



PROCESSING AND CHARACTERISATION OF VARIOUS POLYMER BLENDS TO DEVELOP IMPLANT FOR TISSUE ENGINEERING APPLICATIONS

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ABSTRACT

In the past two decades, the repair and reconstruction of musculoskeletal tissues using biodegradable scaffold materials has emerged as one of the most promising approaches in tissue engineering. The aim of this study is to process, via hot melt extrusion, the biodegradable and biocompatible polymeric materials; poly(ethylene oxide) (PEO), poly(ethylene glycol) (PEG), α -lactose monohydrate and poly(ϵ -caprolactone) (PCL), and investigate their suitability in tissue regenerating applications. Concentrations of the polymer blends were varied in order to optimise the degradation rate of the matrix blend. The effect of extrusion and plasticiser on the thermal and melt viscosity properties of the blends was coincidentally monitored. Materials of both pellet and powder compositions were compared in order to determine which composition provided optimum results. Blends were characterised using melt flow index (MFI), differential scanning calorimetry (DSC), rheometry and degradation analysis. Addition of plasticiser was found to cause a decrease in viscosity and melt temperature of the materials, so too was the extrusion process albeit to a lesser extent, while addition of filler increased melt viscosity and melt temperature of the blend. A vital advantage of this study is the ability to fine tune the properties of the matrix by varying material concentrations, making these promising candidates for tissue engineering applications.

Keywords: Extrusion, PEO, PCL, Biodegradable implant

INTRODUCTION

In the past two decades, the repair and reconstruction of musculoskeletal tissues by using biodegradable scaffold materials has emerged as one of the most promising approaches in tissue engineering (Cancedda et al. 2003). Polymers are the most widely used materials in biomedical

applications due to their biocompatibility, mechanical properties, microstructure and degradation rate, an added advantage being the ability to precisely control these properties by composition and fabrication of scaffold polymer materials (Sabir et al. 2009). These biodegradable materials thus allow for new tissue, as it grows naturally, to take over their load-bearing or other functions without having any of the potential chronic problems associated with the presence of bio-stable implants (Chen and Wang 2002). Biocompatibility and lack of immunogenicity make poly (ethylene oxide) PEO an important polymer for biomedical medical applications. When bound to an immunogenic substrate having a desirable function in the body, PEO tends to reduce or eliminate immune response so that the organism can tolerate the substance (Thompson et al. 2008). Poly (ε-caprolactone) (PCL)'s superior rheological and viscoelastic properties over many of its aliphatic polyester counterparts render PCL easy to manufacture and manipulate into a large range of implants and devices. This, along with inexpensive availability, Food and Drug Administration's (FDA) approval and the possibility to manipulate its degradation kinetics makes PCL a promising material for tissue engineering research (Woodruff and Hutmacher 2010).

The adaptability of hot-melt extrusion (HME) has led the technology to gain wide acceptance in the broad spectrum of manufacturing operations and pharmaceutical research developments. HME has been demonstrated as a robust, novel technique to make solid dispersions in order to provide time controlled, modified, extended, and targeted drug delivery resulting in improved bioavailability as well as taste masking of active pharmaceutical ingredients (APIs) (Repka et al. 2011). In addition to being a proven manufacturing process, HME meets the goal of the FDA's process analytical technology (PAT) scheme for designing, analysing, and controlling the manufacturing process via quality control measurements during active extrusion processes (Charlie 2008). Taking on board the aforementioned advantages of HME, this study investigated the possibility of producing a polymeric matrix for tissue engineering applications. Effects of extrusion on the polymers involved were studied, as well as the effect of plasticiser and filler on thermal, viscous and degradation properties of the matrices. Controlled biodegradation is a critical factor in developing tissue scaffolds that can be gradually reabsorbed by and excreted from the body, thus avoiding the necessity for surgical removal of the used device. It was found that by altering the quantity of PEO to PCL, a tailored degradation rate of the implant was obtained. Thus a vital advantage of this study is the opportunity to fine tune the properties of the scaffold by varying materials and appropriate selection of processing conditions.

EXPERIMENTAL

Materials

Polyethylene oxide (M_w 100,000), polyethylene glycol (M_w 10,000 and 35,000), and α-lactose monohydrate were obtained from Sigma Aldrich and used as received. Poly (ε-caprolactone) (Capa 6500 and 6506: M_w 50,000), were obtained from Perstorp UK. All materials were dried in an oven for 24 hours at 40 °C prior to processing.

