CHAPTER 6

DISCUSSION AND CONCLUSIONS

6.1 Homopolymer and Copolymer Synthesis

In this research project, homopolymers and copolymers of glycolide and δ-valerolactone polyesters were synthesized.

Stannous octoate (SO), $Sn(C_7H_{15}COO)_2$, was used as the initiator. It has the advantages of being an easily handled liquid, is less sensitive to air and moisture than other organometallic initiators, and does not require a "coinitiator" in order to be effective. SO is generally considered to be a monomer insertion-type initiator, acting via the mechanism shown in Scheme 6.1 for the ring-opening polymerization of glycolide. A similar mechanism can be described for the ring-opening polymerization of δ-valerolactone (Scheme 6.2). Since this mechanism is neither anionic nor cationic in nature, theoretically, there would seem to be no obvious termination step. However, in practice, termination reactions undoubtedly do occur which limit the polymer molecular weight attainable. These reactions probably involve initiator deactivation, for example, by hydrolysis by trace amounts of moisture present in the system (SO is known to be hygroscopic) leading to less active or even inactive SO derivatives :

$$C_7H_{15}COO\text{—}Sn\text{—}OOCC_7H_{15} + H_2O \rightleftharpoons C_7H_{15}COO\text{—}Sn\text{—}OH + C_7H_{15}COOH$$

In the case of copolymerization, the composition of the copolymer formed depends primarily on the comonomer feed and the respective comonomer reactivity ratios. While the comonomer feed can be controlled,

the comonomer reactivity ratios cannot. In the systems studied here, these ratios are a measure of the relative reactivities of the two comonomers towards the monomer insertion site. The polymerizability of a ring compound depends on various factors such as :

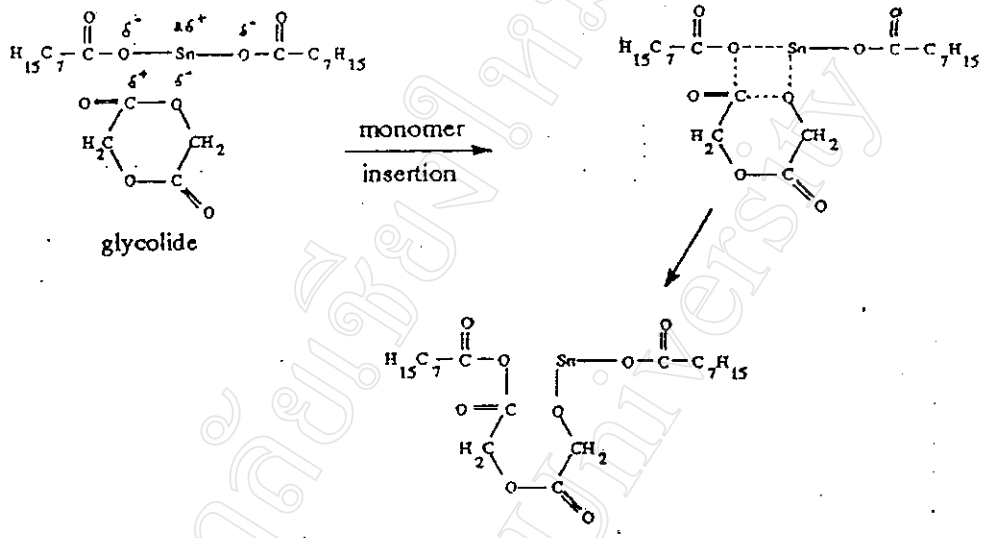
(1) the nature of the atoms in the ring
(2) ring-size and the extent of ring-strain
(3) the nature of any substituents on the ring
(4) the type of intiator used
(5) the experimental conditions employed for the copolymerization reaction

From the combination of analytical techniques used here, the results obtained allow the following conclusions to be drawn regarding the compositions and microstructures of the products obtained. These results are summarized for convenience of comparison in the following Table 6.1.

