CHAPTER 8

Conclusions

The main aim of this research has been to synthesise novel initiators for the ring-opening polymerisation of cyclic esters for use as absorbable surgical sutures. Currently, the most widely used initiator is tin(II) octoate ($Sn(Oct)_2$) because it is effective, easy to handle, soluble in cyclic ester monomers and common organic solvents and, importantly, has been approved as a food additive by the US Food and Drug Administration. However, it has now been established that $Sn(Oct)_2$ is not the true initiating species. Instead, it has been shown that $Sn(Oct)_2$ in combination with an alcohol react together to form a tin(II) monoalkoxide, Sn(Oct)(OR), and/or dialkoxide, $Sn(OR)_2$, *in situ* as the true initiating species [118-122]. Therefore, since the exact initiator concentration generated *in situ* is unknown, the molecular weight of the polymer obtained is unpredictable. It has therefore been of interest to synthesise the true alkoxide initiator prior to polymerisation in order to achieve more predictable and reproducible polymer molecular weights.

However, solid tin(II) alkoxides have the disadvantage of being difficult to dissolve in cyclic ester monomers due to their molecular aggregation [104, 123]. Therefore, in order to eliminate this problem of insolubility, novel soluble liquid tin(II) alkoxides have been prepared and their efficiency compared not only with the solid initiators but also with the conventional $Sn(Oct)_2$. This final chapter of this thesis now summarizes the main conclusions.

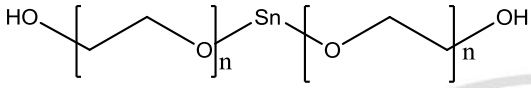
8.1 Novel Initiator Synthesis

In this research, novel tin(II) alkoxides were synthesised by two methods, the first of which was the original method of Morrison and Haendler [101] as shown on the following page.

$$SnCl_2 + 2\ HOROH + 2\ (C_2H_5)_3N \rightarrow Sn(OROH)_2 \downarrow + 2\ (C_2H_5)_3N.HCl \downarrow$$

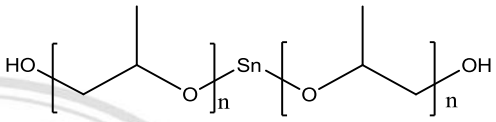
(in an excess of HOROH) ($\downarrow$ = precipitates as it is formed)

The HOROH diols used were polyethylene glycol 300 (PEG300), polypropylene glycol 400 (PPG400), polypropylene glycol 1200 (PPG1200) and diethylene glycol (DEG). The tin(II) alkoxides obtained were as shown below.



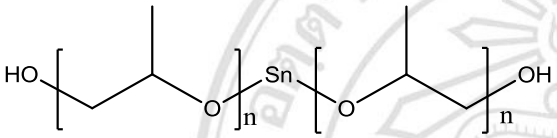
Tin(II) polyethylene glycol 300

[$Sn(PEG300)_2$]



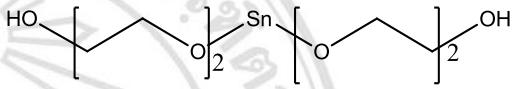
Tin(II) polypropylene glycol 400

[$Sn(PPG400)_2$]



Tin(II) polypropylene glycol 1200

[$Sn(PPG1200)_2$]



Tin(II) diethylene glycol

[$Sn(DEG)_2$]

The purified tin(II) alkoxide products obtained were initially white solid powders but rapidly became yellowish on contact with air. There were only slightly soluble in chloroform but were more soluble in dimethyl sulfoxide (DMSO) and ε-caprolactone.

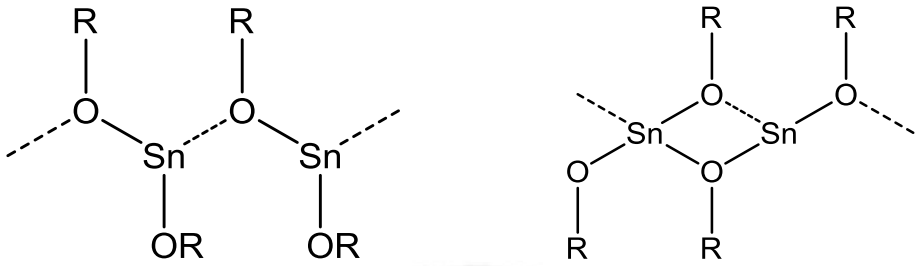
The difficult solubility of the solid tin(II) alkoxides can be attributed to their molecular aggregation which is believed to be a reversible process as shown below [102]. The degree of aggregation, n, is unknown and appears to depend on the nature of the substituents.