Experimental Conditions of Hot Melt Extrusion Conditions (HME)

All melt compounding detailed herein was carried out using a MP 19 TC 25 laboratory-scale co-rotating twin-screw extruder (APV Baker, Newcastle-under-Lyme, UK) having 16mm diameter screws and a length-to-diameter ratio of 25/1. APV co-rotating extruder screws are designed and manufactured in a modular construction. The positions of the heating zones and mixing sections are visible on the schematic diagram of the barrel of the APV twin screw extruder in Figure-1. The compounding temperature profile was established on the APV extruder by means of six temperature controllers placed along the length of the barrel. A seventh temperature controller was used to regulate the temperature at the die. The RPM of the screws was maintained at such a rate as to ensure that the materials were starve-fed into the feed zone of the extruder. This ensured that in all cases throughput was independent of screw RPM. Polymer extrudates were obtained using the extrusion profile outlined in Table-1. The full list of batch compositions can be seen in Table-2 and Table-3. The resultant melt was extruded through a cylindrical die to form a strand. Extrudates were collected 10 minutes after the start of the process in order to allow the extruder to purge and ensure any alien materials remaining inside the barrel were expelled. The extrudates were cooled down to ambient temperature before granulation was carried out.

Figure-1. Schematic representation of APV twin screw extruder

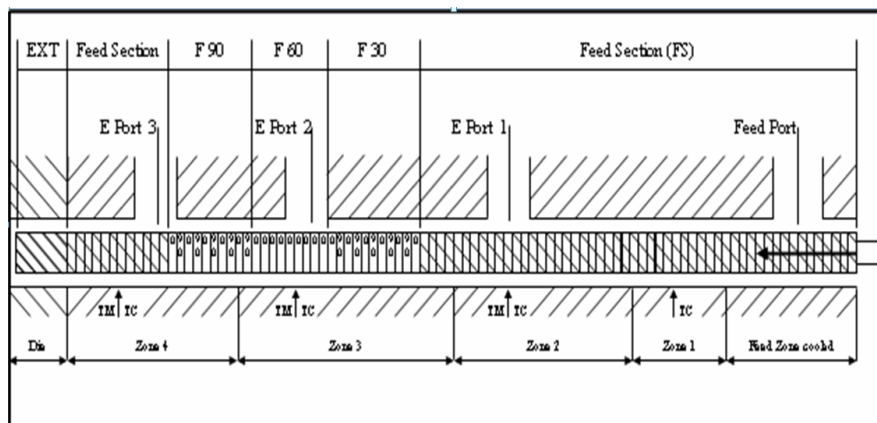


Table-1. Extrusion conditions used in this study

Screw Speed (RPM)	Temperature (°C)						Die
	Zone 1	Zone 2	Zone 3	Zone 4	Zone 5	Zone 6	
50	70	70	75	80	85	90	100

Table-2. Batch A processing trials

Batch No.	PEO MW 100,000	PEG MW 10,000	PEG MW 35,000	Lactose
A1	100	—	—	—
A2	70	30	—	—
A3	70	—	30	—

A4	55	35	–	10
A5	50	30	–	20
A6	55	–	35	10
A7	50	–	30	20

Table-3. Batch B processing trials: Powder vs. Pellet

Batch No.	PEO MW 100,000 (granules)	PEO MW 100,000 (powder)	PCL MW 50,000 (pellet)	PCL MW 50,000 (powder)
B1a)	75	–	25	–
B1b)	65	–	35	–
B2a)	–	75	–	25
B2b)	–	65	–	35

Differential Scanning Calorimetry (DSC)

A TA instruments 2010 DSC was used throughout the course of this work for thermal characterisation of material. Samples of between 8.0 and 10.0mg were weighed out using a Sartorius scales having a resolution of 1×10^{-5} g. Samples were then placed in non-perforated aluminium pans which were crimped before testing, with an empty crimped aluminium pan being used as the reference cell. Volatiles were removed from the purging head with nitrogen gas at a flow rate of 30 ml/min. Calorimetry scans were carried out over varying temperature ranges between -50 and 250 °C. Calibration of the instrument was performed using indium as standard. Sub-ambient DSC was carried out with the test cell being brought to -50 °C with the aid of liquid nitrogen. After each test was completed, the melting point region from the thermograph was analysed to determine heat of fusion (ΔH) and melting point (T_m) of each sample.

Melt Flow Index (MFI)

Melt flow index values of the various samples were measured by using a Melt Flow Indexer (at 100 °C, load 2.16kg) according to the ASTM standard D 1238-04 using a ROSAND Melt Flow Quick Index. The molten material flowed through an orifice of 2.0 mm diameter for 10 minutes and the values were reported in g/10 min as standard.