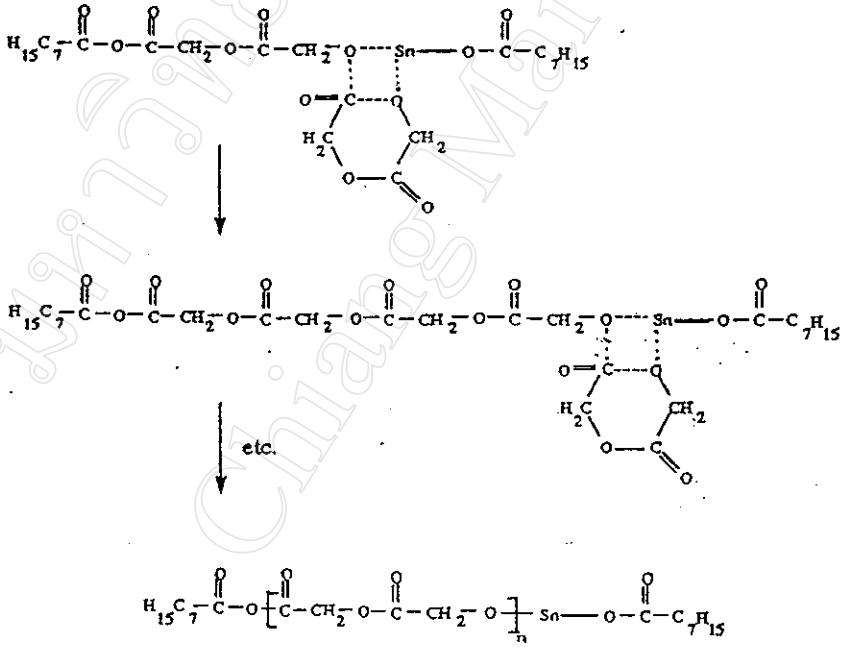
6.2 Copolymer Compositions

The analytical techniques used in this work which have enabled the copolymer composition to be determined are C-13 solid-state NMR and CHNS/O elemental analysis. It can be concluded that, under the conditions of synthesis in bulk employed in this research project, δ-valerolactone (VL) has a much lower reactivity than glycolide. Because glycolide and δ-valerolactone polymerize at such different rates, simultaneous addition leads to non-uniform composition. In other words, there is a "compositional drift" which depends on the relative reactivities of the two monomers. On average, the VL contents of the final copolymer products were found to be about 40% less than that in the initial comonomer feed for the 1:1 P(GA-co-VL) copolymer.

