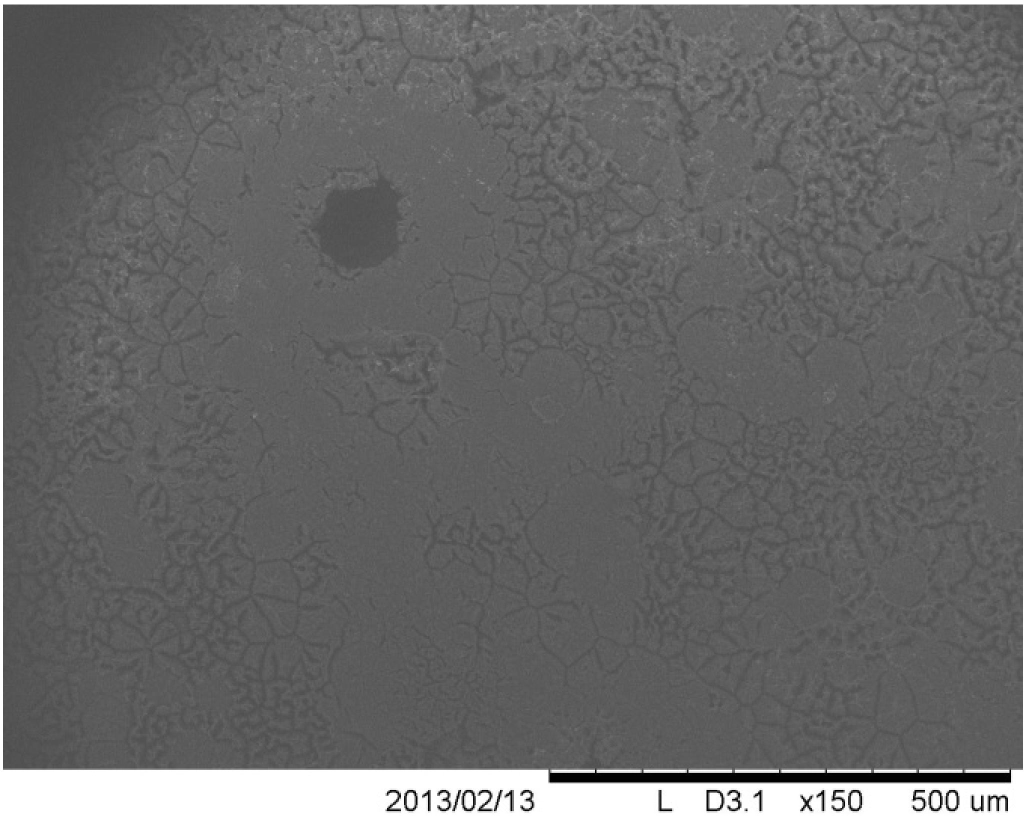


Figure 53 SEM image of the surface of a Welded film after 12 weeks



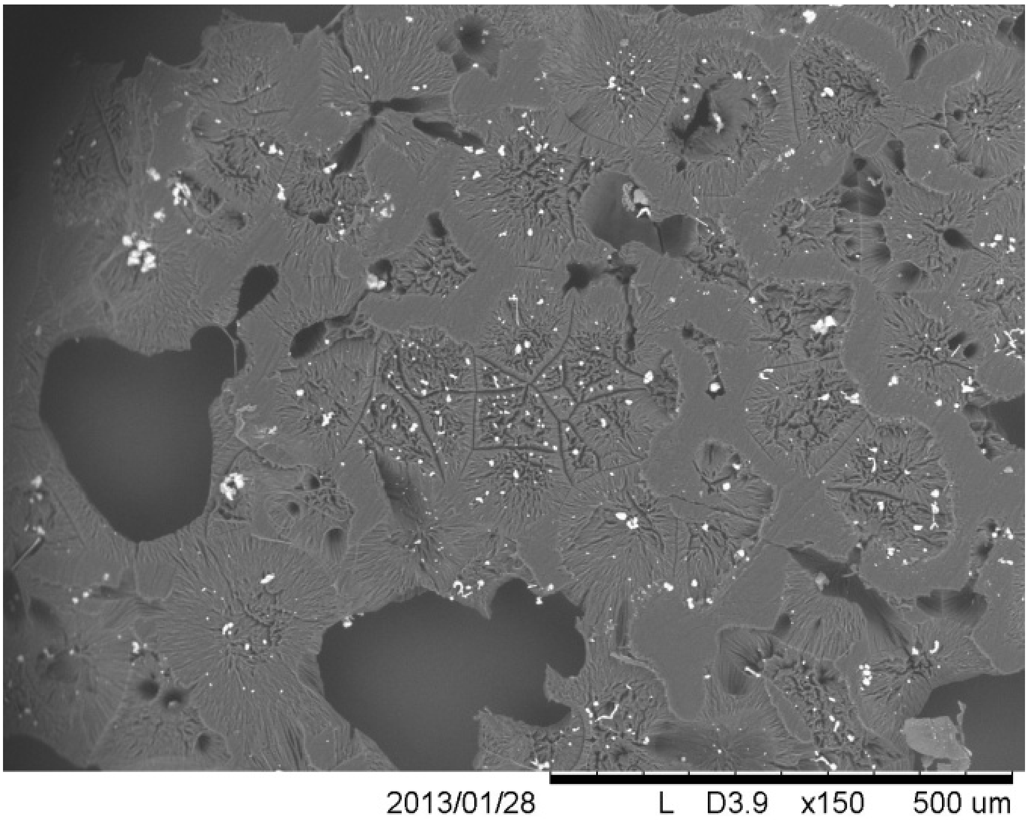
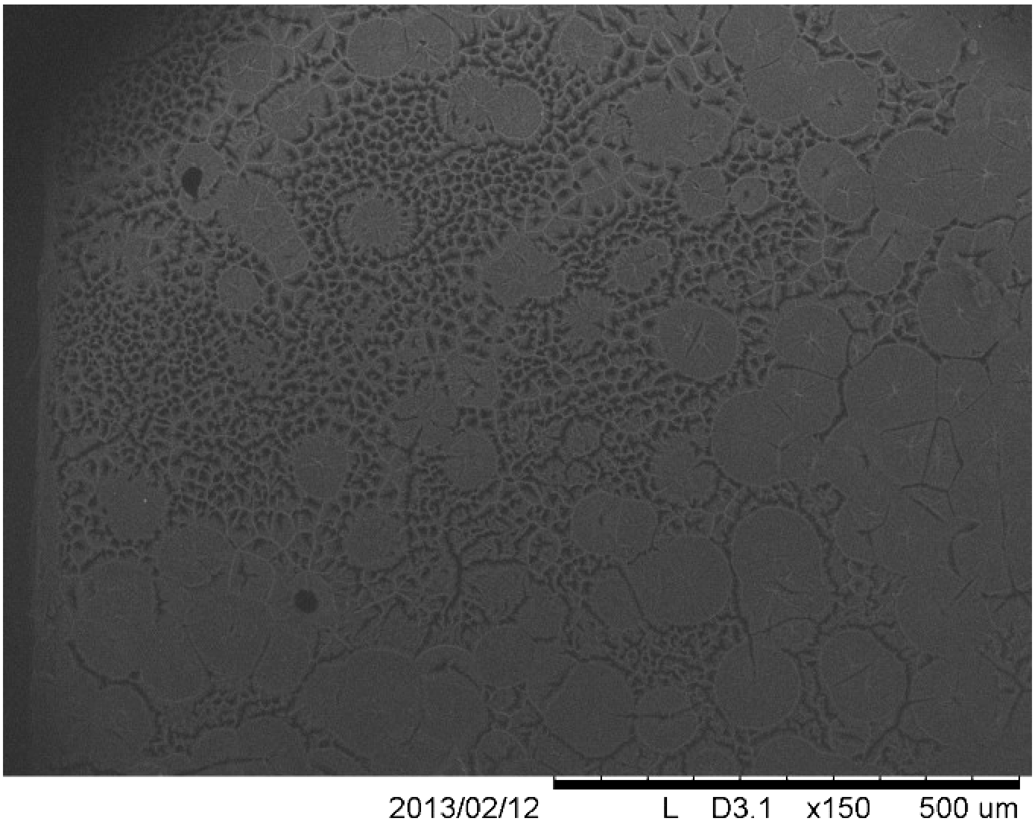


Figure 54 SEM image of the surface of a Non-welded film after 12 weeks

Interval 6: At this interval, a dramatic change occurs to the non-welded film (right). This has occurred because the crystalline molecules have lost so much material that the lipase is finding it easier to attack the remaining chains. This also has the affect of speeding up autocatalysis within the bulk of the material. It also shows up as a slight increase in acidity. The % weight loss graph shows that degradation is still happening, more than likely due to a combination of the last of the amorphous and the start of the lipase attacking the crystalline chains.

Figure 55 SEM image of the surface of a Welded film after 14 weeks.



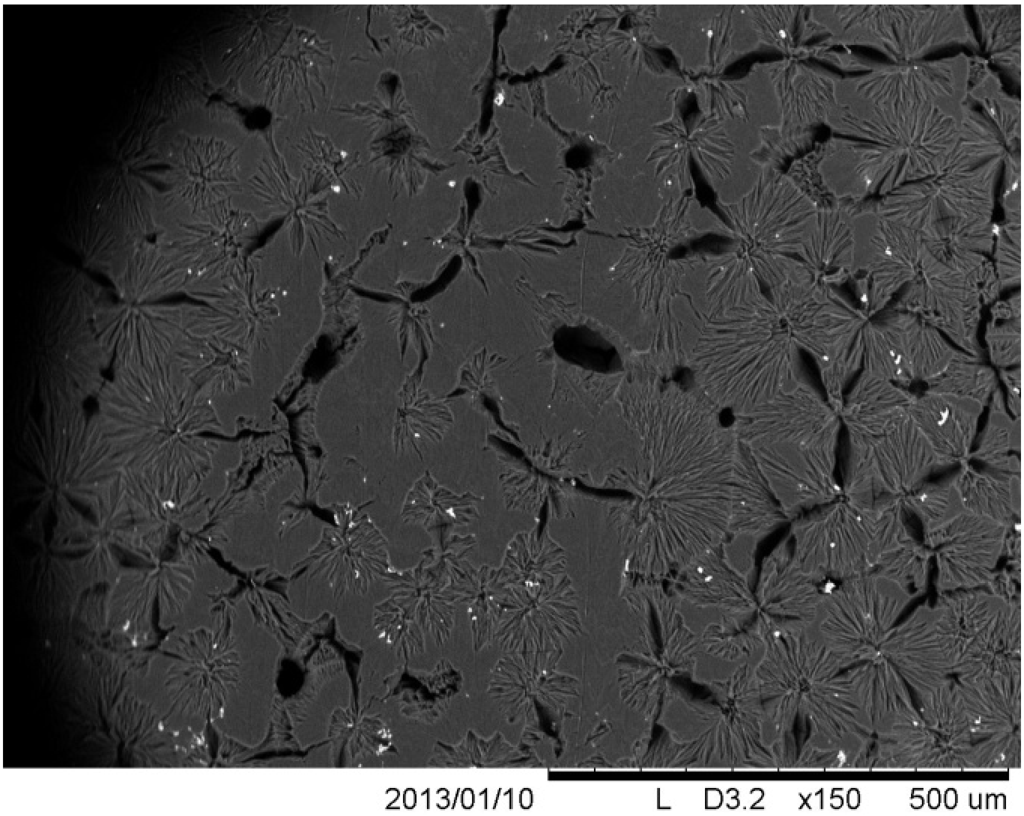


Figure 56 SEM image of the surface of a Non-welded film after 14 weeks

Interval 7: Similar views as interval 6, however the mass loss in the non-welded sample is not as dramatic. There is a slightly more crystalline appearance on the welded films (Fig. 55) than there was in interval 6. The non-welded films also seem to have more pores within the crystalline matrix which could be attributed to the second stage of degradation getting well under way.

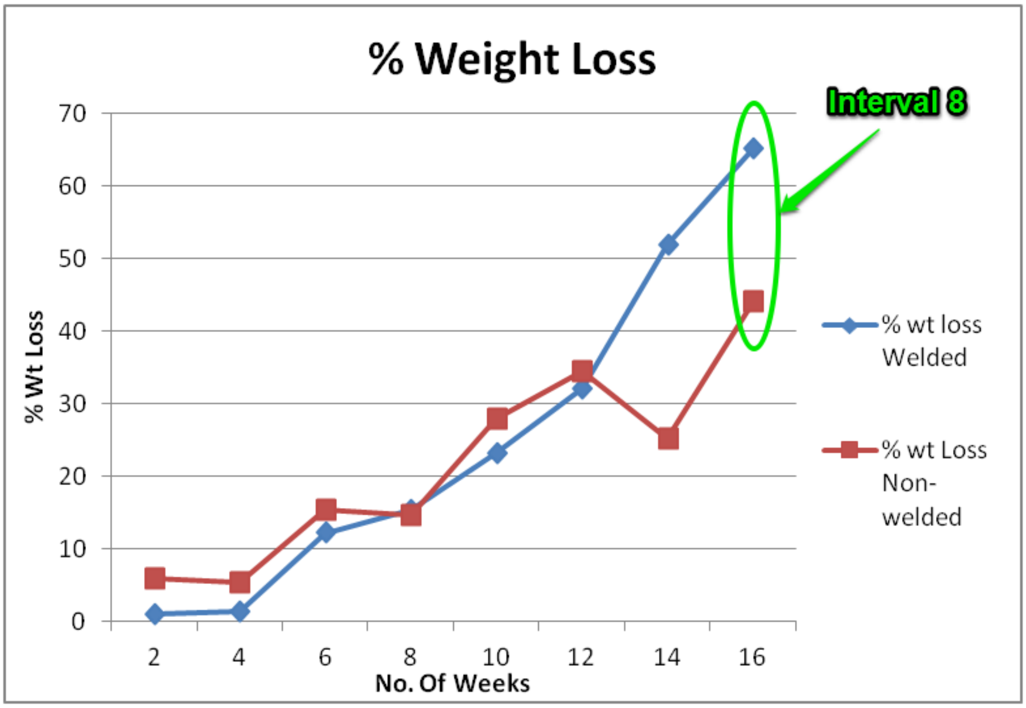
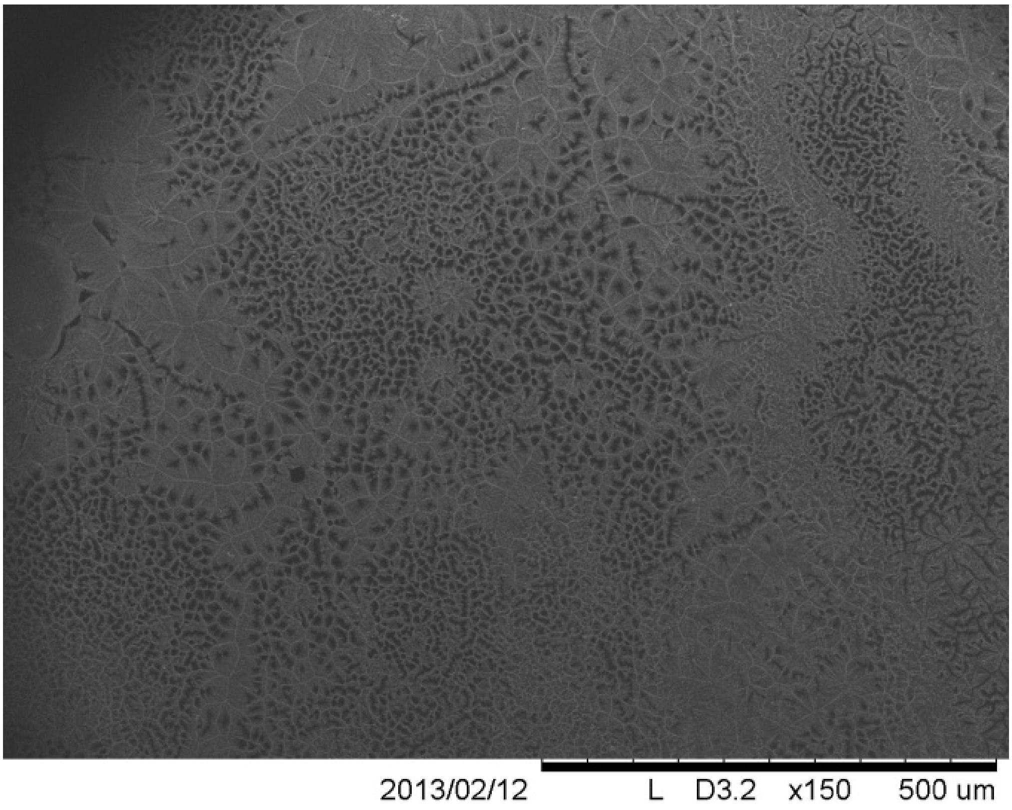