$$n\ Sn(OROH)_2 \rightleftharpoons [Sn(OROH)_2]_n$$

non-aggregated aggregated

Molecular aggregation manifests itself in the form of (a) “oligomeric” species joined together by single oxygen bridges or (b) “polymeric” species joined by double oxygen bridges. This aggregation is derived from the availability of an empty valence “d” orbital on the tin atom to accommodate the lone pair of electrons on the oxygen. Furthermore, it was also observed that the solid tin(II) alkoxides which were white when freshly prepared, rapidly turned pale yellow during storage while their solubility

in organic solvents decreased. The colour change has also been associated with polymerisation (in this case, aggregation) of organic compounds [103, 104].



(a) Single bridge type (b) Double bridge type

Molecular aggregation in tin(II) alkoxides.

The second method shown below was employed to prepare a series of tin(II) alkoxides in liquid form.

$$2\ Sn(Oct)_2 + HO\text{-}R\text{-}OH \rightleftharpoons (Oct)Sn\text{-}O\text{-}R\text{-}O\text{-}Sn(Oct) + 2\ OctH$$

The diols used were diethylene glycol (DEG) and ethylene glycol (EG) resulting in the tin(II) alkoxides shown below.

Bis (tin(II) octoate) diethylene glycol $[Sn(Oct)]_2DEG$

Bis (tin(II) octoate) ethylene glycol $[Sn(Oct)]_2EG$

These tin(II) alkoxide products were obtained as slightly viscous, pale yellow liquids which were readily soluble in polar organic solvents such as chloroform and cyclic esters monomers such as ε-caprolactone. This greater solubility of the liquid tin(II) alkoxides was indicative of a much lower degree of molecular aggregation. Indeed, spectral evidence (IR, NMR) suggested that they may have been completely non-aggregated.

Thermal analyses of the tin(II) alkoxides were carried out by DSC and TGA. The DSC thermograms of the solid tin(II) alkoxides showed no thermal transitions from 0 to 250 ^{o}C. For the TGA thermograms in the range of 50-550 ^{o}C, the solid tin(II) alkoxides gave a maximum weight loss of not more than 50 %, the black residue remaining being SnO. This DSC and TGA data is consistent with their molecular aggregation restricting

molecular motion but increasing thermal stability. In view of this high thermal stability, the double oxygen bridged form seems the more likely [43]. In contrast, the two liquid tin(II) alkoxides gave TGA thermograms which showed a single-step weight loss from approximately 150 ^{o}C to 250-300 ^{o}C with 70-90 % weight loss. From the TGA results, it can be concluded that both solid and liquid tin(II) alkoxides exhibited good thermal stability at 130 ^{o}C (see Figures 3.6 and 3.16) which was the polymerisation temperature at which they were used.

It was also significant to note that the FT-IR spectrum of the liquid $[Sn(Oct)]_2$DEG showed a broad band peak of O-H stretching at 3600-3200 cm^{-1} which was assumed to be due to incomplete reaction of the DEG. This was confirmed by adding a stoichiometric excess of $Sn(Oct)_2$ in the reaction with the diol and then seeing the broad O-H band disappear as the mole ratio of $Sn(Oct)_2$:DEG was increased above the theoretical 2:1 ratio (see Figure 3.9). The disappearance of the O-H band was taken to be indicative of the complete reaction of the O-H groups.

8.2 Kinetic Studies by Dilatometry

Kinetic studies of the bulk ring-opening polymerisation of ε-caprolactone using the soluble tin(II) alkoxides were carried out. The initiators used were bis(tin(II) octoate) diethylene glycol ($[Sn(Oct)]_2$DEG), bis(tin(II) octoate) ethylene glycol ($[Sn(Oct)]_2$EG), commercially available tin(II) octoate and tin(II) octoate / HOROH mixtures. The technique employed was dilatometry using a purpose-built apparatus as a means of following conversion as a function of time. In this technique, the dilatometer assembly was placed in a silicone oil bath at the required temperature (zero time, t=0) and a cathetometer used to measure the volume contraction of the monomer as it polymerised.