(i) Initiation



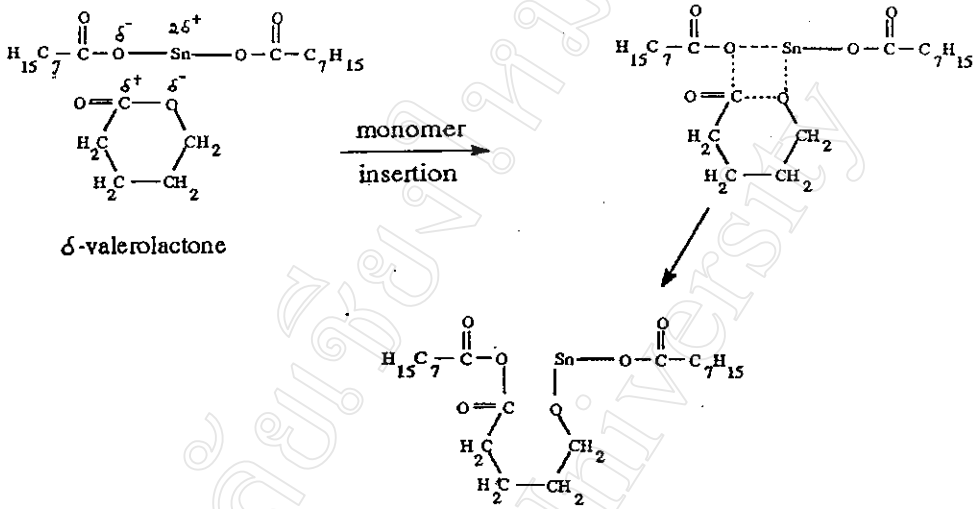
(ii) Propagation



poly(glycolic acid) PGA

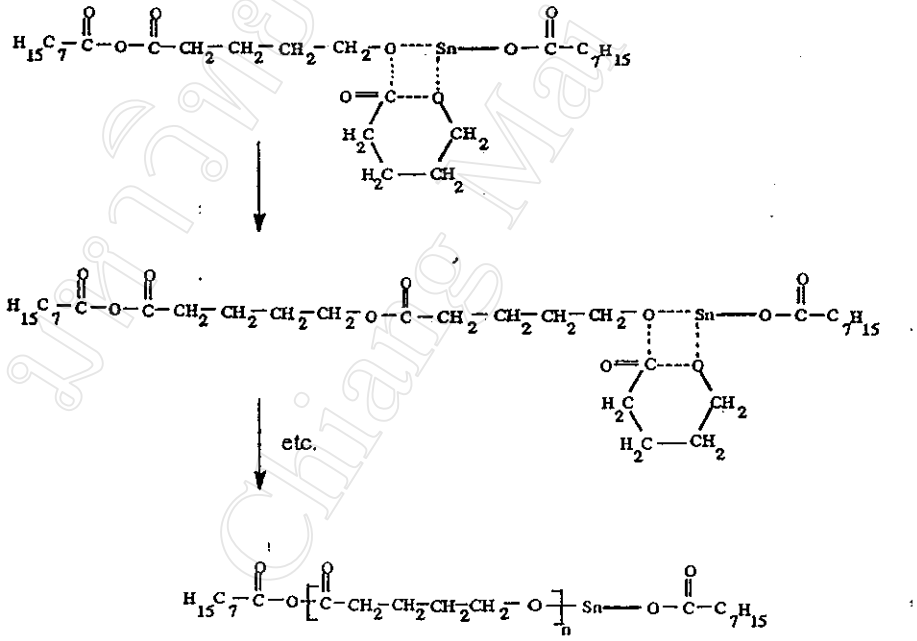
Scheme 6.1 : **Proposed mechanism for the monomer insertion SO-initiated ring-opening polymerization of glycolide.**

(i) Initiation



δ-valerolactone

(ii) Propagation

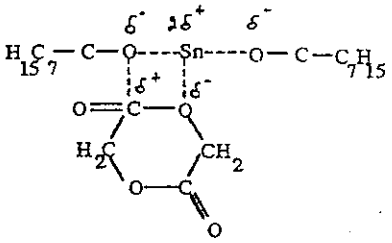


poly(δ-valerolactone)

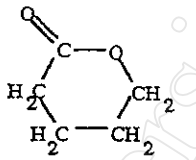
Scheme 6.2 : Proposed mechanism for the monomer insertion SO-initiated ring-opening polymerization of δ-valerolactone.

Thus, the copolymerization reaction can be represented as a combination of Schemes 6.1 and 6.2, as shown in Scheme 6.3 below.

(i) Initiation

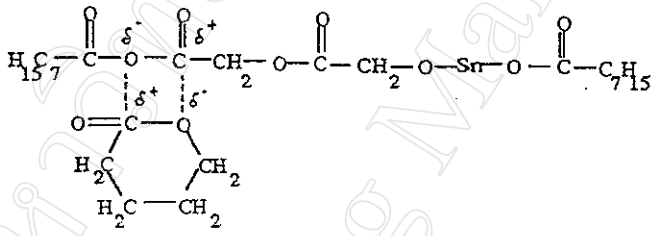


glycolide

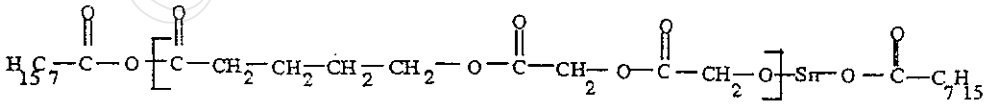


δ-valerolactone

(ii) Propagation



etc.



poly(glycolic acid-co-valerolactone) P(GA-co-VL)

Scheme 6.3 : Monomer insertion mechanism for the ring-opening copolymerizaton of glycolide and δ-valerolactone using SO as initiator.

Table 6.1 : Comparison of homo-and copolymerization products of glycolide and δ-valerolactone using SO as initiator.

Synthesis	Properties of Polymer								
Homopolymer or Copolymer	Initial Comonomer Feed (mole %)	Physical Appearance	% Yield	Best Solvent	DSC		TG	Copolymer Composition (mol %)	
					Tm Peak [max] (°C)	Heat of Fusion (J/J)	Td (°C)	NMR	CHNS/O
PVL	-	white powder	87	$CHCl_3$	52.64	121.44	190-340	-	-
PGA	-	white powder	75	DMSO	220.56	106.81	250-4000	-	-
P(GA-co-VL)	50 : 50	white powder	74	DMSO	187.48	66.89	240-390	90 : 10	88 : 12
P(GA-co-VL)	67 : 33	white powder	86	DMSO	205.15	57.87	240-360	-	99:1

6.3 Copolymer Microstructure

From the previous section on copolymer synthesis, if the comonomer insertion mechanism proposed in Scheme 6.3 is competitive, then the products obtained should be random copolymers. The most appropriate technique for studying copolymer microstructure, in particular the monomer sequence distribution, is C-13 NMR. However, the C-13 NMR spectra obtained from the copolymer products obtained in this work have suggested that the monomer sequence distribution is somewhere between that of a random and a block copolymer. This is a direct consequence of the marked difference in monomer reactivity ratios, as mentioned previously. Because glycolide is so much more reactive than valerolactone, it tends to homopolymerize with itself until its concentration becomes so reduced that copolymerization with valerolactone becomes more competitive. Thus, the P(GA-co-VL) copolymers that were obtained, although (strictly speaking) random by definition, tended to be rather "blocky" in character.