Figure 57 Interval 8, Welded



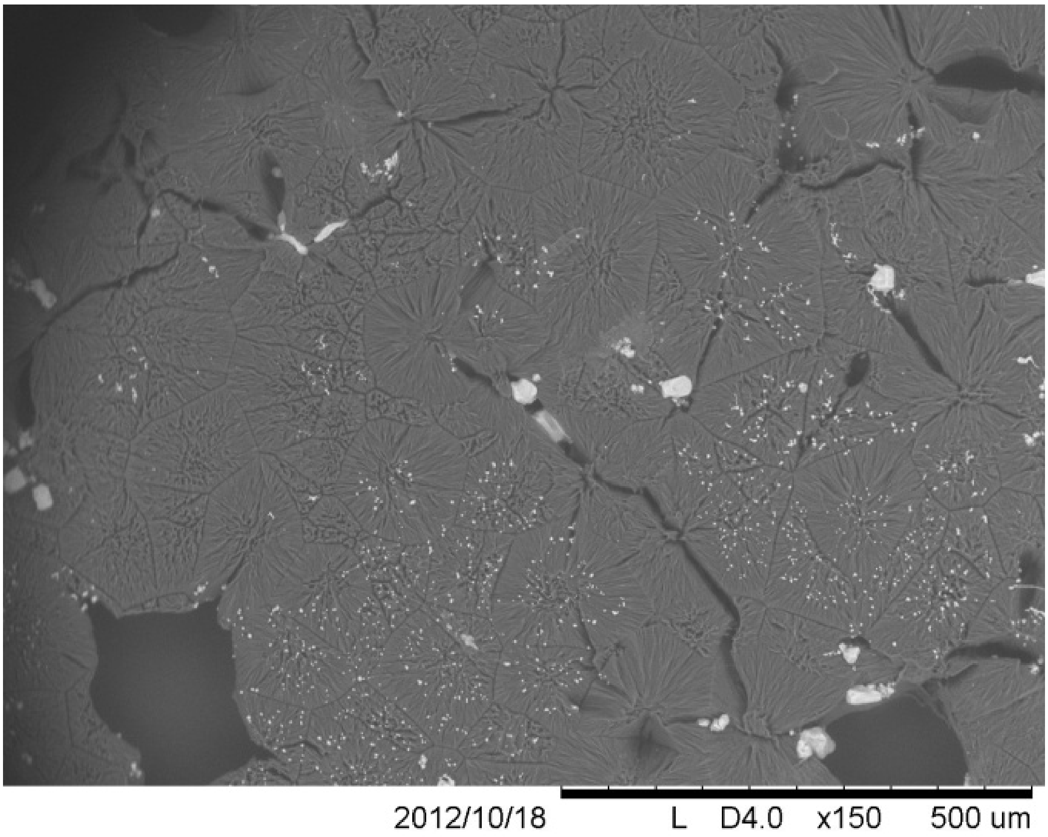


Figure 58 Interval 8, Non-welded

Interval 8: Welded samples continue to show effects of degradation, as the surface is stippled with pores. The non-welded films are the same, except that the holes are bigger but are smaller in number. There appears to be large cracks appearing across surface of the non-welded films indicating that the films are starting to lose mechanical integrity and approaching total degradation. The welded films still seem to have retained mechanical integrity at this stage, but %weight loss rate is still increasing indicating that degradation is still progressing.

Liquid Chromatography

The results obtained from the liquid chromatography were inconclusive. The chromatograms themselves were not robust enough to obtain any usable data. It is hoped that future work will be able to qualitatively and quantitatively discern degradation products in the supernatant. See Appendix C for sample chromatographs.

Statistical Analysis

In order to analyze this data further, statistical analysis was carried out on the individual % weight loss of all twenty four experimental films. Student T tests carried out on the individual Interval sample sets appear to support this fact that % weight loss was similar for the first twelve weeks. The P values for the first 6 intervals were greater than 0.05. The P-values for those results are shown in the table below.

Time Interval	% Mass loss Non-welded	% Mass loss Welded	P-value
Interval 1	2.294246	0.912647	0.111912
	7.235255	1.052221	
	8.338558	1.060396	
Interval 2	3.020355	1.815112	0.113332
	5.538315	0.864909	
	7.959049	1.702296	
Interval 3	15.49839	12.4812	0.453851
	22.6209	13.10025	
	8.374223	11.11516	
Interval 4	10.63036	14.01836	0.783944
	14.97366	17.29167	
	18.59449	14.94418	
Interval 5	10.1836	23.94075	0.696132
	30.36031	24.91289	
	43.23444	20.7648	
Interval 6	43.56923	34.59038	0.67907
	42.07906	36.17778	
	17.87418	25.44732	
Interval 7	26.83721	52.57193	0.002268
	21.76428	50.95735	
	26.86047	51.95777	
Interval 8	49.25244	77.29049	0.071862

Time Interval	% Mass loss Non-welded	% Mass loss Welded	P-value
	38.2447	64.28022	
	44.84174	54.02387	

Table 3 P-Values for Interval % weight loss measurements

The Null Hypothesis for these samples was that both % weight loss measurements for each data set were the same. For the results after fourteen weeks the P value was less than 0.05, thereby rejecting the null hypothesis (i.e. the results from Intervals 7 and 8 are significantly different).

Taking intro account this statistical information provided here and the evidence presented by the weight loss data, there appears to be a number of factors responsible for the difference in weight loss percentage of the films from Interval 6 onwards. The single most factor that we have identified for this seems to be that the non-welded films entered the second phase of degradation at least four weeks before the welded films, thereby degrading faster. This suggests that the laser welding effects the polymorphism of the polymer material indirectly, by a rapid heating and cooling during the welding function. This in turn affects the ability of aqueous solution to penetrate into the bulk of the material at an earlier stage, making the films appear to be degrading faster.

SUMMARY

Initial degradation experiments were carried out on film samples in order to obtain some baseline data on the actual degradation rate of Polycaprolactone. Two major points were discovered at this stage:

1. Full sized films needed to be used to generate results at sufficient levels that could be monitored with the instruments that were available to the researcher at the time
2. The degradation process could be speeded up using lipase at concentrations of 1mg/L

Once these factors were established, three sets of films were degraded in the PBS/lipase mediums:

1. Non-welded samples x3
2. Laser welded samples x3
3. Laser treated samples x3

The samples were placed into three sets of three and placed into the degradation medium concurrently. (i.e. the films that were recorded as degrading for 16 weeks were placed first, and labelled as Interval 8, then films that were recorded as Interval 7 were placed into the degradation medium two weeks later etc). At the end of the 16 week, each set of films for each interval were dried out and weighed and recorded on a graph. Also, SEM images were obtained of each of the degraded films to build up a pictorial archive to track the degradation process in conjunction with the weight loss results.

When all the data was collected, weight loss graphs for the welded and non-welded films were compared in a Student T test to see if there were any significant differences attached to the results.

Other experiments were carried at on the films at the same time as the ones above, (HPLC, pH) but no usable data was obtained. Conclusions to weight loss experiments and how the Laser welding process affects the degradation properties of the PCL films are discussed in the next chapter.

Chapter 5 Conclusion and Future Work

In this chapter, the results of the laser welding and degradation are discussed. The goal of this body of work was to discover if the process of laser welding had any effect on the biodegradation rates of the material. The key questions were "Does the laser welding process have an effect and if there is, does it speed up or slowdown the degradation?" The results from the SEM and weight loss will provide some of the talking points starting with the weight loss. A brief outline of where the process may be improved and a brief discussion on possible future work that could be carried out.

CONCLUSIONS

It has been well documented in several research papers that degradation happens preferentially, and faster, in the amorphous regions, but takes longer to degrade in the crystalline regions. From the results reported in the previous chapter, it is clear that both welded and non-welded films follow the same two-step process.

The difference that the laser welding makes to the films is the fact that the laser welding process somehow increases the ratio between the amorphous and crystalline parts of the material, in favour of the amorphous. This in turn delays the time taken to degrade the welded films by approximately 4 weeks. This is evident in the SEM images taken of the welded and non-welded films from Interval 6 or 12 weeks into the degradation process. You can see in the image below that there seems to be more material loss in the non-welded films than the welded films. You can also see how highly crystalline the material is at this point even though both films have almost the same rate of % weight loss.

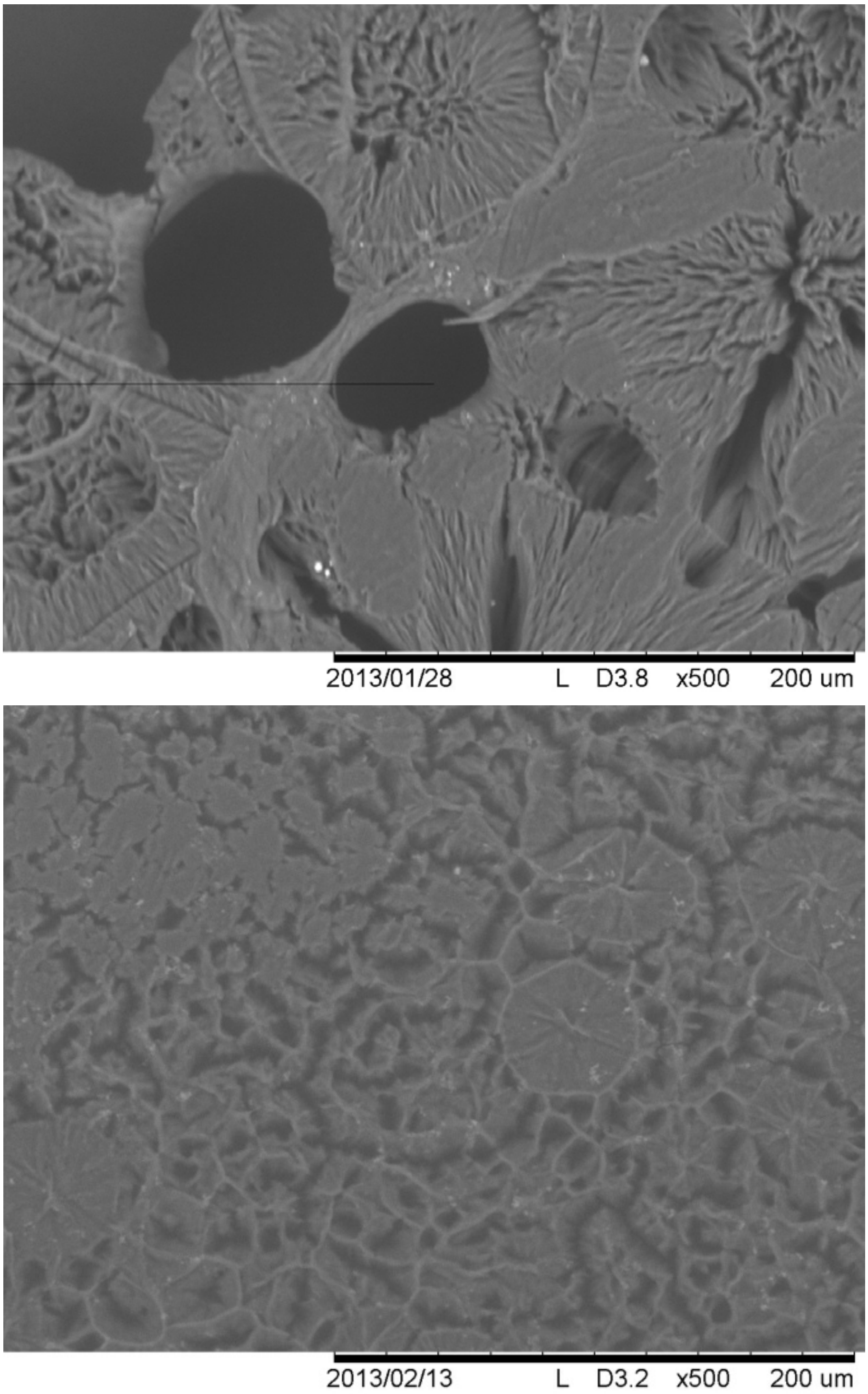


Figure 59 Interval 6 Non-welded versus Welded films at x500 magnification (non-welded on the left)

Upon taken the holistic view of the % weight loss graphs in isolation, it appears that both types of films (welded and non-welded) have similar rates of degradation all the way up to this point at 12 weeks. You can see this in the graph below

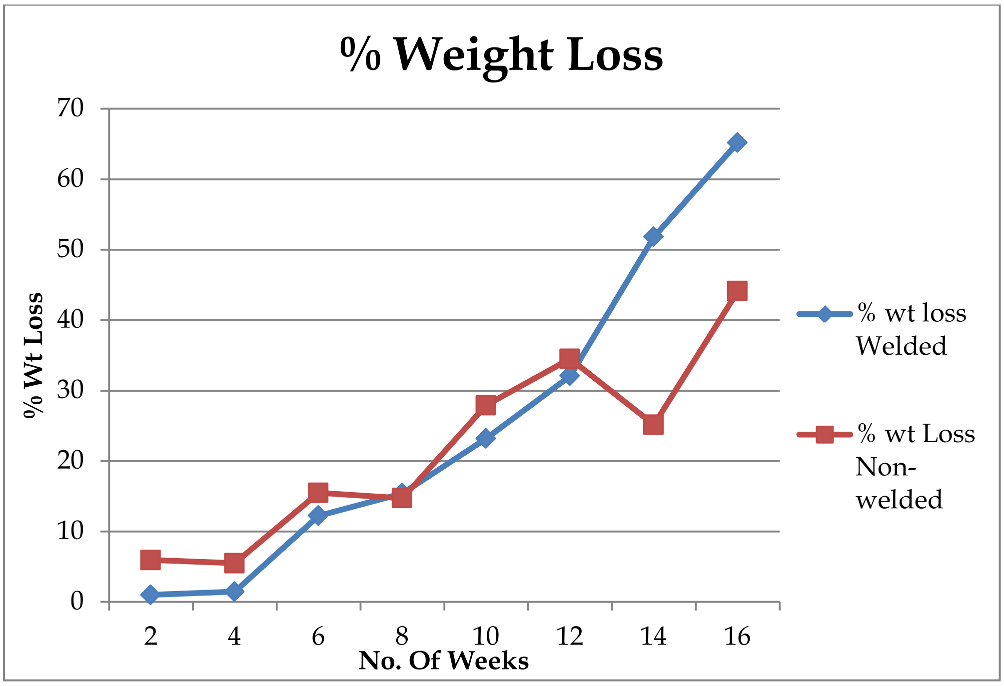


Figure 60 % weight loss of Welded and non-welded films.