Rheometry

Rheological analysis was performed on a TA Instruments AR1000 rheometer fitted with 25mm stainless steel plate geometry. Frequency sweep experiments were conducted between 0.01 and 1000 rads/s at 100 °C using a strain of 1%, i.e., within the linear viscoelastic region as determined from strain sweep experiments at a frequency of 1Hz. After each test a bronze scraper was used to remove the sample from the plates, before the machine was brought back to temperature for the next sample.

Degradation Studies

Degradation was measured as a percentage weight over an extended period. Pre-cut extruded samples measuring ~0.5g were weighed and placed into 20mls pre-heated buffer solution (pH 7.4

in order to mimic physiological conditions). Samples were then placed in a static environment in an oven at 37 ± 0.1 °C for the duration of the test. At regular time intervals samples were dried and their weight recorded before being placed back in the oven in fresh pre-heated buffer solution and the procedure was repeated at predetermined times. Percentage weight loss of the samples was calculated using equation 1:

$$(W_i - W_d / W_i) \times 100$$

Where W_i is the initial weight of the sample and W_d is the degraded weight of the samples.

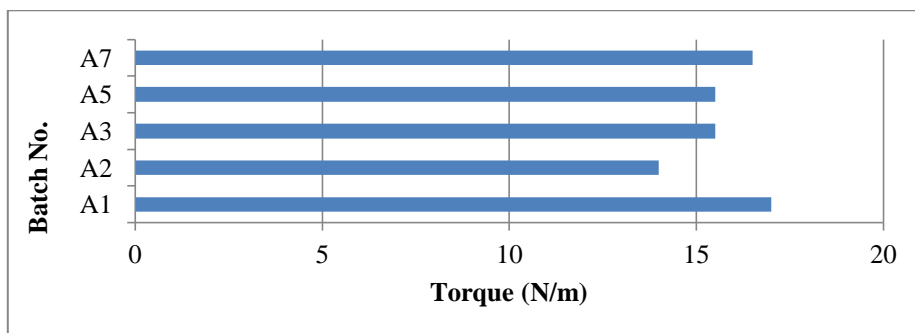
RESULTS & DISCUSSION

Hot Melt Extrusion (HME)

Polyethylene oxide (PEO) is a free flowing, semi-crystalline and hydrophilic thermoplastic which has previously been studied in hot melt extrusion applications such as drug delivery (Crowley et al. 2002) and the production of implants (Agrawal et al. 2000). Polyethylene glycol is a hydrophilic, low molecular weight polymer (oligomer) which is currently the most used polymer in the biomedical field of drug delivery and the only polymeric therapeutic that has market approval for different drugs (Knop et al. 2010). Lactose is a naturally occurring simple carbohydrate, or sugar. It is the disaccharide of the simple sugars D-galactose and D-glucose. It has good physical and chemical stability, is water soluble (Guo 2004) and has been used in hot melt extrusion applications (Liu et al. 2001). Polycaprolactone is a ductile, semi-crystalline, hydrophobic and bioresorbable polymer whose mechanical properties can easily be modulated by varying the crystallisation degree (Chiono et al. 2009).

The extrudability of a material is generally characterised by the extrusion torque during the process, material output rate and the physical appearance of the extrudates (Liu et al. 2001). The torque is a measure of the resistance that the motor experiences as a consequence of the viscosity inside the barrel (Verreck et al. 2006). Higher viscosity melts will exert more pressure than melts with lower viscosities (Lyons et al. 2008). In this study the torque was used as an indicator to evaluate viscosity of the materials being processed. Torque values were recorded during the processing of batches outlined in Table-2-Table-3 and can be seen in Figure-1 - Figure-3. Torque measurements observed in this study indicate PEO alone required the most effort to extrude Figure-2. This was reduced on addition of plasticiser, PEG. By using polyethylene glycol of two differing molecular weights, the effect of plasticisers and their molecular weight on the processability of the blends could be investigated. A marginal but proportional decrease in viscosity was observed for samples containing the lower molecular weight plasticiser. Incorporation of the filler; lactose, into the PEO/PEG blend caused the viscosity of the sample to increase slightly, likely to be due to its high melting temperature and dispersion in the sample.