6.4 Polymer Molecular Weight

In this research project, dilute-solution viscometry and vapour pressure osmometry were used to provide some indication of the level of molecular weight of the homopolymers and copolymers prepared.

From the vapour pressure osmometry results presented in Chapter 4, the calculated values of the number-average molecular weights, $\overline{M}_n$, are compared in Table 6.2.

Table 6.2 : Comparison of the number-average molecular weights, $\overline{M}_n$, of the homopolymers and copolymers synthesized using SO as initiator.

Homopolymer or Copolymer	$\overline{M}_n$ (g/mol)
PVL	2.0×10^3
PGA	1.1×10^3
P(GA-co-VL) 1 : 1	4.2×10^3
P(GA-co-VL) 2 : 1	4.1×10^3

From these results in Table 6.2, the $\overline{M}_n$ values are all relatively low. The two P(GA-co-VL) copolymers gave the highest molecular weights although the differences are perhaps too small to be really significant. For polymers such as these to find use in absorbable suture applications, they need to have $\overline{M}_n$ values an order of magnitude ($> 10^4$) higher than those obtained here in order to confer sufficient mechanical strength to the polymer.

From dilute solution viscometry, the viscosity-average molecular weight, $\overline{M}_V$, is calculated from the measured intrinsic viscosity [η] from the Mark-Houwink-Sakurada Equation, $[\eta] = K\overline{M}_V^a$. However, the values of the polymer-solvent interaction constants, K and a, in this equation are not available for any of the polymers synthesized here. Hence, only their [η] values can be determined, as summarized in Table 6.3 .

Table 6.3 : Comparison of the intrinsic viscosities, [η], of the homopolymers and copolymers synthesized using SO as initiator.

Homopolymer or Copolymer	[η] (dl/g)
PVL	0.26
P(GA-co-VL) 1 : 1	0.41
P(GA-co-VL) 2 : 1	0.33

However, despite the fact that their $\overline{M}_V$ values cannot be calculated, some indication of their molecular weight levels can be gauged from the following guidelines [32] :

Low $\overline{M}_V$: [η] less than 0.2 dl/g
Medium $\overline{M}_V$: [η] greater than 0.2 but less than 0.8 dl/g
High $\overline{M}_V$: [η] greater than 0.8 dl/g

Therefore, these values for [η] of the PVL and P(GA-co-VL) products in the range of 0.2-0.5 dl/g support the view that they all have relatively low to medium molecular weights. In comparison, commercial PGA sutures (DEXON) were characterized in an earlier project [58] as having an intrinsic viscosity of :

[η] = 0.8 dl/g in DMSO at 120°C

Since a sufficiently high molecular weight is an essential property requirement of a polymer, further research should focus its attention on determining the optimum conditions for high molecular weight attainment, such as type and concentration of the initiator, polymerization time and temperature.

6.5 Polymer Morphology

In this research project, information relating to polymer morphology has been provided by studying the melting behavior via differential scanning calorimetry (DSC). From the DSC curves, melting temperatures and heats of fusion (% crystallinities) have been determined. From the results obtained, the PGA homopolymers synthesized here were semicrystalline materials with melting ranges of 210-230°C.

In the case of the P(GA-co-VL) copolymers, their DSC curves also showed single peaks, although well below that of PGA. This at least provides some qualitative evidence to suggest that they are indeed genuine copolymers, but with a wide range of composition and crystallite size.

From their heats of fusion, the PGA and P(GA-co-VL) copolymers cannot be compared directly since their chemical structures are different. However, the magnitude of the differences, bearing in mind their similarities in structure, suggests that copolymerization decreases the heat of fusion and, hence, % crystallinity. This is as would be expected since copolymerization increases the degree of disorder in the polymer chain, thereby making it more difficult for the chains to crystallize.

6.6 Polymer Thermal Stability

Since the ultimate objective of this research project is to produce a material which can be melt spun into a monofilament fibre for use as a surgical

suture, thermal stability in the melt state is an important consideration. This has obvious implications in surgery since any thermal degradation products present in the spun fibre may be the cause of post-operative tissue reaction in the patient. Polymer purity must therefore be a prime consideration in any biomedical application.