If the degradation experiments were carried out beyond the sixteen weeks that was done here, the welded films would most likely show a similar slow down in the degradation rate as the non-welded samples at the twenty week mark. However, there is too little data here to say this for sure. There are hints in the SEM images from the welded samples at intervals 5 to 8 that the remaining material is starting to look more crystalline in nature and if it will start to slow down, possibly with 2 to 4 weeks after Interval 8. Another point to note is that the SEM analysis shows the effect of degradation at the surface of the films, even though the degradation process occurs in bulk.

Another possibility would be that the laser welding had changed the ratio between amorphous to crystalline that the remaining material would have so little crystalline material left that it would not be adequate to slow down the mass loss during the degradation in the later stages. This could open the possibility that both type of films would in fact degrade at the same time. However the research from other sources indicates that the degradation happens in a two stage process, with hydrolytic degradation occurring first in the amorphous regions and the second stage where degradation occurs on the remaining crystalline material through dissolution. There are no indicators apparent in this body of work that point to any significant differences to the established theories.

Taking the current information gathered from the results of the numerous experiments listed, does the laser welding process have an effect on the degradation properties of Polycaprolactone? Results suggest that it does, in and indirect way, especially between weeks 12 and 14. More work may need to done to determine what the exact cause or causes are. What was put forward in the discussion above may become a good start point to find out.

FUTURE WORK

Following on from the work above, there a number of avenues to pursue in which to increase the knowledge base. The obvious and most important one would be to increase the degradation time intervals until there the films completely degrade. This will give important results into whether an increase in crystallinity slows down the degradation rates for the welded samples as well as the non-welded samples. It will also give definitive results on rate of degradation of both types of films.

Another avenue to explore would be to carry out some Gel Permeation Chromatography (GPC) to the degradation process. GPC is a size exclusion chromatography type of analysis and is used in a lot of polymer analysis. GPC has a well-defined separation time due to the fact that there is a final elution volume for all unretained analytes. It also provides narrow bands, although this aspect of GPC is more difficult for polymer samples that have broad ranges of molecular weights present in the degrading films. Also the analytes do not interact chemically or physically with the column, there is a lower chance for analyte loss to occur. GPC would have provided good information to changes to the average molecular weights that the films would go through, and would provide more data to enhance the current data provided by the pH graphs. It was hoped that the HPLC results would have provided similar data, but issues with the testing suitability and robustness hampered efforts. Making the change to a different HPLC column may have helped with the issues however, and if time permitted, this would have been the next option to take.

Differential Scanning Calorimetry (DSC) was another analytical technique that was discussed at the start of the process to track possible changes in crystallinity through the degradation process. DSC is a thermo-analytical technique in which the difference in the amount of heat required to increase the temperature the PCL sample and reference (usually polystyrene) is measured as a function of temperature. Glass transitions (the reversible transition in amorphous materials or in amorphous regions within semi crystalline materials from a hard and relatively brittle state into a molten or rubber-like state) may occur as the temperature of an amorphous solid is increased. These transitions appear as a step in the baseline of the recorded DSC signal. This is due to the sample undergoing a change in heat capacity; no formal phase change occurs. (Woodruff & Hutmacher 2010)

However, the time it would take to get the processes up and running proved to be prohibitive for this body of work. DSC could have provided more definitive data on the effects of crystallinity on the degradation rates of the films, and could go a long way to proving some of the hypothesis discussed in the conclusions above.

The results of this work also opened some other possible lines of inquiry into the effects of laser welding on biodegradable materials. The results of this project indicate that similar studies need to be run some on other families of biodegradable polymers. Examining the degradation rate of PCL and other copolymers would also prove worthwhile. With significant advances being made over the past number of years in the development of biodegradable materials, more research needs to be carried out on the processing techniques to observe any changes of the degradation rates. With the increasing use of biodegradable materials as replacement of current therapeutic materials, this is becoming increasingly important in order to achieve approval from regulatory authorities to help commercialise these technological advances.

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Appendix A Laser Welding Program

Weld Program for Multiple Welds:

Step	Cnd	Cmnd	Operand 1	Comment	Pst
1		VEL	10	Speed of Movement	
2		ACC	0.3	Acceleration	
3		BTON	303	Warn light on	
4		BTON	308	laser diode on	
5		BTON	309	Laser Interlock	
6		TIMW	5.0	Time Delay	
7		BTON	315	Laser On	
8		MVLI	1		
9		BTOF	315		
10		MVLI	2		
11		BTOF	309		
12		BTOF	303		
13		EXIT			
14					

Position Programming for multiple welds

Step	Acc	Vel	Axis 1	Axis 2	Axis 3
1	7		0.000	0.000	20.000
2	7		0.000	0.000	- 20.000

Appendix B Energy Dispersive X-ray Results

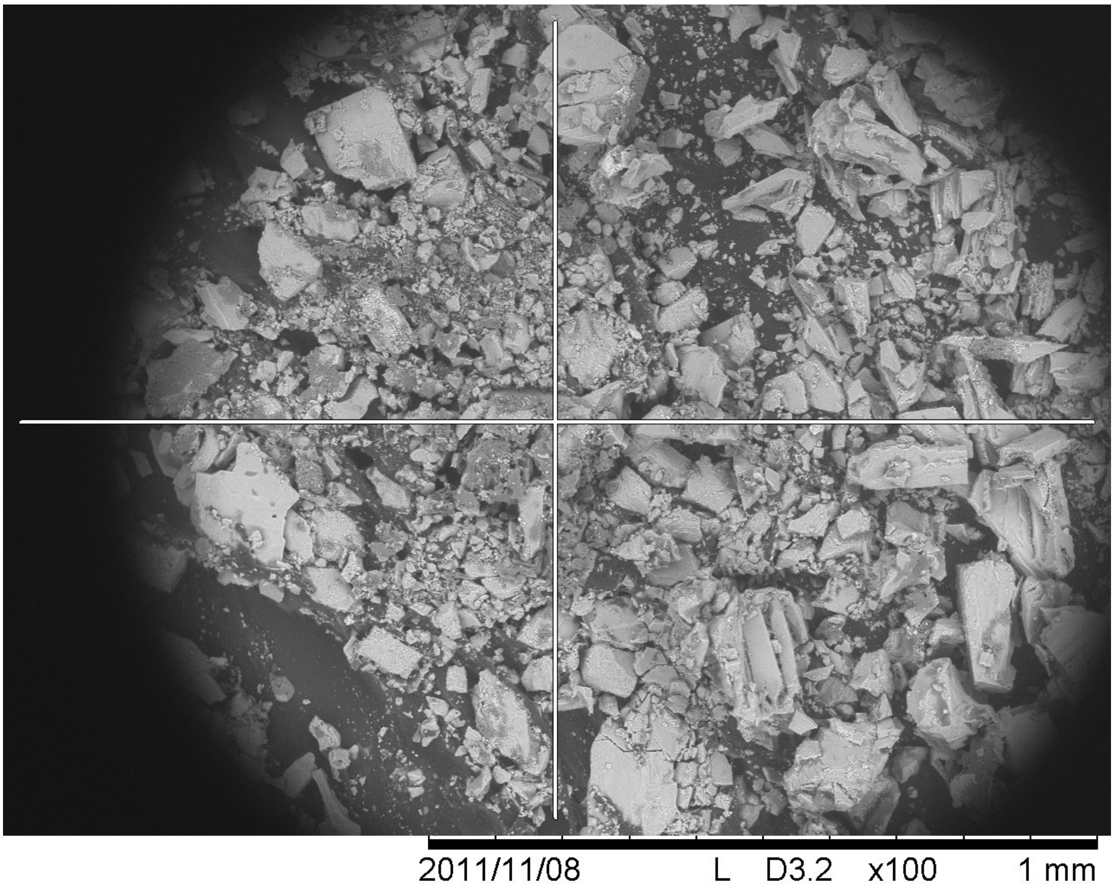


Figure 61 Examples of ‘White Blobs’ Analyzed with EDx

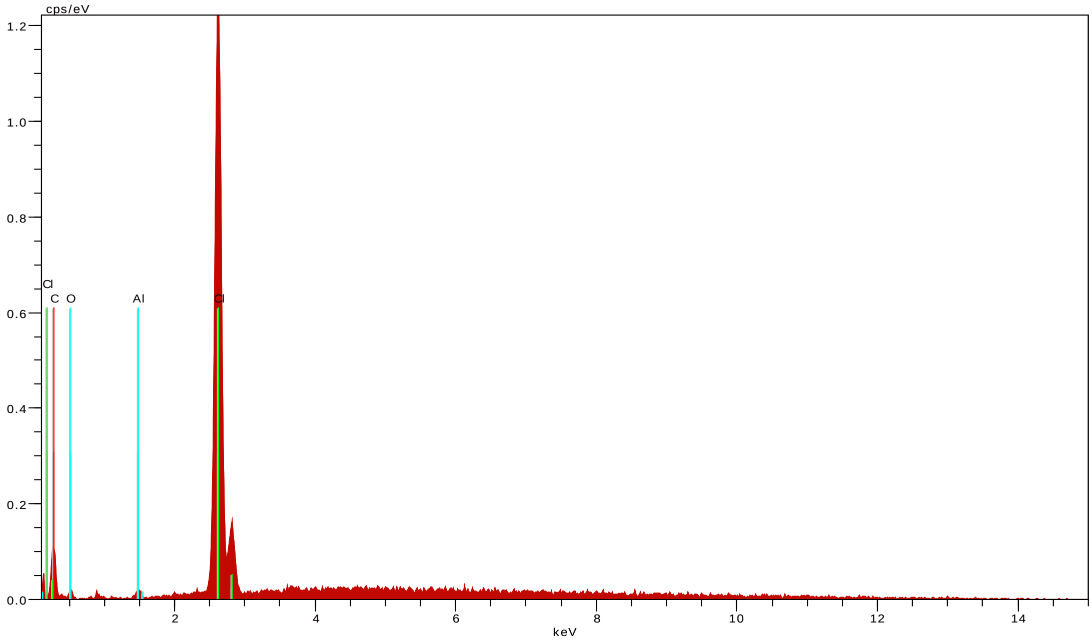


Figure 62 EDx Spectrum Graph of fig 61.

```
Spectrum: Acquisition

Element   AN  Series   unn. C norm. C Atom. C Error
                       [wt.%]  [wt.%]  [at.%]   [%]
--------------------------------------------------
Carbon     6  K-series  60.33   61.30   78.02  21.2
Chlorine  17  K-series  26.65   27.07   11.67   0.9
Oxygen     8  K-series   9.42    9.57    9.15   3.5
Aluminium 13  K-series   2.02    2.05    1.16   0.2
--------------------------------------------------
               Total:   98.42  100.00  100.00
```

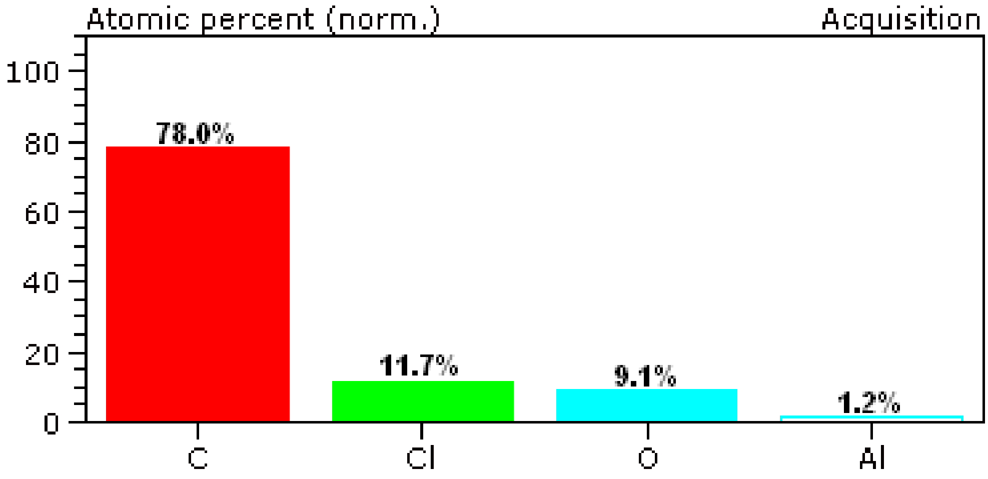


Figure 63 Acquisition table and Histogram of fig 61.