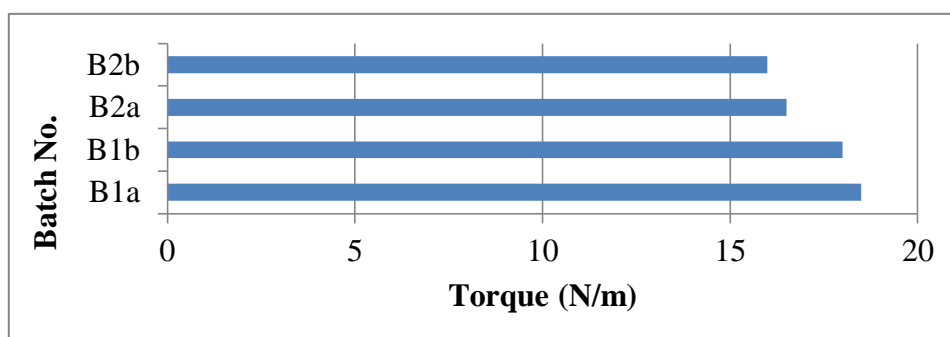
Figure-2. Extruder torque values observed during hot melt processing of representative Batch A samples



The effect of replacing PEG with PCL was examined in Batch B samples as per Table-2 as well the effect of the consistency of the mixed blends on feeding into the extruder. Identical ratio blends comprising powder PEO and powder PCL were observed for differences from blends comprising granular PEO and pellet PCL. Torque values were recorded for each sample on addition into the extruder as shown in Figure-3. The higher the percentage PCL incorporated, the lower the torque value, thus indicating that PCL reduces the viscosity of the overall sample. Similar results were observed in a previous study by Lyons et al. (2008).

It can be inferred from Figure-3 that powder samples have a marginally lower viscosity in comparison the pellet/granule samples. This information is of value when using materials of higher viscosity in order to keep torque value low and avoid problems associated with machines torquing out. These trends are discussed and contrasted with MFI and rheological analysis in sections below.

Figure-3. Extruder torque values observed during hot melt processing of Batch B samples



Melt Flow Index (MFI)

Melt flow indexing was performed on Batches A and B samples pre and post extrusion.

Table-4 displays the melt flow index results of five selected samples from Batch A which are representative of the samples obtained during testing (Table-2). The compositions were tested by MFI as simple mixtures prior to extrusion, and MFI tested again as extrudates after extrusion. The high viscosity of PEO has been widely reported (Crowley et al. 2004). This was confirmed in this study with sample A1 (virgin PEO) revealing the highest melt viscosity. A2 comprises a blend of

PEO and the lowest molecular weight plasticiser (PEG M_w 10,000). As would be expected A2 has the highest MFI value as the addition of a lower molecular weight plasticiser decreases its melt viscosity and thus increase its MFI. Sample A3 contains the higher molecular weight plasticiser (PEG M_w 35,000) in identical mix ratio the ratio of sample A2; MFI values for A3 were slightly lower, indicating an increase in viscosity. This in turn shows that the plasticiser has a reducing effect on the melt viscosity of the polymer. In contrast, measurements for pure lactose alone could not be obtained due to its high melt temperature. Hence, the addition of lactose to PEO and the PEG plasticisers, (samples A5-A7) led to a substantial decrease in MFI in comparison to PEO and PEG matrices alone (samples A1-A3). This shows that the addition of lactose leads to an increase in melt viscosity.

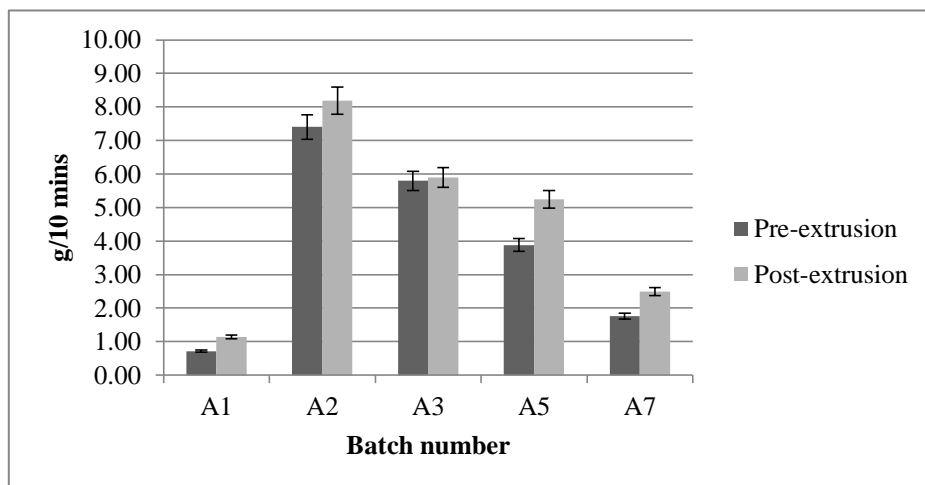
Materials are subjected to high temperatures, mixing and kneading during the extrusion process. There is a high level of shear in the extruder which causes the bonds of the materials to break and re-arrange. It can be seen in Figure-4 that after extrusion the materials have a lower melt viscosity than they had prior to extrusion because of the physical changes they underwent during the extrusion process. Similar results were obtained by (Crowley et al. 2004) as regards molecular weight of the polymer. A decrease in drive load on the extruder motor suggests a reduction in melt viscosity (shear thinning), degradation (formation of lower molecular weight polymer chains) and/or an improvement in polymer chain mobility. This correlated with results obtained in this study with a higher MFI value being observed with the extruded PEO granules compared to the virgin powder form.