Kinetic experiments were carried out by setting the temperature of the silicone oil bath at 130 ^{o}C. The dilatometer, filled with a sample mixture of ε-caprolactone and the chosen initiator, was then placed in the oil bath. Upon immersion of the dilatometer, the temperature of the oil bath quickly dropped by up to 7 ^{o}C before gradually increasing back up to 130 ^{o}C over a period of up to 12 minutes. This led to an initial period of thermal equilibration during which the meniscus movement in the capillary was due to both thermal expansion of the liquid sample and contraction due to the onset of

polymerisation. Data taken during this equilibration period was used to estimate the meniscus height at zero time (h_o).

One way of shortening the thermal equilibration period was to start at a slightly higher temperature of 140 ^oC. Immediately after immersing the dilatometer in the oil bath, the temperature was then re-set to 130 ^oC whereupon the oil bath temperature dropped to about 127 ^oC, only 3 ^oC below the required temperature. In this way, the time for thermal equilibration was reduced by up to a half with the result that more data points could be obtained during the early stages of the polymerisation.

The experimental data used for kinetic calculations were taken from the 20-70 % conversion range for constructing both first-order and zero-order rate plots according to equations 4.26 and 4.27 (page 93). It was interesting to note that the kinetic data in some cases fitted a zero-order rate plot more closely than a first-order rate plot. According to the literature, it is widely accepted that the coordination-insertion mechanism should be kinetically first-order with respect to the monomer concentration. However, there are various effects which may result in deviation from first-order kinetics. For example, diffusion-controlled effects (e.g. Trommsdorf effect) as the viscosity of the system increases with % conversion may become influential in the later stages of the polymerisation. Increased viscosity also increases the viscous drag of the liquid meniscus on the glass surface of the dilatometer's capillary. Thus, there are both internal and external factors which may contribute towards a deviation from the expected first-order kinetics.

8.3 Initiator Efficiency

In the bulk ROP of ε-caprolactone (ε-CL), both the solid and the liquid tin(II) alkoxide initiators were studied in order to compare their efficiencies both in terms of kinetics and polymer molecular weight. All of the initiators, both solid and liquid, yielded PCL products in the low-to-medium molecular weight range. The highest M_v came from the liquid $[Sn(Oct)]_2EG$ initiator.

The most obvious difference was that, whereas the liquid initiators were completely soluble in the CL monomer, the solid initiators were only partially soluble although solubility did increase with time at the polymerisation temperature of 130 ^oC. Consequently, whereas initiation by the liquid initiators was completely homogeneous

from start to finish, initiation by the solid initiators was partly homogeneous (soluble fraction) and partly heterogeneous (insoluble fraction), the ratio of which was indeterminate. Furthermore, the undissolved solid initiator was clearly visible in the solid polymer as an impurity and needed to be removed by careful purification. Therefore, from the point of view of initiator solubility and polymer purity, the liquid initiators were more suitable, especially for synthesising biomedical polymers.

It is reasonable to assume that the lower the degree of molecular aggregation, the more efficient will be the initiator since the Sn-O bonds, which are the active sites for coordination-insertion, will be more accessible to the monomer. This is borne out by the fact that the liquid initiators consistently gave higher polymer molecular weights than the solid initiators at the same concentration.

It is also significant to note in Table 4.8 (page 122) that the first-order rate constants (k_1, min^{-1}) for the pre-prepared liquid initiators tended to be higher than for the corresponding $Sn(Oct)_2$ / diol mixtures. This is as would be expected and shows the advantage of preparing the true initiator separately and using it directly rather than generating it *in situ* in an uncertain concentration.

8.4 Poly (L-lactide-co-ε-caprolactone) Synthesis

PLC copolymers were synthesised via the bulk ROP of L-lactide and ε-caprolactone in a ratio of 75:25 mol % using both solid and liquid tin(II) alkoxide initiators. The copolymers were all obtained in near-quantitative (> 90 %) yields with compositions (mol %) from their ^{1}H-NMR spectra corresponding very closely to the initial comonomer feed ratio (LL:CL = 75:25 mol %). From their ^{13}C-NMR spectra, it could be concluded that the monomer sequencing in the copolymers was partly random and partly blocky due to the widely differing monomer reactivity ratios (LL > CL). However, this was considered to be beneficial since the longer LL sequences helped to enhance crystallisability for fibre processing purposes.