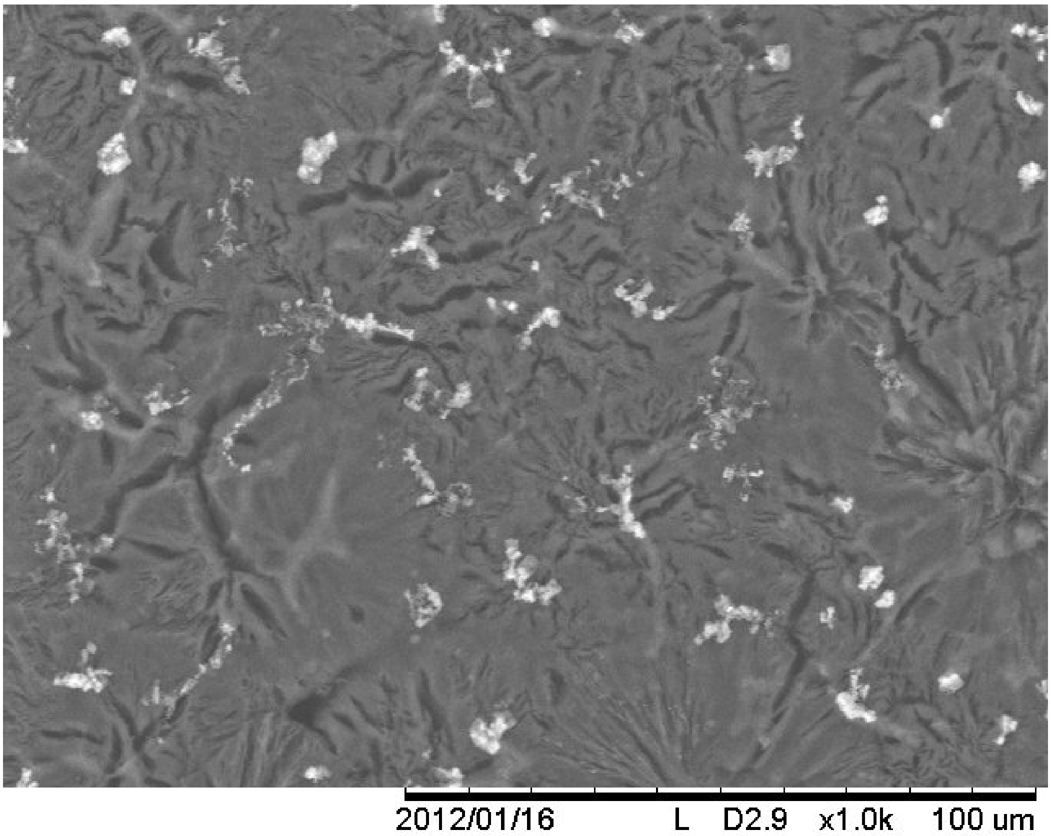


Figure 64 EDx Area analysis of partially degraded PCL films

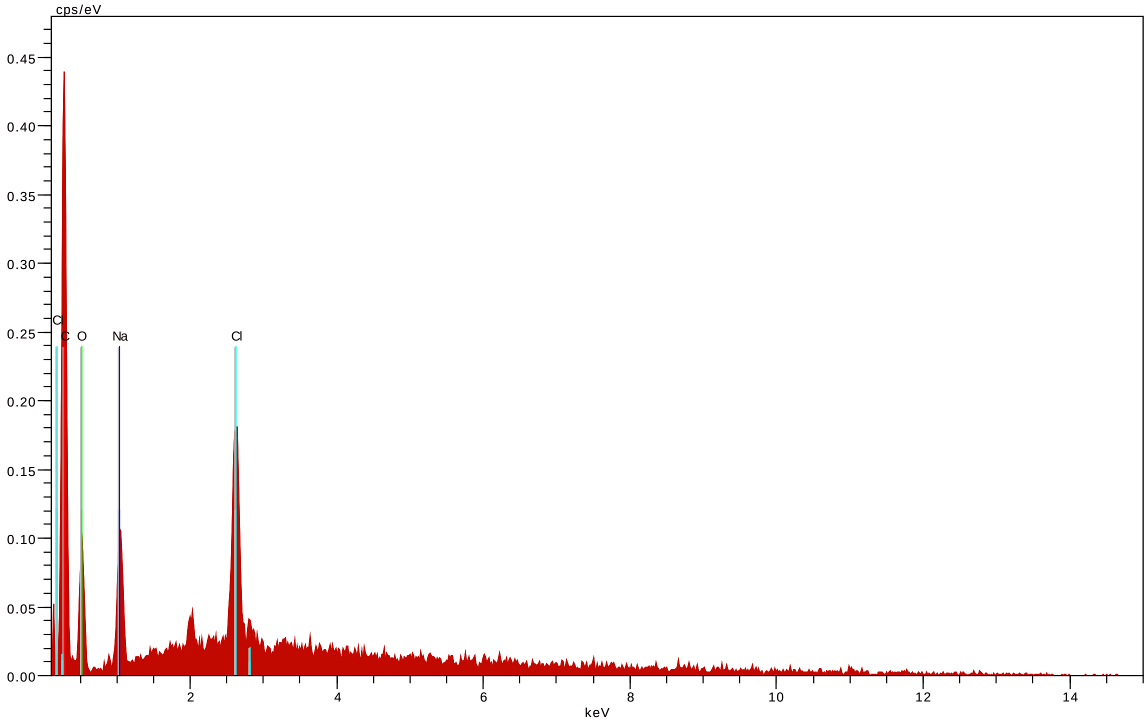


Figure 65 Spectrum Graph of fig 64.

```
Spectrum: Acquisition

Element   AN  Series   unn. C norm. C Atom. C Error
                       [wt.%]  [wt.%]  [at.%]   [%]
--------------------------------------------------
Carbon    6  K-series  66.37   66.37   74.37  15.3
Oxygen    8  K-series  25.77   25.77   21.67   5.9
Sodium    11 K-series   4.71    4.71    2.76   0.4
Chlorine 17 K-series    3.15    3.15    1.20   0.2
--------------------------------------------------
              Total: 100.00  100.00  100.00
```

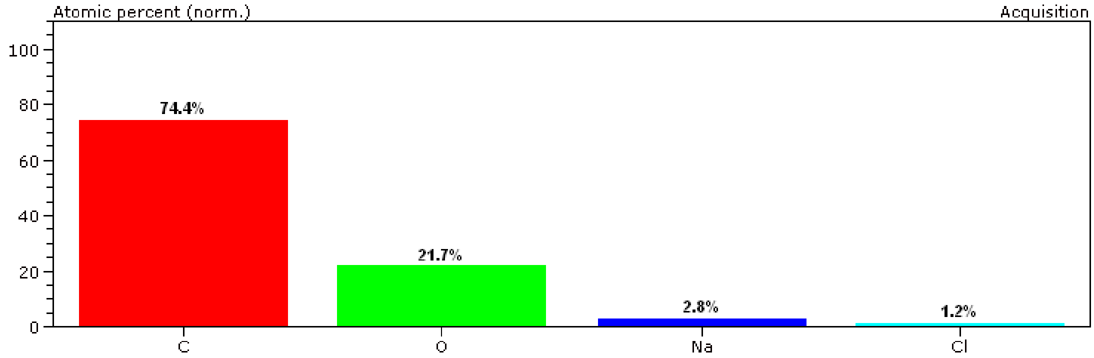


Figure 66 Acquisition table and Histogram of fig 64

Traces of sodium and chloride present or most due to trace amounts from the degradation medium (PBS with lipase). The aluminum present most likely came from contact made during the film processing phase (when cut into sections) or from contact with the stub that the film samples were placed on prior to being examined in the SEM.

Appendix C HPLC Chromatograms

Initially it was hoped to link the experimental results from the pH analysis with the HPLC analysis experiments. The pH results were hoped to provide a visual representation of the degradation rates and the HPLC analysis providing the empirical results. However, with the small quantities involved with those degradation experimental results, it proved extremely difficult to draw specific conclusion from the data. Regardless, the results obtained for both welded and un-welded films are provided here for reference.