Batch B samples yielded similar results correlating well with values observed during processing (data not shown). Samples containing higher percentage of PCL provided higher MFI values. In regards to the form of the polymers in Batch B, the powder form of blends also yielded a higher MFI in comparison to the pellet/granule blends.

Table-4. MFI results pre- and post- extrusion of Batch A selected samples

Batch Number		A1	A2	A3	A5	A7
MFI	Pre-extrusion	0.72	7.40	5.80	3.88	1.77
(g/10mins)	Post-extrusion	1.14	8.19	5.90	5.25	2.49

Figure-4. Comparison of MFI values of powder blends versus matrix blends (before and after extrusion)



Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry was carried out on virgin materials as well as Batch A and B samples in order to determine the effect of hot melt extrusion on the thermal properties of the polymers PEO and PCL Figure-5. The effect of incorporating a plasticiser PEG and a high melting point filler (lactose) into a blend were also coincidentally investigated. As well as this, a study was carried out to investigate whether a difference exists thermally, between blends consisting of pellets/granules and blends consisting of powder. Virgin PEO, PEG M_w 10,000, PEG M_w 35,000, lactose and PCL exhibited melting temperatures (T_m) of 73.85, 65.47, 71.36, 219 and 63 °C respectively. These results correspond with previous studies which reported the T_m of virgin PEO to be in the range of 57-73 °C (Crowley et al. 2002), PEG M_w 10,000 having a melting temperature of 65 °C (Tao 2001) and PEG M_w 35,000 having a T_m of 64-69 °C (Graham et al. 2011). Lactose has a high T_m of 210-220 °C (Islam and Langrish 2010) therefore the temperature profile used for extrusion of the blends would not enable the melting of lactose but would simply allow it to become dispersed throughout the matrix. PCL has been reported to have a T_m in the range of 59 to 64 °C (Woodruff and Hutmacher 2010).

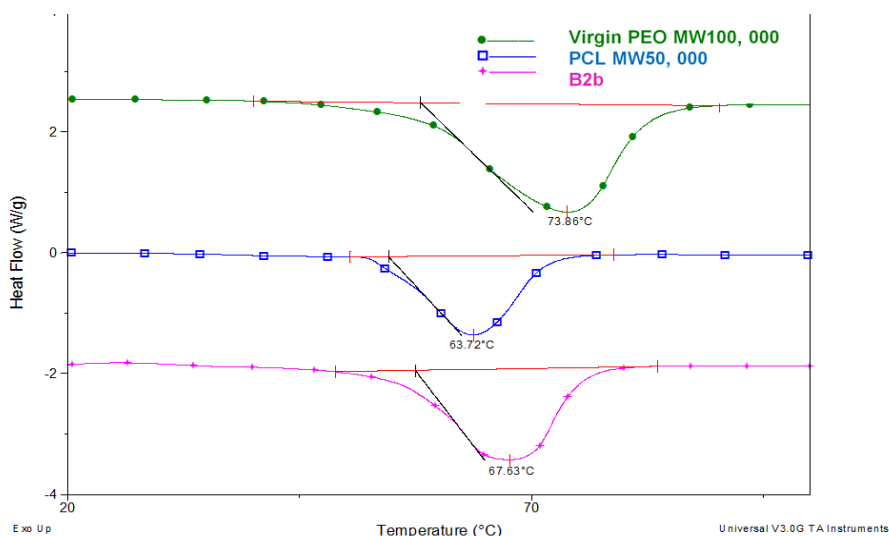
Table-5. Melt temperature of selected samples

Sample	Melt temp (°C)
A1	68.02
A2	65.47
A3	67.86
A4	72.96
A5	75.13
A6	74.02
A7	74.77
B1b	66.81
B2b	67.63

The extrusion process was found to increase PEO's melt temperature by about 6 °C. During hot melt extrusion, polymers are subjected to mechanical, thermal and oxidative degradation. Mechanical degradation may be induced by the shear effects imposed by the rotating screw (Crowley et al. 2002). The occurrence of mechanical degradation may have caused the depression in melt temperature after extrusion of the PEO sample. It has been noted in literature, that the extrusion process caused a decrease in the melt temperature of samples containing PEO and a chosen drug (Crowley et al. 2004). This was hypothesised to be due to the transition of the extended chain crystallites into folded chain crystallites upon rapid cooling of the melt after HME. The less stable folded-chain crystallites melt at a lower temperature than the melting point of extended crystals. It was also reported that the greater the number of folds, the lower the melting point (Mididoddi and Repka 2007). This decrease in melting point can also possibly be due to drug-polymer interactions (Crowley et al. 2004).