One of the problems encountered with increasing the flexibility of a polymer chain is the adverse effect that it can have on thermal stability. This is particularly true here since all of the copolymers prepared have lower thermal stabilities than PGA (see the TG curves on page 99).

From the thermogravimetry (TG) results described earlier, the indications are that the PVL homopolymer and P(GA-co-VL) copolymers prepared in this research project have lower thermal stabilities than PGA. In this context, the temperature used in melt processing usually needs to be at least 10°C higher than Tm (max) and preferably not less than 40-50°C lower than Td (min). If this condition is not satisfied, the so-called "processing window" will be too narrow, thus increasing the possibility that some thermal degradation may occur during melt processing. As mentioned previously, only the PVL and P(GA-co-VL) samples could be melt spun into monofilament fibres. The PGA seemed to degrade during melt processing due to its narrow "processing window". Melt instability is one of the main problems with PGA (Tm ≈ 220°C, Td ≈ 250°C) which complicates its processing and which copolymerization can help to overcome.

6.7 Structure-Property Correlations from in the In Vitro Biodegradation of PVL and P(GA-co-VL) [59,60]

In vitro testing under conditions designed to simulate various aspects of the human body can provide useful and often quite accurate indications of the rate at which biodegradation will occur in the physiological environment. This is especially true of "simple hydrolysis" reactions in which agents such as enzymes and bacteria are not specifically required for catalysis, although they

may have an effect. Biodegradability is a polymer property dependent not only on chemical structure but also on various physical characteristics such as geometric configuration, surface-to-bulk ratio, porosity, molecular weight and its distribution, and matrix morphology.

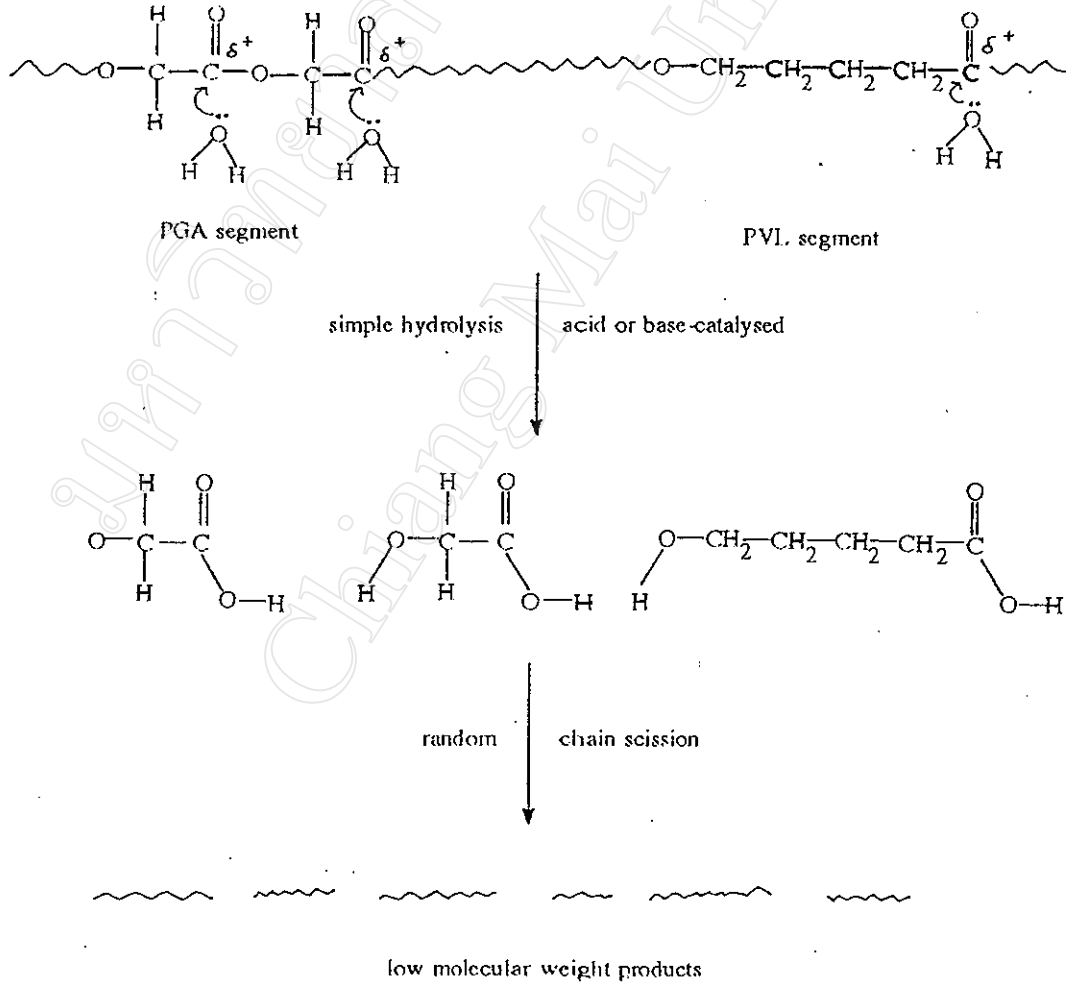
The weight and intrinsic viscosity (molecular weight) changes in the PVL and P(GA-co-VL) fibres during their in vitro biodegradation were described earlier in Chapter 5. On the basis of these results, an insight into the biodegradation mechanism is provided. As seen in Fig. 5.2 (page 109), the sample weights started to decrease significantly after about weeks 3 and 5 for the P(GA-co-VL), comonomer mole ratios 2:1 and 1:1 respectively. However, for the PVL sample, there was no onset of accelerated weight loss over the whole of the 24-week period of the experiment. This difference in response demonstrates the sensitivity of biodegradability to even slight changes in chemical structure.