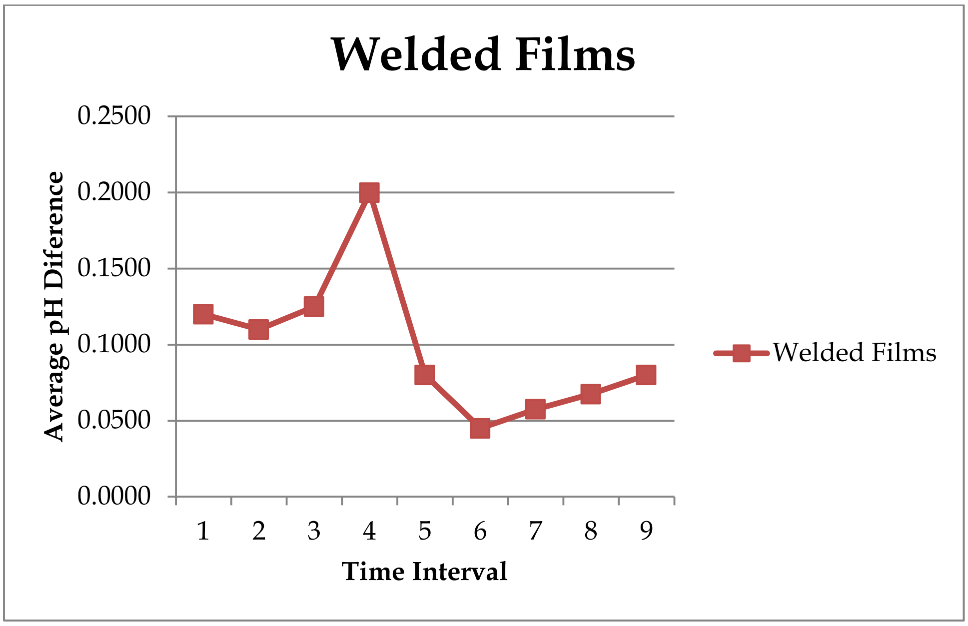


Figure 67 pH Measurements Welded films

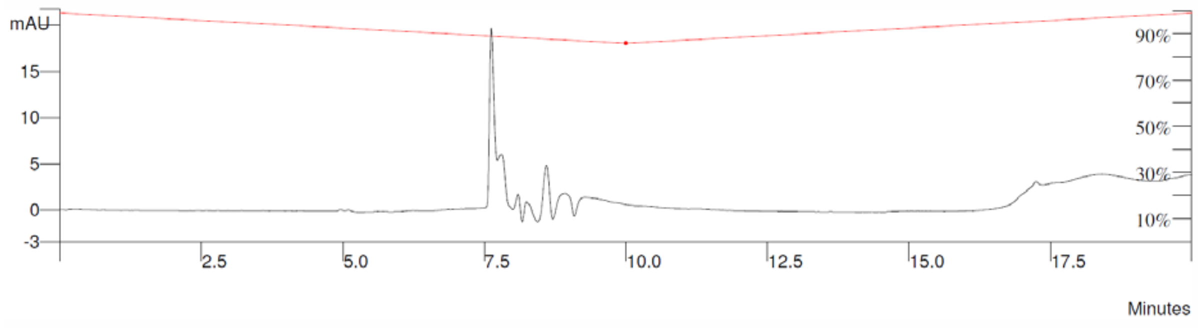


Figure 68 Welded films Interval 2

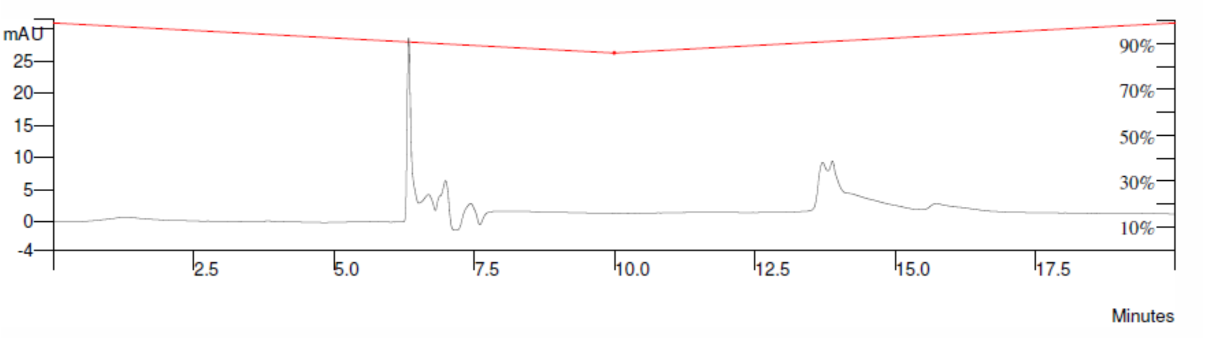


Figure 69 Welded Films Interval 3

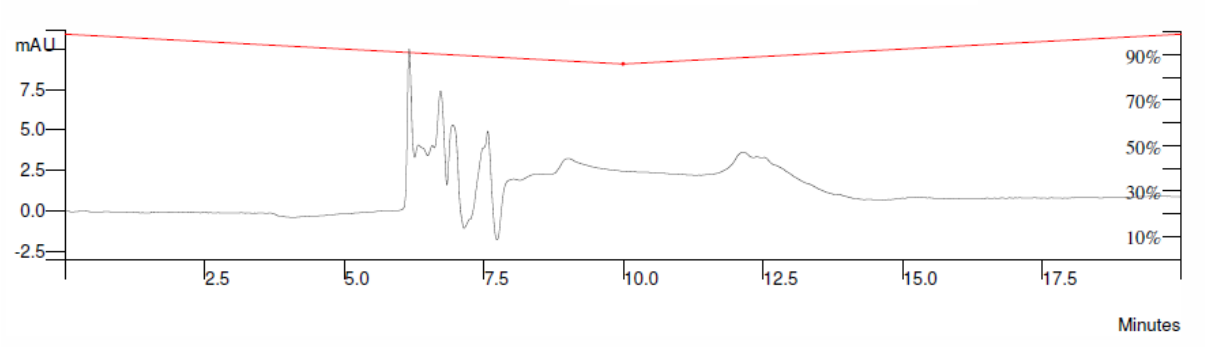


Figure 70 Welded films Interval 4

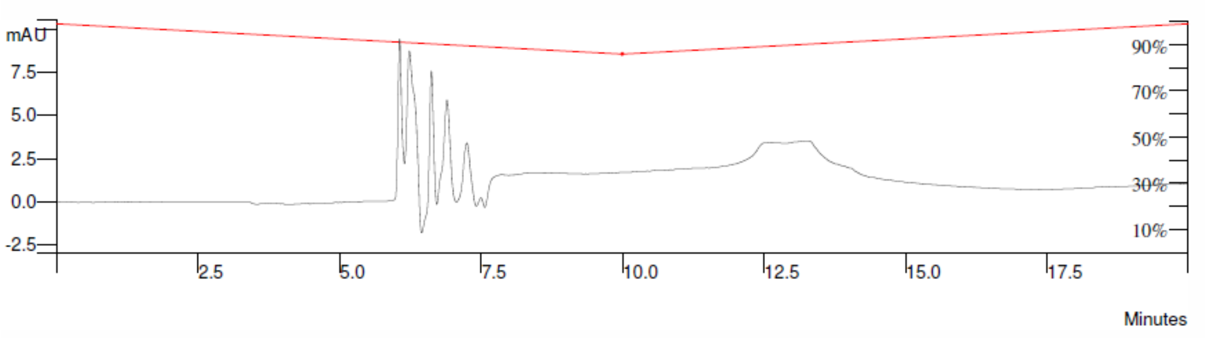


Figure 71 Welded films Interval 5

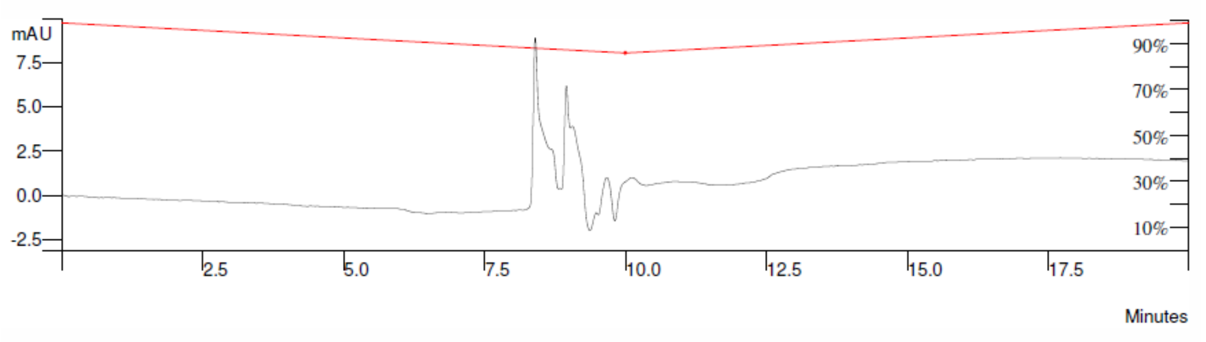


Figure 72 Welded Films Interval 6

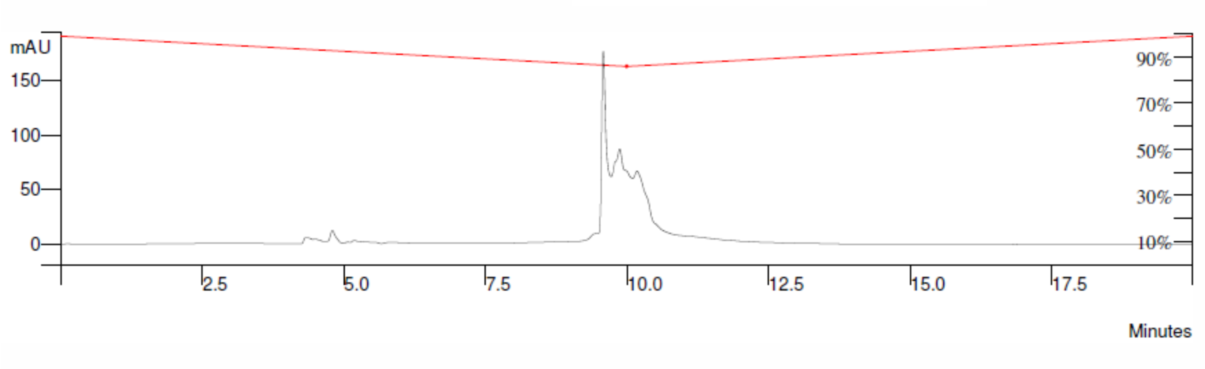


Figure 73 Welded films Interval 7

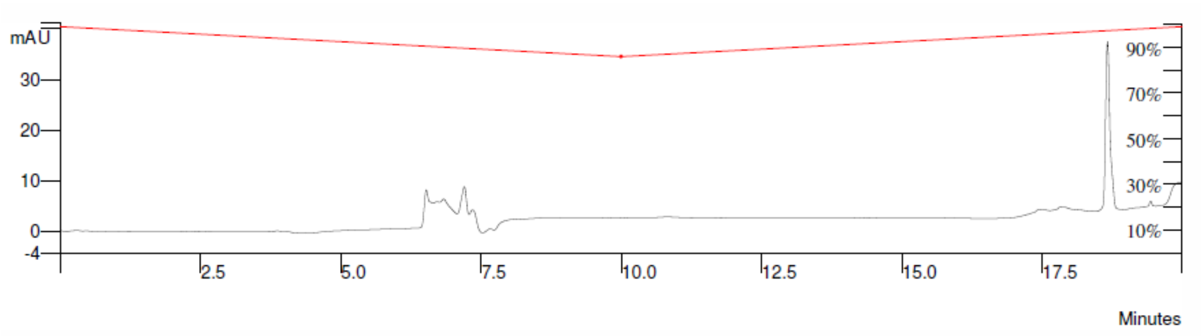


Figure 74 Welded films Interval 8

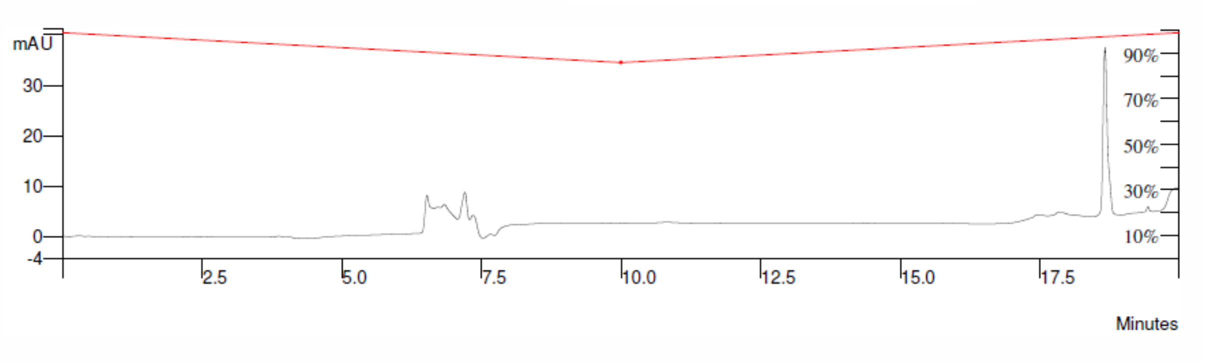


Figure 75 Welded films Interval 9

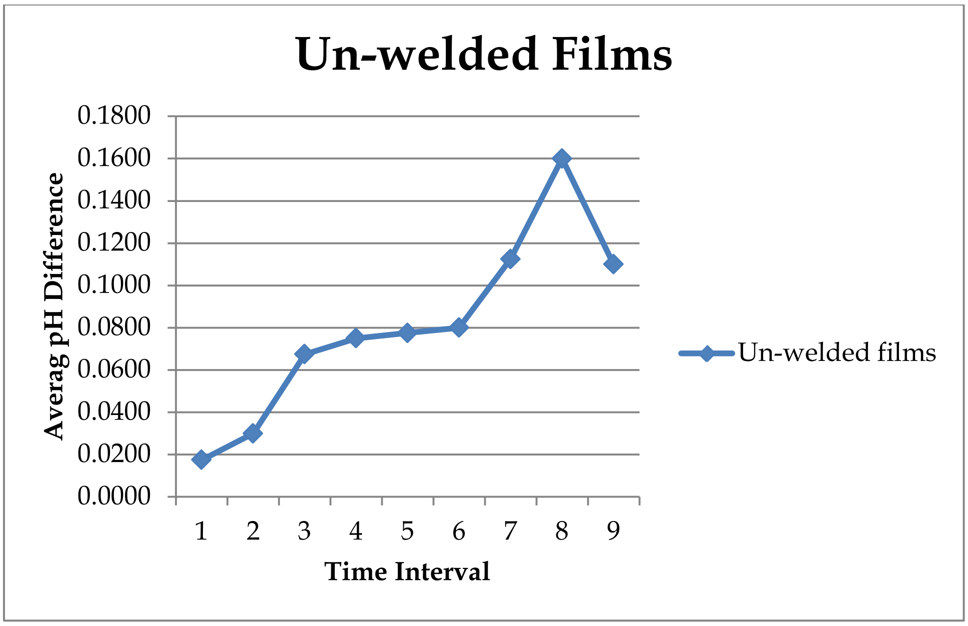


Figure 76 pH measurements of un-welded films

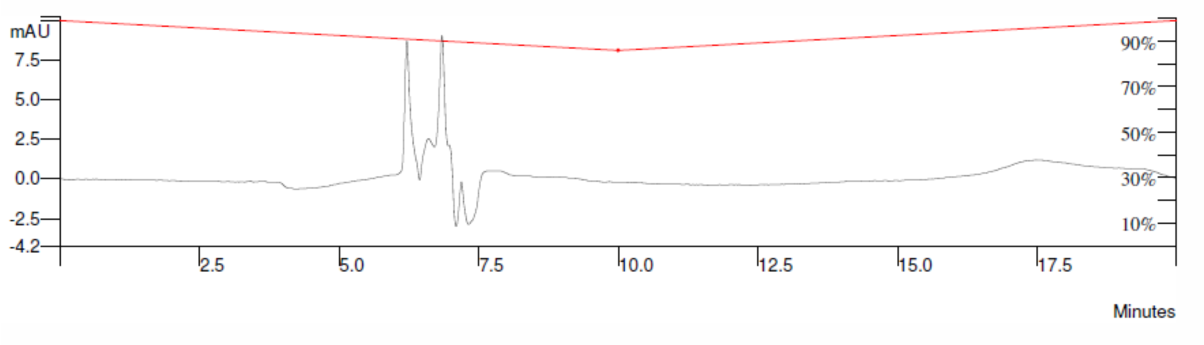


Figure 77 Un-welded films Interval 2

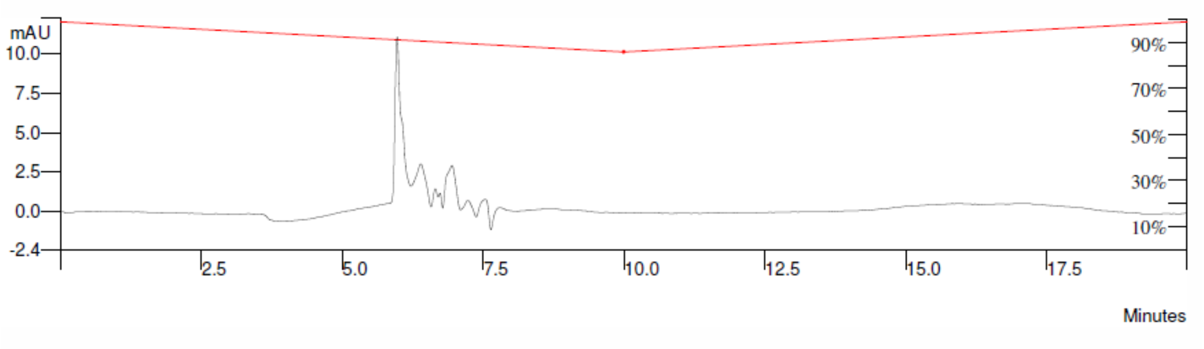


Figure 78 Un-welded films Interval 3

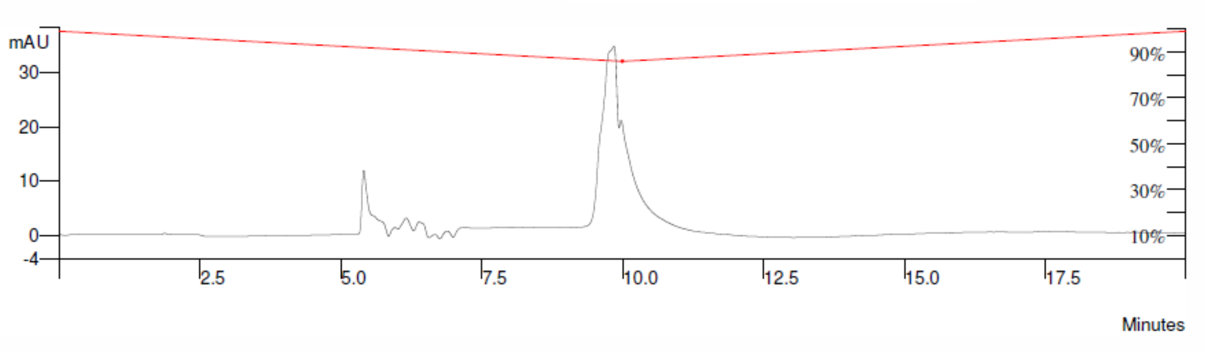


Figure 79 Un-welded films Interval 4

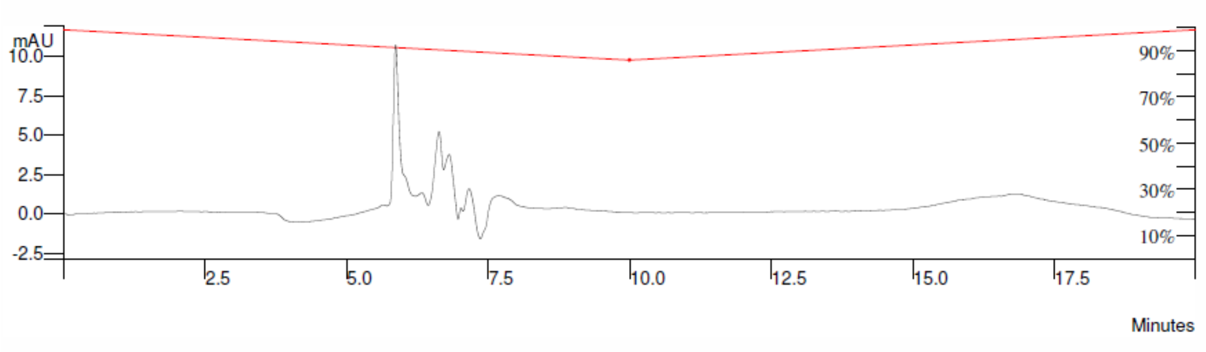


Figure 80 Un-welded films Interval 5

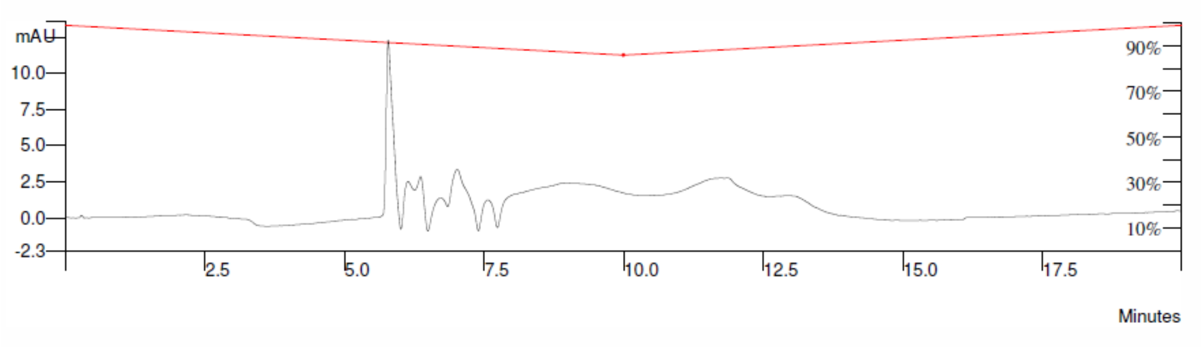