A comparison of virgin powder PCL, virgin pellet PCL and extruded PCL all of M_w 50,000 also revealed that extrusion caused a reduction in T_m of 4 °C. Similar findings have been reported by (Villmow et al. 2010). Comparison of virgin PEO and virgin PCL to a mixed blend (B2b) was analysed. Virgin PEO and PCL revealed melt temperatures of 73.86 °C and 63.61 °C respectively. A blend comprising both polymers revealed one melting peak of 67.63 °C (Figure-5). It can be concluded that inclusion of PCL gives a reduction in the melting point of the matrix. This behaviour has been noted in literature (Lyons et al. 2008), (Qiu et al. 2003).

Figure-5. DSC overlay of PEO, PCL and PEO/PCL blend

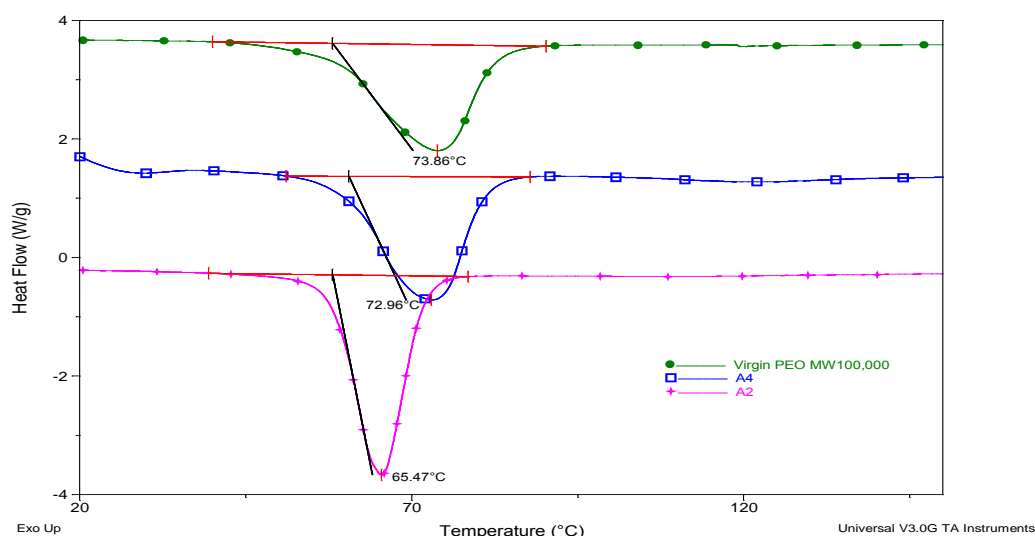


The thermal effect of incorporating a plasticiser into a blend was studied. PEG is a low molecular weight plasticiser; allowing it to increase the free volume between polymer chains and in turn enhance mobility (Crowley et al. 2007). The addition of differing molecular weight plasticisers caused a marginal but proportional decrease in the melt temperature of the blend, i.e. the lower

molecular weight plasticiser caused a larger decrease in the melt temperature of the blend compared to the higher molecular weight plasticiser.

Incorporating lactose into these blends containing lower molecular weight plasticiser, resulted in an increase of the overall melt temperature. This may be due to the high melting temperature of the filler and the higher number of chains involved due to the higher molecular weight plasticiser. Figure-6 shows the effect of plasticiser and filler on PEO after melt blending. The melt temperature of virgin PEO can be seen to be 73.86 °C. Addition of plasticiser to this decreases the melt temperature by 8 °C, while further adding lactose to the blend increases the melt temperature up 6 °C again.