These results indicate that the hydrolytic degradations of both the 2:1 and 1:1 copolymers commence early on, leading to immediate decreases in polymer molecular weight. Simple hydrolysis of aliphatic polyesters is believed to be a random chain hydrolysis reaction, as illustrated in Scheme 6.4. This hydrolysis reaction can be base-catalysed in an aqueous medium of pH>7 (as in this case where the pH = 7.4) or acid-catalysed in the event that the new COOH end groups formed causes the pH of the medium to drop below 7. The results previously shown in Figs. 5.3 and 5.4 (pages 112 and 115) show that the rate of degradation in terms of weight loss of P(GA-co-VL) is slower than that of the PGA (DEXON) sutures but faster than that of the P(GA-co-TMC) (MAXON) sutures, and decreases with the amount of VL in the copolymer.

This is as would be expected from structural considerations. Increasing the VL content, and therefore the number of hydrophobic $-(-CH_2-)-$ units in the copolymer, increases chain flexibility but decreases hydrolysability and lengthens the absorption period. Chemical processes, such as hydrolysis, and physical processes, such as diffusion, each with their own rate constant, will be affected in different ways by factors such as hydrophilicity and matrix

morphology (% crystallinity, crystalline packing), all of which relate back to the copolymer's chemical microstructure. Weight loss represents the diffusion out of the polymer matrix of low molecular weight hydrolysis products.

Although chemical structure is the dominant factor, physical configuration is also important. The weight loss profiles in Fig. 5.5 (page 117) are quite different for P(GA-co-VL) discs from a previous study [33] and the P(GA-co-VL) fibres from this study. This suggests that the rate is being controlled by physical factors such as the porosity of the polymer surface in contact with the immersion medium and the surface-to-bulk ratio. Furthermore, rate of weight loss may also be limited by the diffusion of hydrolysis products through the matrix.



Scheme 6.4 : Simple ester hydrolysis in a P(GA-co-VL) copolymer.

6.7.1 A Mechanistic View of the Biodegradation Process

The first step in any polymer biodegradation process in which hydrolysis is the dominant mechanism is the adsorption of water and wetting at the polymer surface. The efficiencies and, therefore, the rates of these physical processes depend primarily on the hydrophilicity of the polymer and the amount of surface area available for interaction. Since both the PGA and P(GA-co-VL) copolymers are simple aliphatic polyesters, adsorption and wetting can be expected to occur easily and quickly.

This is then followed by ester hydrolysis at the surface leading to the formation of micro-defects which facilitate the diffusion of water into the bulk interior of the polymer matrix. The exact nature of these surface defects (i.e., whether they are pores or cracks, etc.) has apparently not yet been studied systematically. As water diffuses into the polymer's semi-crystalline matrix, as shown in Fig. 6.1, ester hydrolysis occurs preferentially in the amorphous regions where the chains are more loosely packed than in the highly-ordered crystalline regions. This can help to explain why the net remaining heat of fusion (% crystallinity) of the polymer usually increases slightly during the initial weight loss period. As hydrolysis proceeds, the polymer molecular weight decreases until the degradation products are small enough in size to diffuse out of the matrix.