Figure 81 Un-welded films Interval 6

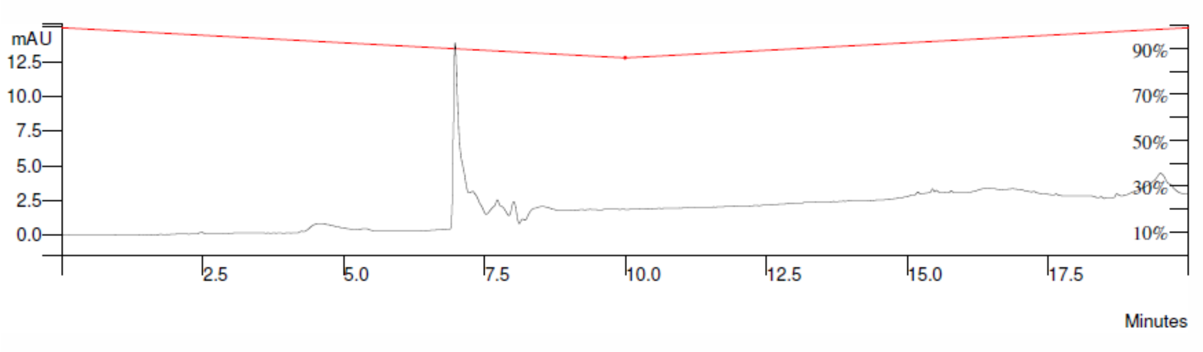


Figure 82 Un-welded films Interval 7

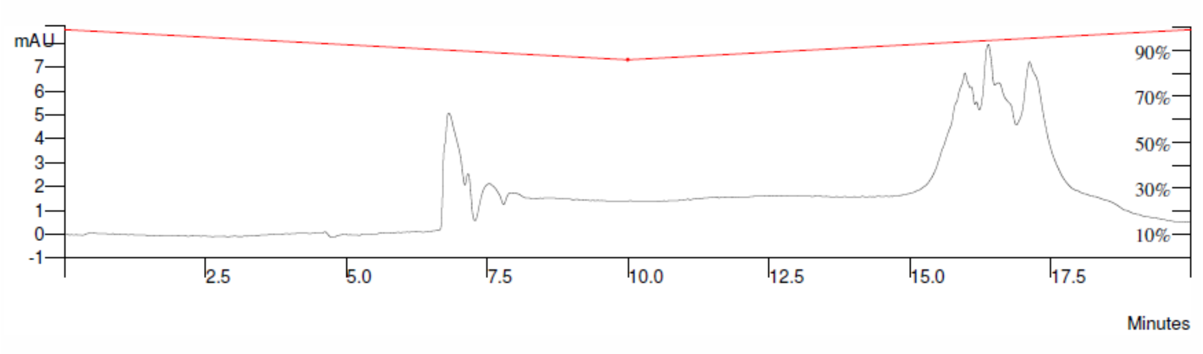


Figure 83 Un-welded films Interval 8

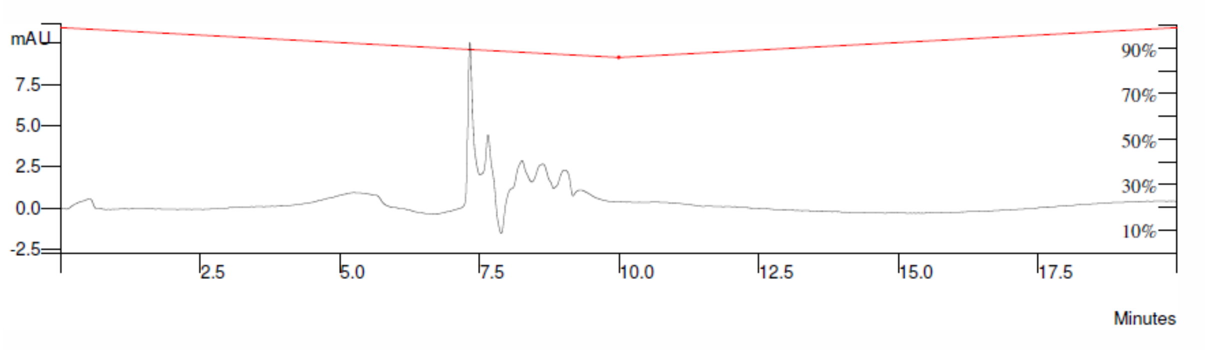


Figure 84 Un-welded films Interval 9

Index of Figures

The first sample observed in the SEM was of the film that was left to evaporate for more than 14 hours. At the lower magnification (x 150) the films had shown numerous micro voids of around 500 - 1000μm across. The images obtained were from the topside of the film (the bottom side would have been in direct contact with the microslide). The surface shown here was typical of the surfaces at various positions of the sample. (See Figure 17)

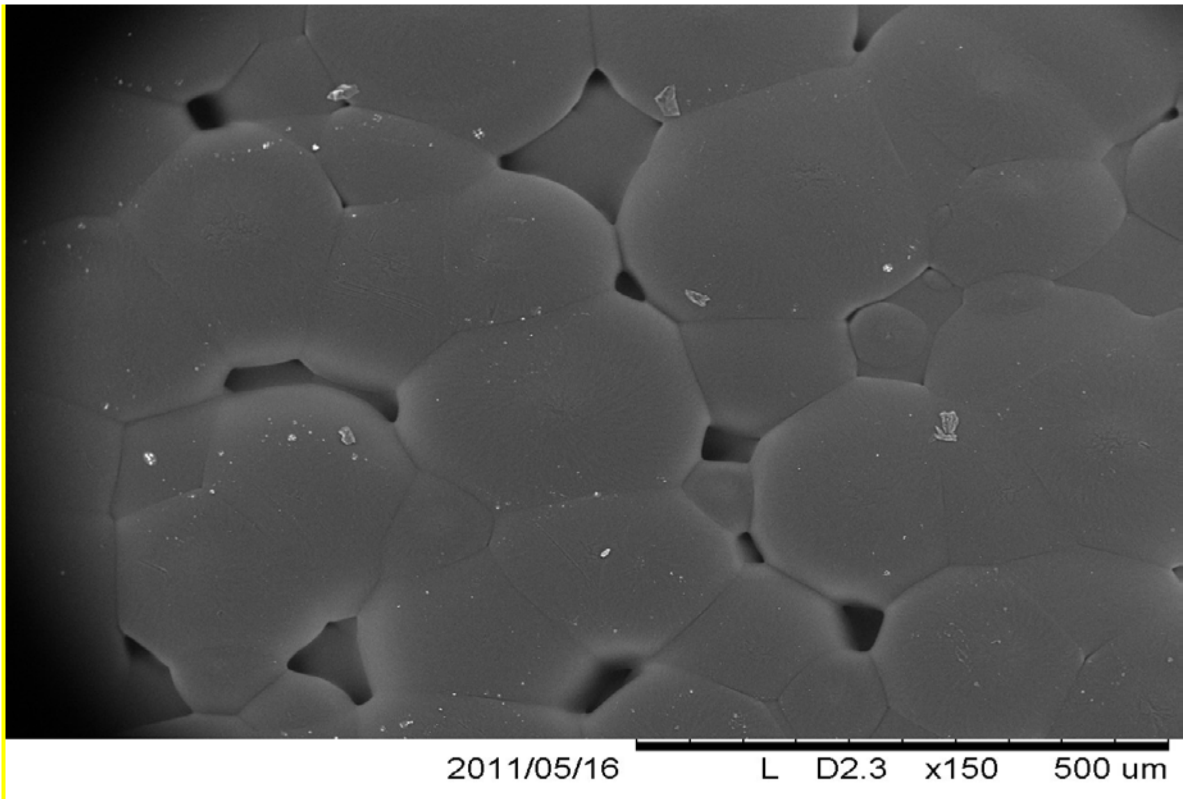


Figure 16 SEM image of the top side of the sample 1 after been left to dry for more than 14 hours. The bottom side of the sample appeared a lot smoother at the same magnification. (see figure 17) 33

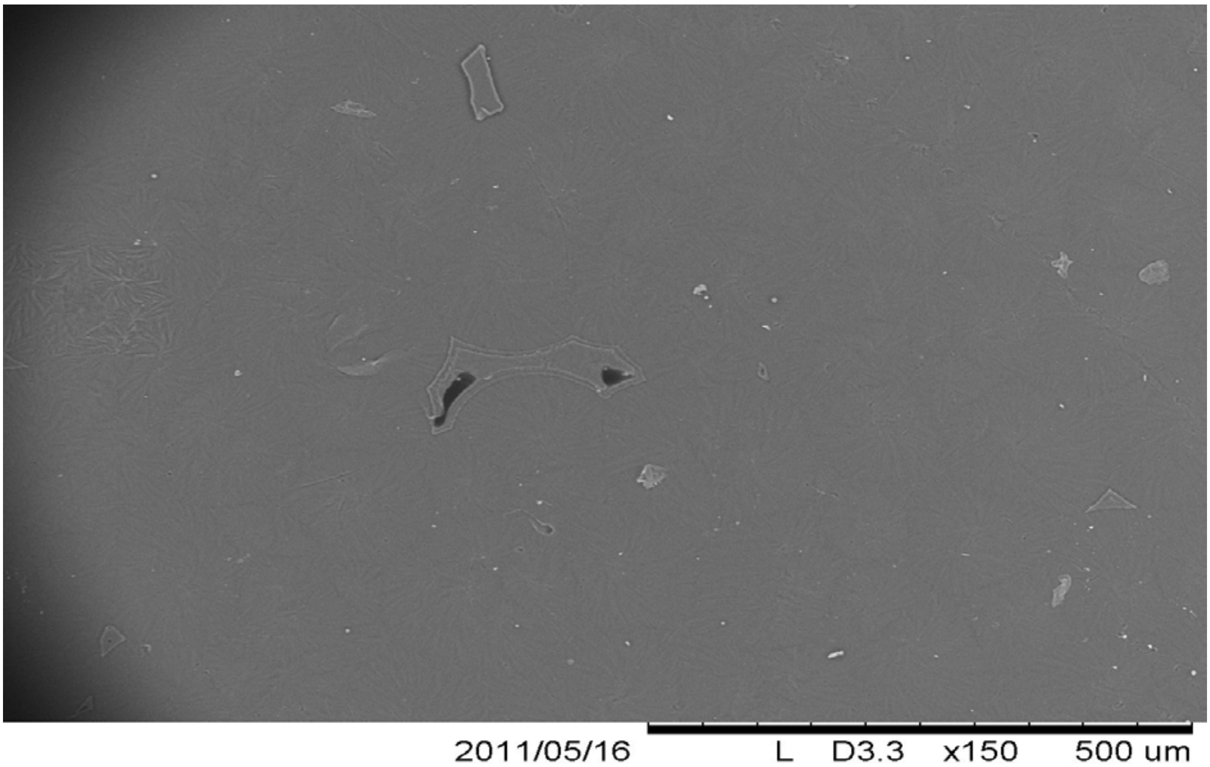


Figure 17 SEM of the bottom side of sample 1 after been left to dry for more than 14 hours(x150 Mag).. 35