Figure-6. DSC overlay depicting the effect of plasticiser and filler on a blend's T_m



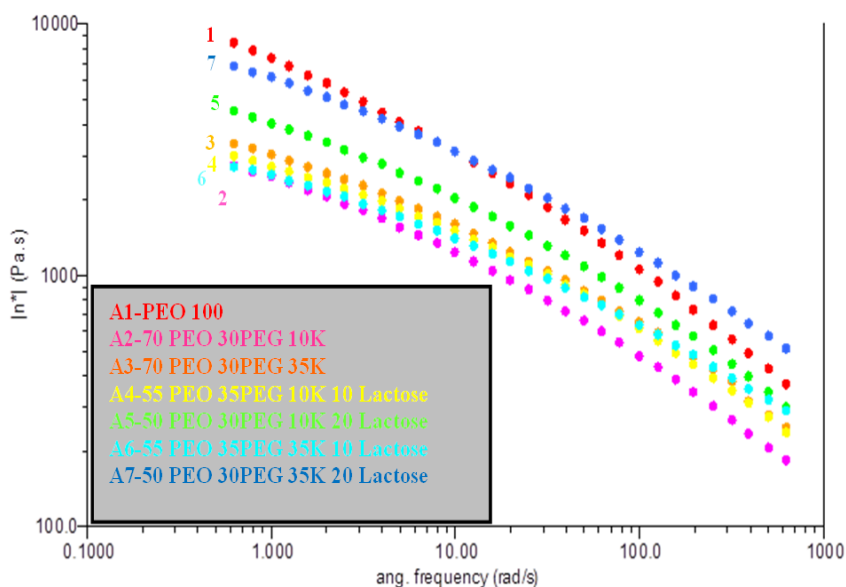
DSC analysis was carried out on samples B1b (pellet) and B2b (powder) in order to investigate if the composition of the samples influences the thermal properties. As can be seen in Table-5, there is minimal difference in T_m of the two blends (~ 1 °C), indicating composition of the blends is irrelevant. As sample B1b was processed twice, in order to convert it to granular form, the effect of reprocessing also proves to be indistinct on the polymer's thermal properties. PEO has been found to maintain its stability throughout multiple repetitive processing trials (Lyons 2007).

Rheometry

Steady state rheometry was performed on all Batch B matrices in order to further examine the rheological effects of melt mixing PEO, PEG and lactose. The effect of plasticiser and filler on the viscosity of a material can be seen in Figure-7 with complex viscosity displayed as a function of frequency. Virgin PEO (A1) had the highest melt viscosity of any of the blends tested herein. The addition of plasticiser to PEO had a sizeable effect on its viscosity and it can be seen to greatly

reduce the viscosity of A2. A greater decrease in melt viscosity was observed for the lower molecular weight plasticiser due to greater chain mobility encouraged by the plasticiser. The incorporation of lactose into the blend was found to increase the melt viscosity of the samples in comparison to PEO and PEG based matrices. This increase was proportional to the percentage filler incorporated. The increase in melt viscosity became more pronounced as the percentage filler was increased. These results are in agreement with observations made during the processing of the blends and MFI analysis. As mentioned earlier, lactose is a high melting point filler, therefore temperatures utilised throughout this study would not enable it to melt, but simply disperse throughout the matrix. Difference in the flow properties of blends can often times be attributed to the dispersion of filler. The more evenly dispersed a filler is, the less it will impinge upon the ability of the polymer to flow (Gunning et al. 2011). This would indicate that the filler material has been evenly dispersed in the matrices obtained.

Figure-7. Rheometry measurements for Batch A samples



Degradation Study

Understanding and controlling the rate of degradation of samples is of great interest to this study since degradation is essential in many small and large molecule release applications as well as implantable devices. These include temporary biomedical applications such as controlled release systems and orthopaedic implants as the necessity for surgical removal of the spent device is avoided (McDonald et al. 2010). Therefore samples extruded were placed in physiological buffer at pH 7.4 at 37°C and their rate of degradation was investigated.

Batch A samples degraded in a matter of hours, with samples containing the highest percentage filler holding shape slightly longer (Figure-8). Similar findings have been reported by (Perissutti et

al. 2002), they noted that incorporation of lactose reduced the dissolution rate of PEG and a drug blend. Similar degradation profiles were also reported by (Verhoeven 2008) who found that mini-matrices consisting of 70% PEG/PEO dissolved after approximately 1hr. This therefore prevented further weight analysis of these batches. The rapid degradation is not surprising given that both PEO and PEG are highly hydrophilic polymers. PEO is miscible with water in all ratios due to hydration of the ether oxygen.