In vitro, the degradation products simply dissolve in the immersion medium, often causing the pH to change, whereas in the human body, i.e., in vivo, the products would be removed by the body's natural processes of metabolism and excretion. In the case of PGA and P(GA-co-VL), the main hydrolysis product, glycolic acid, would be converted into Kreb's Cycle intermediates (e.g., acetic acid) which would then break down to give carbon dioxide and water before being excreted through the respiratory and urinary systems.

Although Fig. 6.1 presents what is obviously a very simplified picture of polymer absorption, it does at least give some idea of the complex balance

of the various physical, chemical and biological processes involved. As this discussion has tried to explain, these processes are all interrelated with each other and with all aspects of the polymer's / copolymer's microstructure. Even slight variations in copolymer characteristics such as molecular weight, % crystallinity, composition, and monomer sequence distribution can have quite marked effects on the rate of absorption. This places great demands on the degree of control required in both copolymer synthesis and fibre spinning.

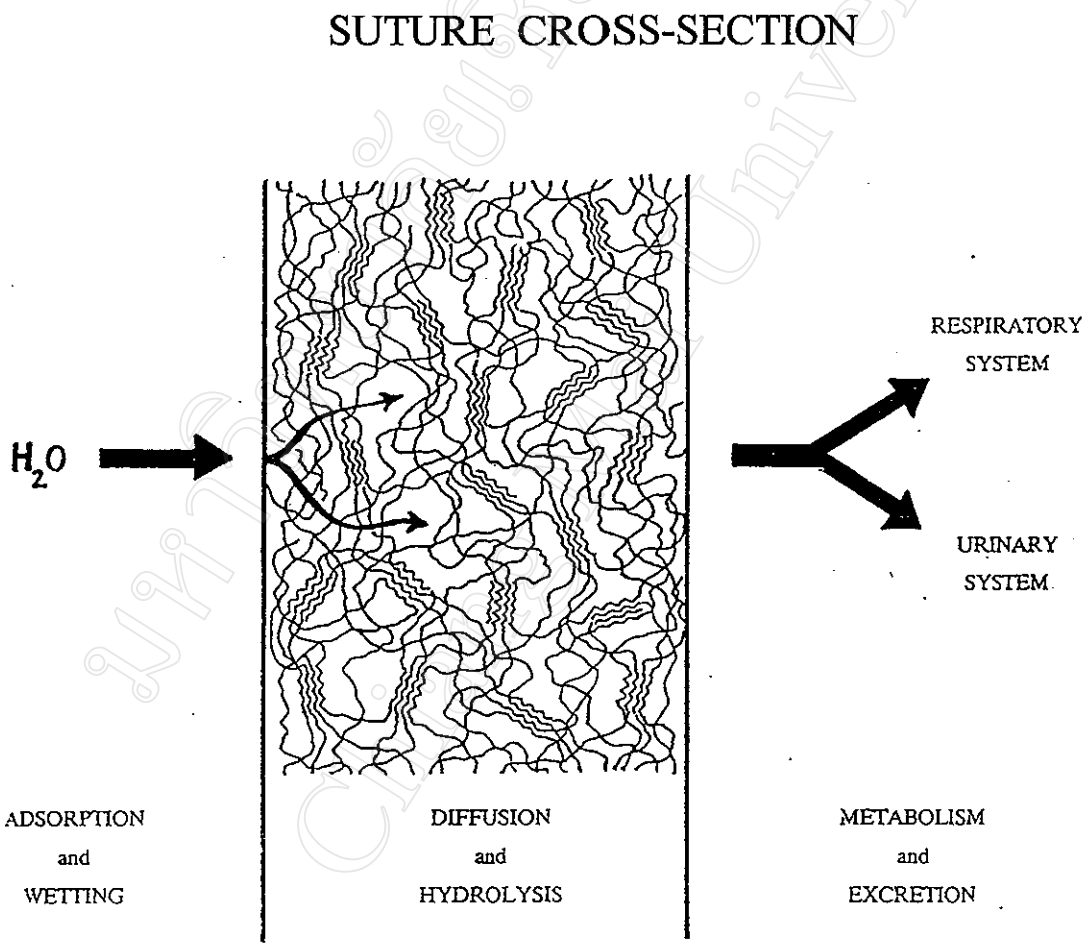
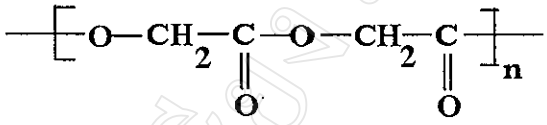


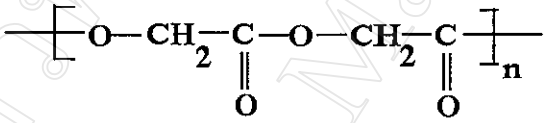
Fig. 6.1 : The various physico-chemical processes involved in suture absorption.