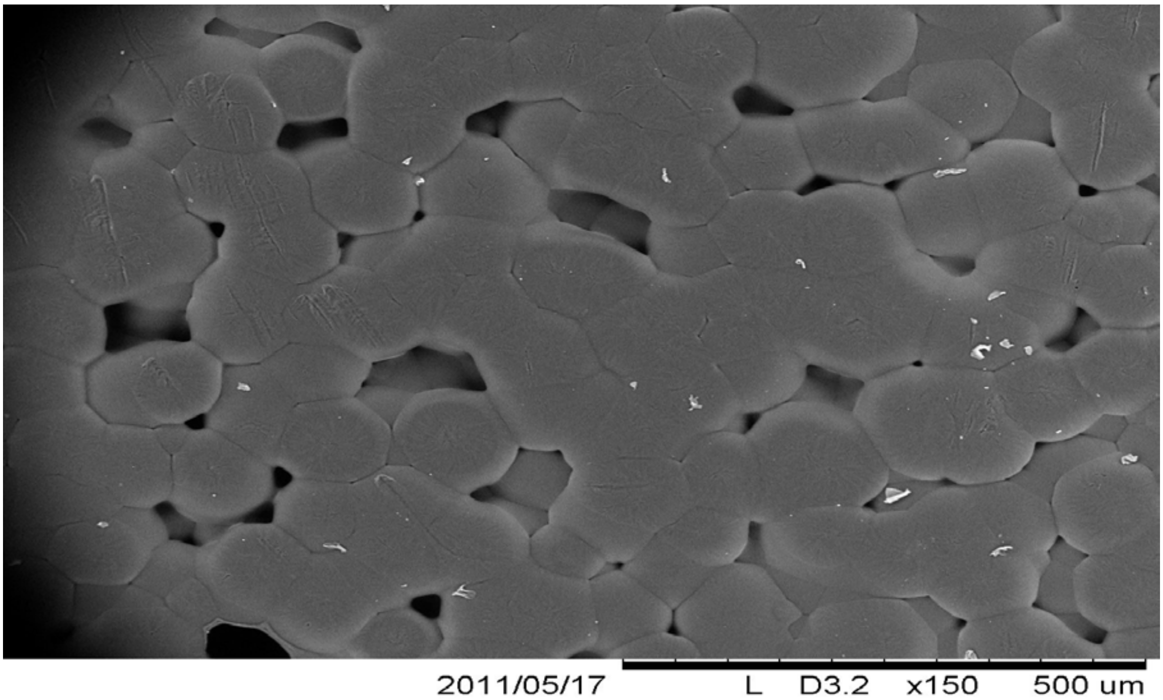
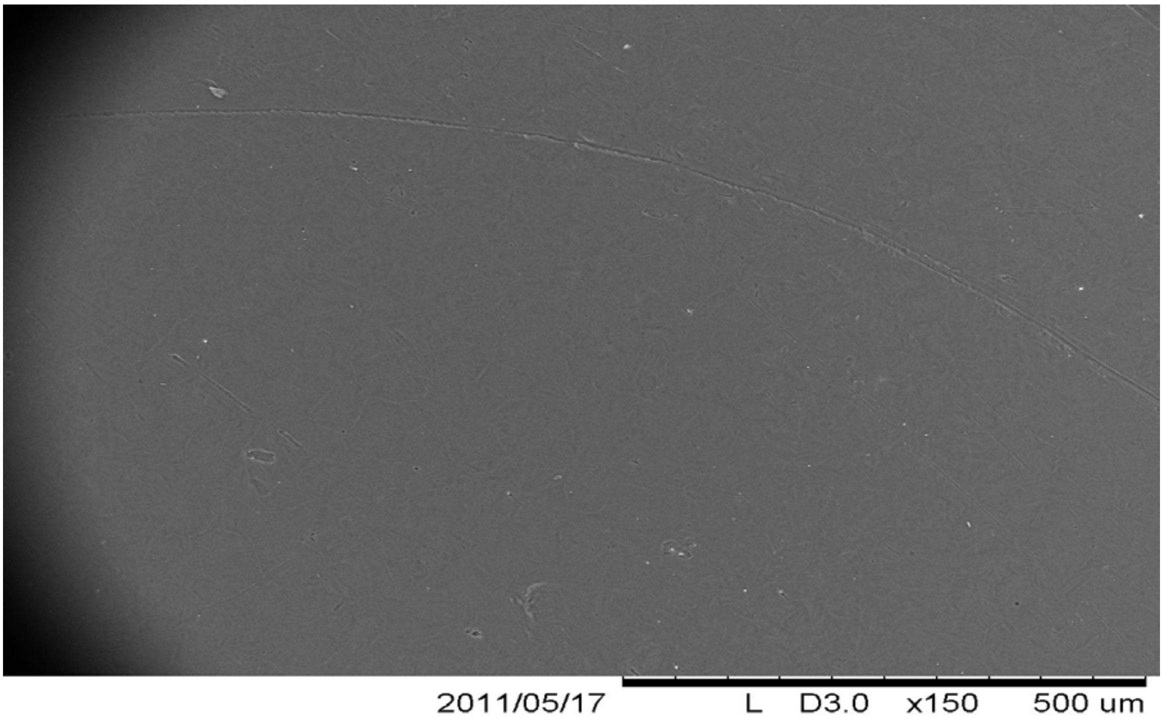
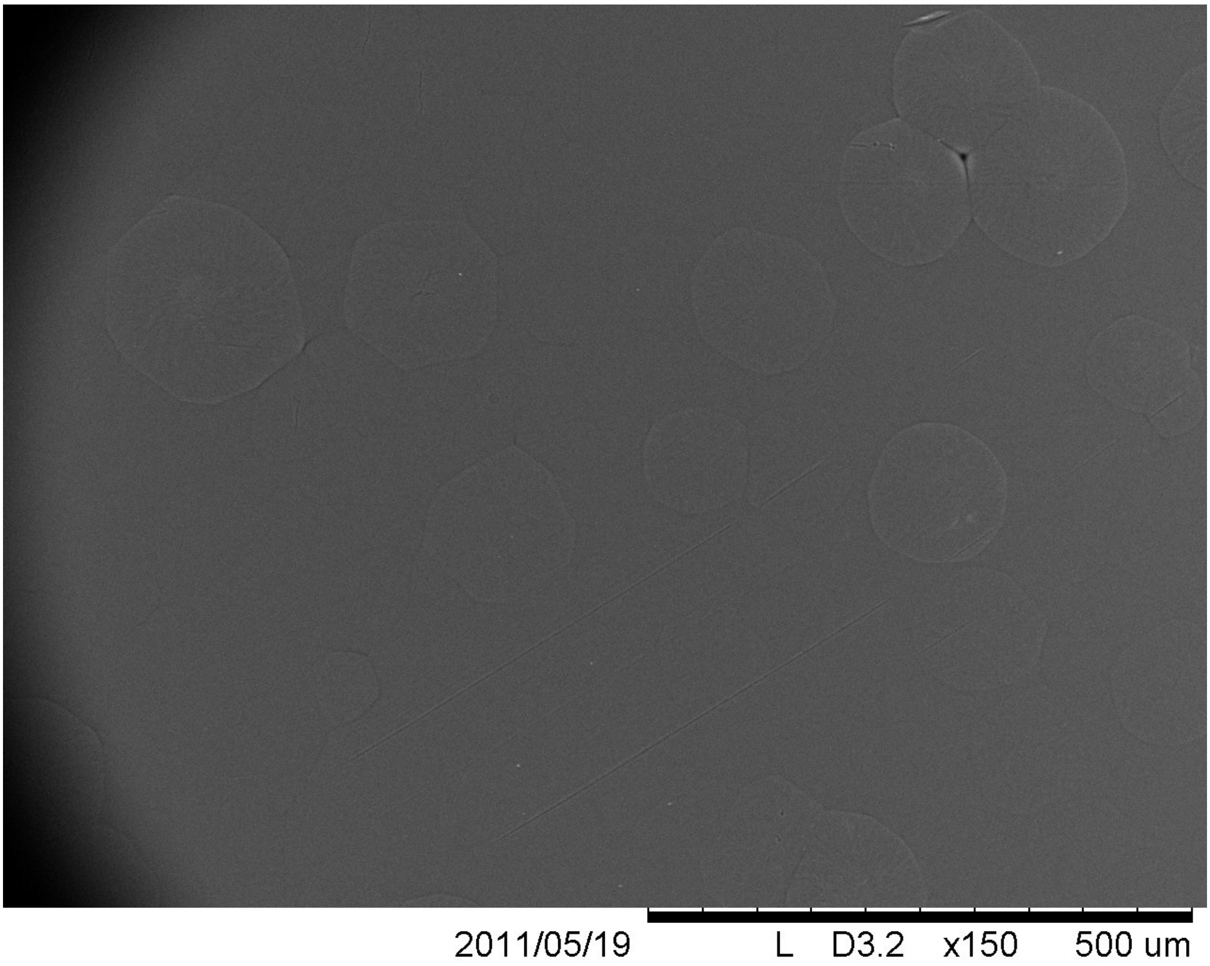
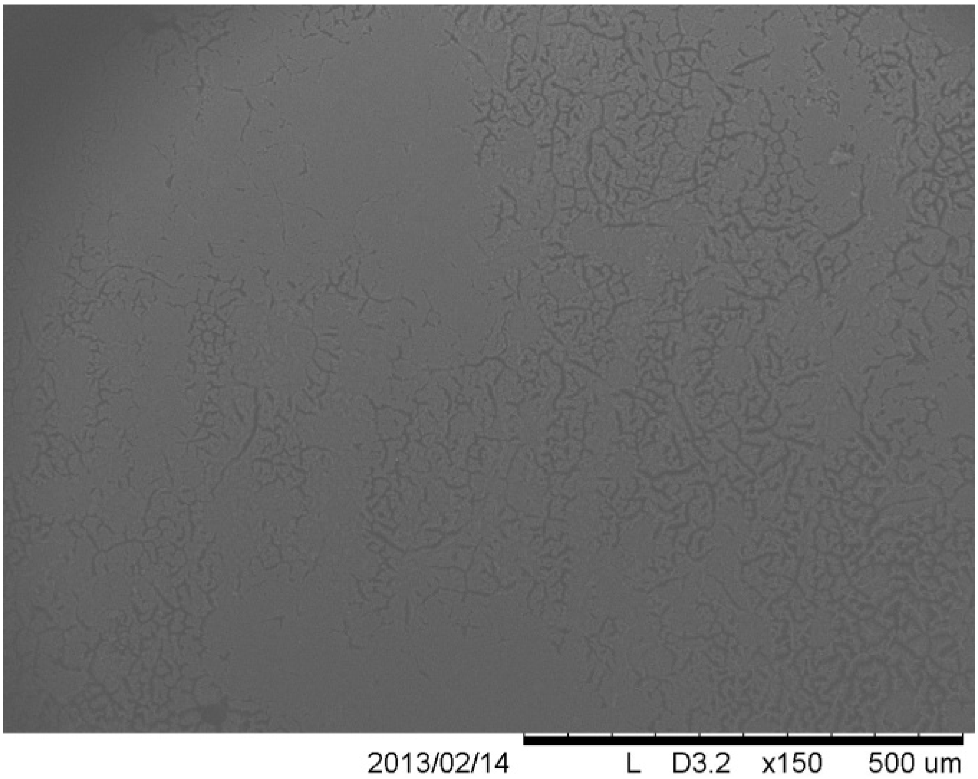
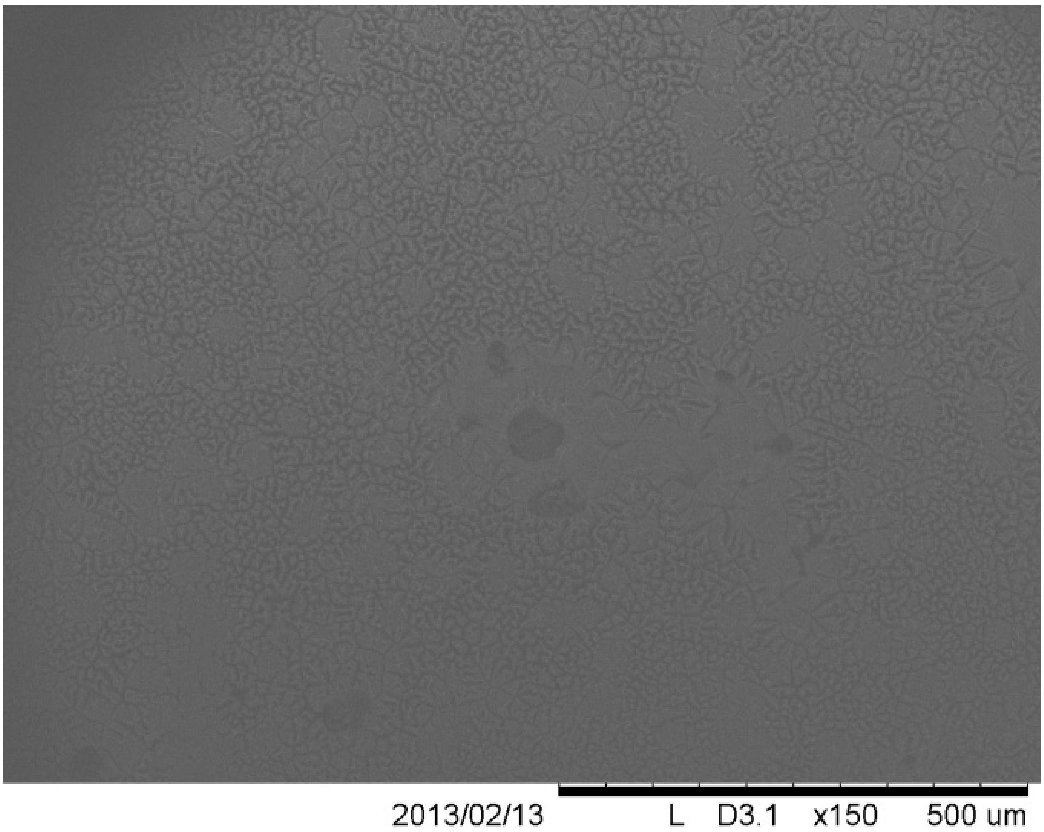


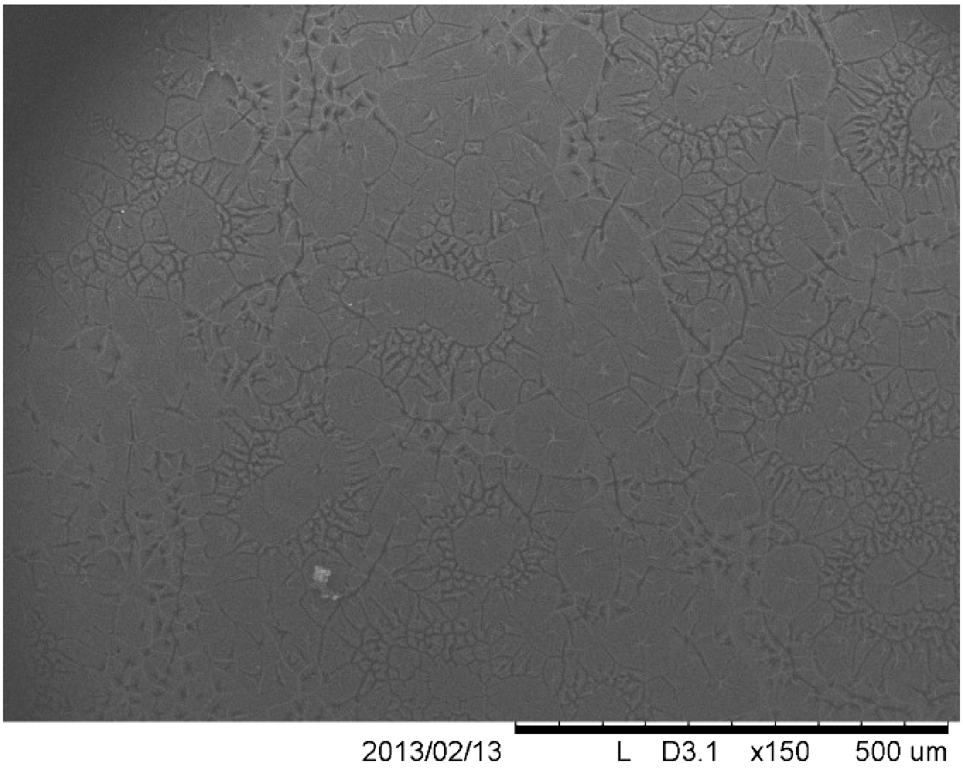
Figure 18 SEM image Sample 2 Topside... 35