From the GPC results, the PLC copolymers using the liquid synthesised tin(II) alkoxides were found to give higher molecular weights. The GPC results were consistent with those obtained from dilute-solution viscometry. In contrast, the mixed initiators gave rather low molecular weights compared to the corresponding liquid

initiators (e.g., $Sn(Oct)_2$ / EG ([η] = 0.415 dl/g) and $[Sn(Oct)]_2EG$ ([η] = 1.321 dl/g). The solid initiators also gave lower molecular weights due to their slow and often incomplete solubility.

The DSC thermograms of the PLC copolymers showed thermal transitions of T_g, T_c and T_m as listed in Table 6.4 (page 173). TGA was used to determine the thermal stability of the copolymers and showed that they only started to degrade at over 250 ^oC. This was particularly relevant to their processing into monofilament fibres since the melt spinning temperature needed to be at least 50 ^oC below the thermal degradation (initial weight loss) temperature.

8.5 Melt Spinning of PLC into Monofilament Fibres

The melt spinning process was used to produce monofilament fibres of PLC synthesised from both solid and liquid tin(II) alkoxides. Since monofilament sutures require a very specific balance of properties, all of which are morphology-dependent, the processes of melt extrusion, hot-drawing and annealing were separated so that they could be more accurately controlled and the effects of each studied independently. Initially, melt extrusion was carried out with minimal draw and quench cooling so that the as-spun fibres were largely unoriented and with limited crystallinity. Molecular orientation and further crystallization were then gradually built into the fibres through a series of hot-drawing and annealing steps, both of which were temperature and time-dependent. In this way, fibres could be produced which had an appropriate balance of strength and flexibility such as is required for convenient handling in surgery as a monofilament suture.

From the combined tensile test and DSC data in Table 7.4, it was possible to relate the changes in tensile properties to changes in matrix morphology. By developing an understanding of what the molecules were doing during hot-drawing and annealing, the weak and highly extensible as-spun fibres could be transformed into fibres with tensile strengths in excess of 300 MPa, strengths which are comparable with those of commercial monofilaments. The best quality fibres were those obtained from PLC synthesised using the liquid initiators which had yielded the highest copolymer molecular weights. Higher molecular weights means longer chains which can be extended by hot-drawing without the loss of chain entanglements.

In conclusion, the preparation of a fibre for potential use as a monofilament absorbable suture is a highly specialized process starting from molecular design of the polymer, through synthesis and characterisation, and finishing with processing and testing. It requires control of the polymer's chemical microstructure at every stage of its synthesis and control of the fibre's physical microstructure at every stage of its processing. In this thesis, some novel initiators have been described which have been shown to be more effective than some currently used initiators such as $Sn(Oct)_2$. Predictability and reproducibility are essential in speciality polymer manufacture due to the stringent property requirements of the application and polymerisation initiators have an important role to play. The novel liquid tin(II) alkoxide initiators described here are attractive alternatives to the initiators currently being used while the PLC copolymers have potential for further development as suture materials.

SUGGESTIONS FOR FURTHER WORK

In continuation of the work described in this thesis, the following suggestions for further work are made.

1) In this work, dilatometry was the chosen method for kinetic studies since it is a continuous method in which the data is obtained in real time. However, the method is limited to liquid monomers which give molten polymers at the polymerization temperature, such as ε-caprolactone. Another difficulty, as described in Chapter 4, is that there is inevitably a thermal equilibration period at the start during which the temperature is not constant. Other continuous methods, such as DSC, should be investigated.
2) As described in Chapter 3, liquid chromatography-mass spectrometry (LC-MS) was unable to provide any useful information due to not being able to find the appropriate analytical conditions suitable for our samples. If more time could be spent on this technique and the optimum conditions could be found, the data would fill a gap in characterization of the liquid initiators.
3) Copolymer molecular weight is an important factor in fibre processing since chain length determines to what extent the fibre can be hot-drawn (draw ratio) without breaking. There are various ways in which the molecular weight can be increased but one way which has not get been investigated is solid-state post-polymerisation by heating the copolymer at a temperature between T_c and T_m either in an inert atmosphere or under vacuum.
4) Having successfully synthesized and processed the copolymers into monofilament fibres with strengths comparable with commercial monofilament sutures, the logical next step would be to test their absorbability both *in vitro* and *in vivo*. While this study was not within the original scope of this thesis, the choice of L-lactide and ε-caprolactone as comonomers was made with their known absorbability in the human body in mind. PLC copolymers have already been used in some biomedical applications.