Figure-8. Degradation analysis of representative Batch A7 sample



Given the application of the study is a potential implant for tissue engineering, a degradation profile of one hour is less than ideal. A suitable implant should aid the regeneration of tissue over time as the implant degrades. A study to examine the ideal composition and ratio of samples was therefore undertaken by replacing PEG and lactose with PCL. PCL is highly hydrophobic with a long degradation rate of between 3 to 4 years (Woodruff and Hutmacher 2010). However, by blending PEO with PCL it was hypothesised that the degradation profiles of the polymers could be tailored. When bound to a water insoluble compound such as PCL, the resulting PEO conjugate generally displays increased water solubility (Thompson et al. 2008). Blending of two or more components is now widely applied with the aim of obtaining samples with improved properties. The properties of these new materials are a combination of their component properties with synergetic effect emerging from special morphologies (Malik et al. 2006). By blending these materials it was envisaged that a strong, biocompatible, biodegradable implant would be obtained. As can be seen in Figure-9 and

Figure-10, samples consisting of 75:25 PEO : PCL ratio (a samples) degraded almost immediately, possibly due to the higher ratio of the hydrophilic polymer present. Samples consisting of the 65:35 ratios (b samples) remained intact in excess of 11 weeks, with weight consistently decreasing over time. B2b samples consisting of powder blends appear to result in a more even rate of degradation. These samples provide an optimum degradation over time and making this ratio the ratio of choice. Little differences exist between powder and pellet blends. Providing both materials are of identical compositions, similar degradation patterns will be obtained.

Figure-9. Degradation study of Batch B samples

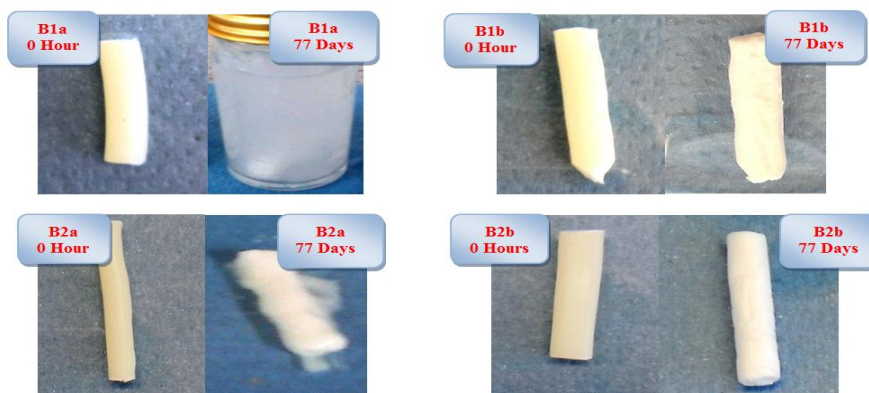
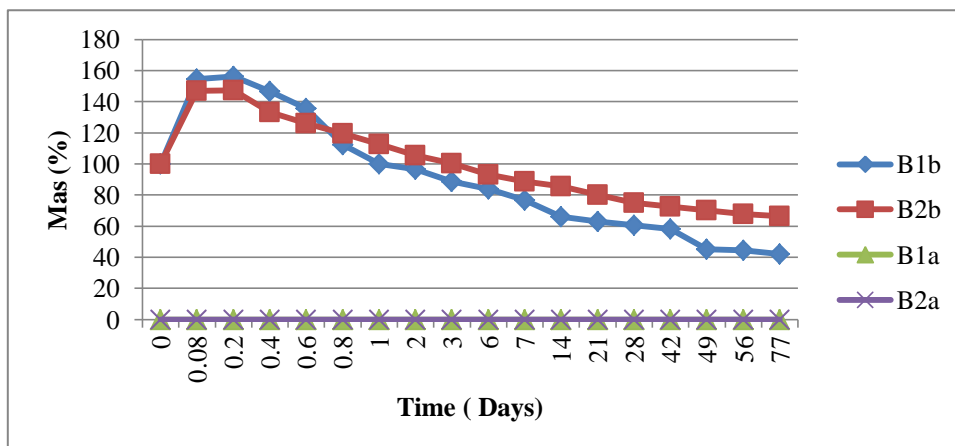


Figure-10. Percentage mass versus degradation time for Batch B samples



CONCLUSION

Polymers and polymer blends of varying compositions were processed by hot melt extrusion technology. The effect of extrusion on these polymers and blends was examined, as well as the effect of plasticiser, filler and blend composition. Differential scanning calorimetry revealed extrusion caused a decrease in the melt temperatures of the polymers, as did addition of plasticiser, while lactose slightly increased the melt temperature. MFI and rheometry measurements confirmed melt viscosity was reduced after the extrusion process and on addition of plasticiser.

Conversely, incorporation of the filler lactose caused a slight increase in the viscosity of the blends. Powder batches were slightly less viscous and displayed a steadier degradation pattern in comparison to pellet blends. It was found that by altering the quantity of PEO to PCL, the degradation rate of the matrix could be tailored to degrade over a given time period.

Future work will involve replacing the non-molten lactose with a similarly non-molten bio-ceramic TCP, and its effect on the blends investigated to determine its applicability for bone regeneration

applications. Overall this work demonstrates that the use of the PEO and PCL mixture has potential for use in tissue engineering applications.

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