2011/05/17
L
D3.0
x150
500 um


2011/05/19
L D3.2 x150 500 um


2013/02/14
L
D3.2
x150
500 um


2013/02/13
L
D3.1
x150
500 um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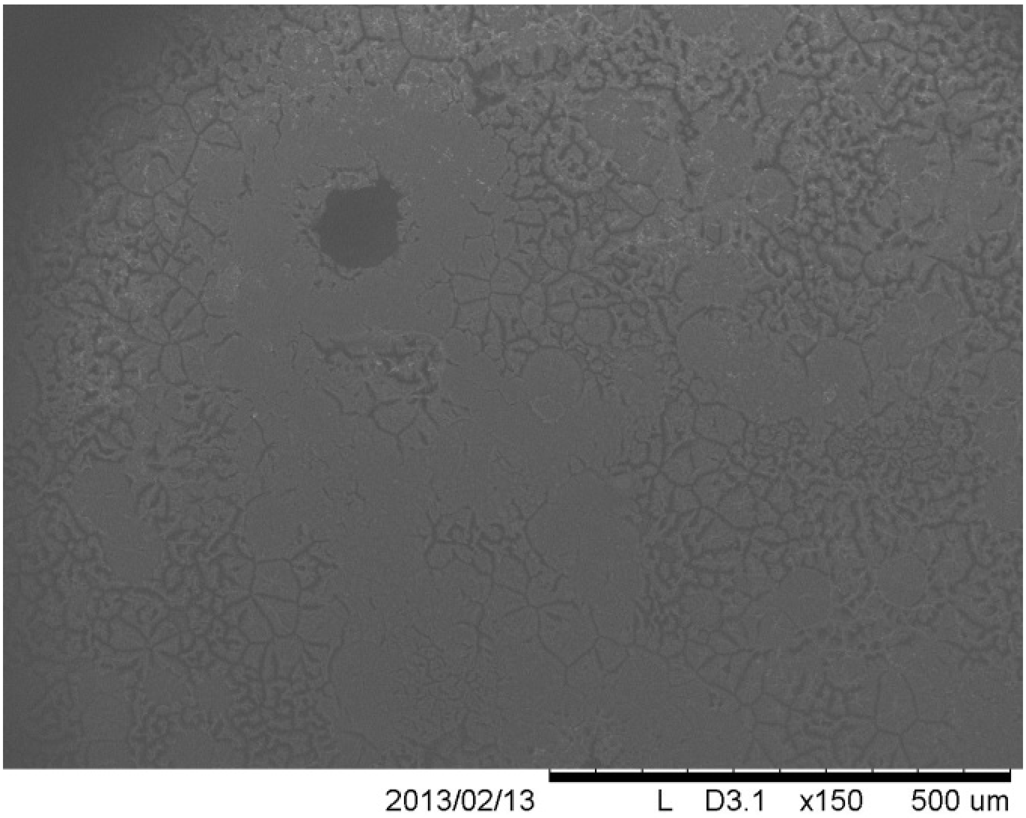
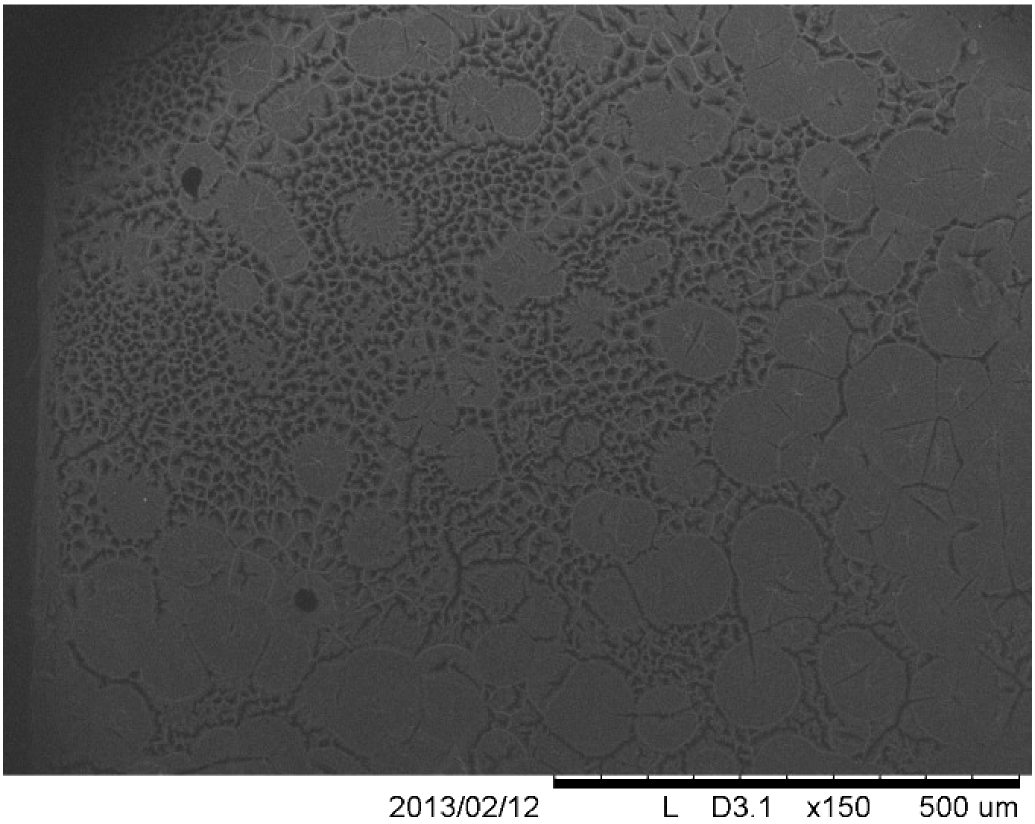
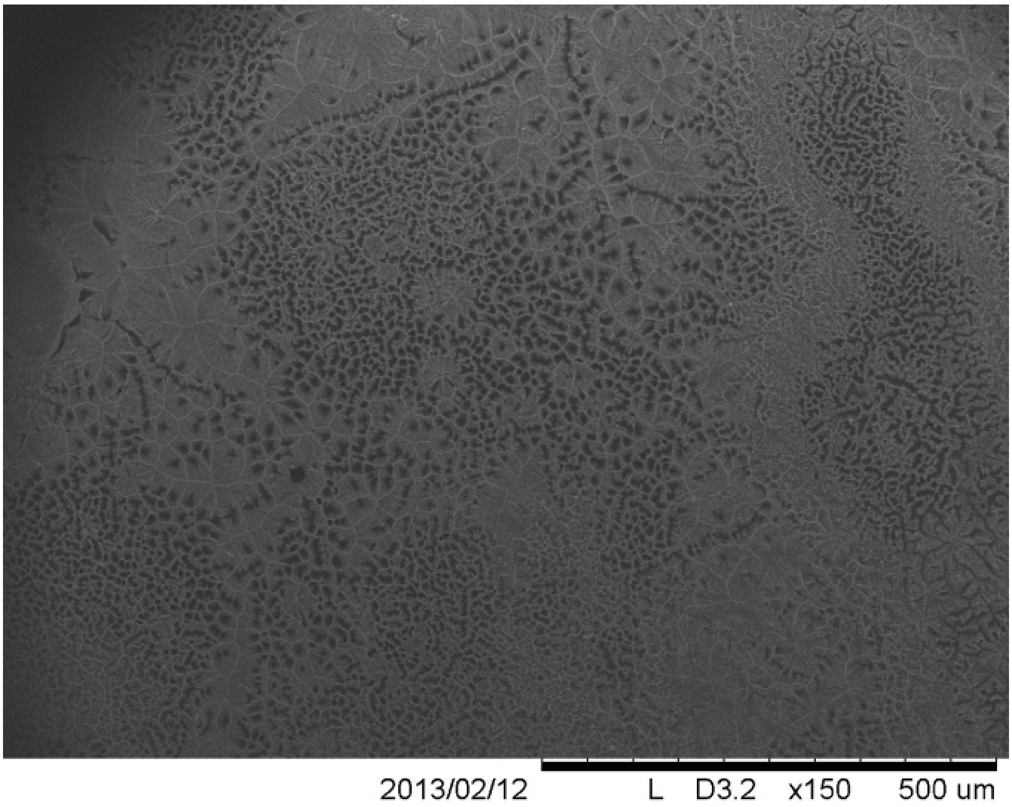
L
D3.1
x150
500 um


2013/02/13
L D3.1 x150 500 um


2013/02/12
L
D3.1
x150
500 um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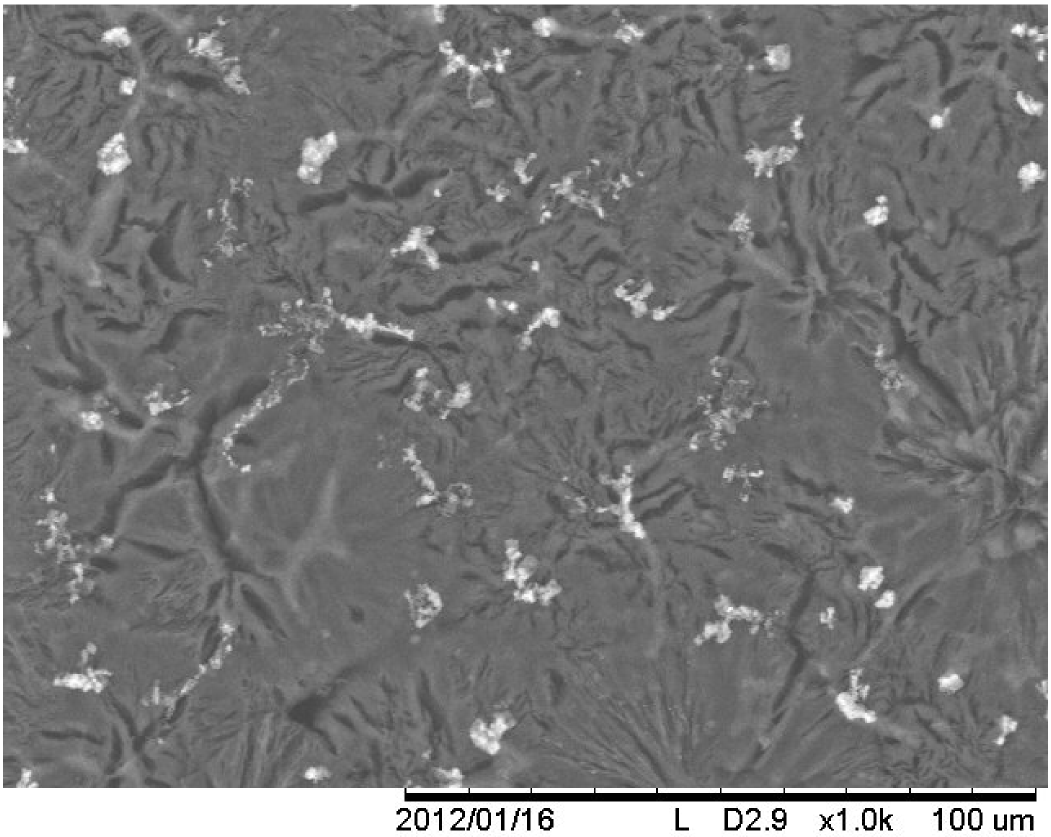
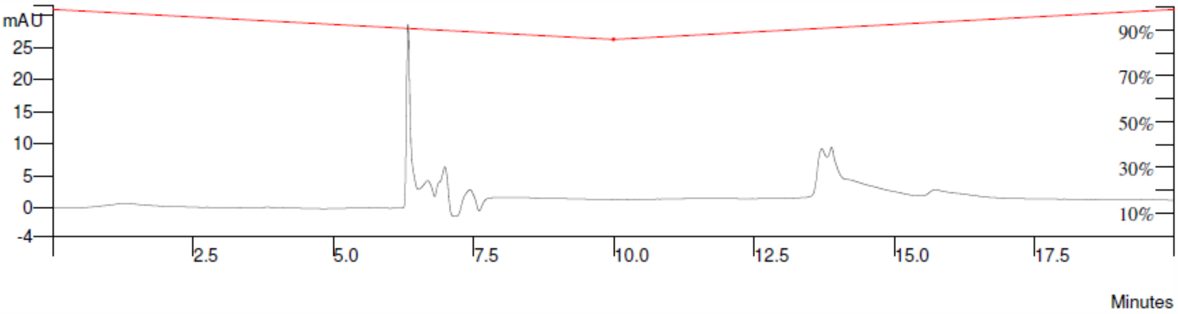
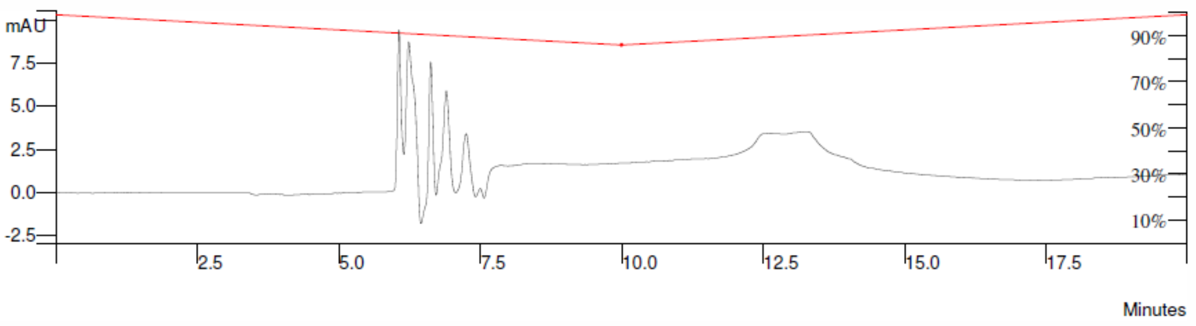
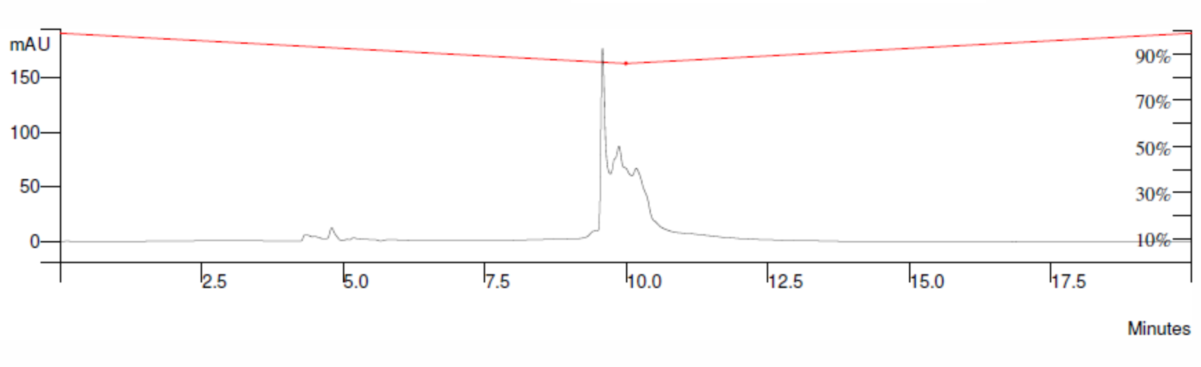
D3.2
x150
500 um


2012/01/16
L
D2.9
x1.0k
100 um


mAU
25
20
15
10
5
0
-4
2.5
5.0
7.5
10.0
12.5
15.0
17.5
Minutes
90%
70%
50%
30%
10%


mAU
7.5
5.0
2.5
0.0
-2.5
2.5
5.0
7.5
10.0
12.5
15.0
17.5
Minutes
90%
70%
50%
30%
10%


mAU
150
100
50
0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
Minutes
90%
70%
50%
30%
10%