The PVL and P(GA-co-VL) copolymer samples show weight losses of about 20% and 50% respectively throughout the course of the experiment (24 weeks). This demonstrates that polymer biodegradation is generally a slow process. The exception to this appears to be the simplest of all the polyesters, poly(glycolic acid) (PGA), which degrades completely within about 10 weeks.

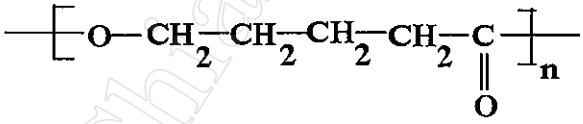


poly(glycolic acid), PGA

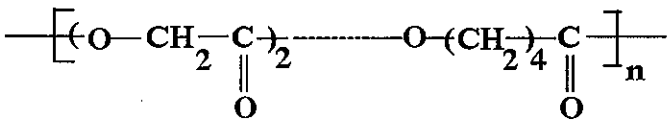
In the form of DEXON absorbable multifilament sutures, PGA has been reported [58] to hydrolyse completely in vivo (99% weight loss) within a period of only 10 weeks. This shows quite clearly how changes in chemical structure (cf., PGA, PVL and P(GA-co-VL) below) can seriously affect polymer properties.



poly(glycolic acid), PGA



poly(δ-valerolactone), PVL



poly(glycolic acid-co-valerolactone), P(GA-co-VL)

In PGA, there is a maximum number of ester groups per unit chain length and only single -CH_2- linkages. Consequently, PGA is the most hydrophilic and the most readily hydrolysable of all known synthetic polymers. As soon as more methylene units appear, e.g. -CH_2-CH_2-CH_2-CH_2- in PVL and P(GA-co-VL), the polymer hydrophilicity decreases dramatically which, in turn, slows down the rate-determining steps in the hydrolysis process, i.e., water adsorption at the polymer surface and water diffusion through the matrix. From these structural comparisons, it becomes immediately obvious that the inclusion of additional -CH_2- or even -O- linkages to increases chain flexibility will simultaneously decrease biodegradability. It is knowing how to strike the ideal balance between these opposing effects which represents the main challenge to the polymer chemist in the development of new absorbable suture materials.

From Fig. 5.8 (page 123), despite the almost complete loss of intrinsic viscosity for the P(GA-co-VL) samples, there is relatively little accompanying weight loss. This must be because the low molecular weight fragments, formed as a results of hydrolysis, are still unable to diffuse out of the degrading matrix. This is presumably due to the fact that they are still too large compared with the small water molecules which can easily diffuse in.

SUGGESTIONS FOR FURTHER WORK

Continuing on from the work described in this research project, the following suggestions for further work are made :

1. The initiator used in this study, stannous octoate ($Sn(C_7H_{15}COO)_2$), was chosen for its ease of handling and ready availability. However, it is quite possible that other types of initiator may be more effective for glycolide-valerolactone copolymerization, especially for increasing the molecular weight.

2. Other cyclic ester monomers such as ε-caprolactone should be considered as comonomers with glycolide instead of δ-valerolactone. They may give copolyesters with improved properties for use in the biomedical field.

3. From the C-13 solid-state NMR and CHNS/O elemental analysis results, it was found that the P(GA-co-VL) copolymers contained much less VL than their initial comonomer feeds. Sequential glycolide addition and/or solid-state post-transesterification may enable more VL to enter into the copolymer chain than the conventional bulk copolymerization route employed here.

4. High-resolution proton nuclear magnetic resonance spectrometry (^{1}H-NMR) should also be considered in conjunction with C-13 solid-state NMR for the study of copolymer microstructure.

5. A more complete physical and microstructural characterization of the homopolymers and copolymers should be undertaken using additional techniques such as X-ray diffraction (which can determine the % crystallinity of the sample directly) and high temperature gel permeation chromatography (GPC) for molecular weight (including distribution) determination.

6. A more effective melt spinning apparatus should be used to prepare monofilament samples for the in vitro biodegradation work. Samples need to be consistent in quality if meaningful comparisons are to be made possible.