CHAPTER 3

A NEW BIODEGRADABLE POLYMER FOR USE AS AN ABSORBABLE MONOFILAMENT SUTURE

There are various approaches to the design of biodegradable polymers for use in medical applications. The use of cyclic ester monomers in the formation of polyesters for the fabrication of synthetic surgical articles is well known. Comonomers have often been employed to modify the characteristics of the various polyesters.

The end-use application toward which the molecular design of the terpolymers studied in this work was directed was a highly specialized biomedical one, namely: **absorbable monofilament surgical sutures**. This specialist application has very stringent property requirement which, in turn, place great demands on molecular design to meet these requirement.

In this work, it was decided that L-lactide would be the main component rather than glycolide in order to produce a material that was different to the current commercial ones and lower in price. However, poly(lactide) itself cannot be used because its glass transition temperature, T_g, is too high which gives rise to a monofilament fiber that is too stiff and springy. Also, its rate of biodegradation in the human body is considered to be too slow for suture application. Consequently, poly(L-lactide) needs to be modified in order to improve both its handling and healing characteristics as a potential suture material. One of the most convenient way of doing this in polymer chemistry, which gives the polymer chemist a wide range of options and scope for adjustment, is **copolymerization** in which 2 or more monomers are combined; in the case if 3 monomers, as in this work, it can be termed terpolymerization.

Using this methodology, 2 modifying comonomers were chosen to (a) decrease T_g and increase chain flexibility, and (b) increase hydrophilicity and rate of absorption relative to poly(L-lactide). This 2 comonomers were ε-caprolactone and glycolide respectively. This 3 components: L-lactide, ε-caprolactone and glycolide, will now be described in more detail in the following section.

3.1 Poly(glycolide): PG

Poly(glycolide) is the simplest linear aliphatic polyester. PG was used to develop the first totally synthetic absorbable suture that has been marketed as DEXON since the 1960s by Davis and Geck. Glycolide monomer is synthesized from the dimerization of glycolic acid. The ring opening polymerization of glycolide yields high-molecular-weight materials with about 1-3% residual monomer present (Fig. 3.1) [2].

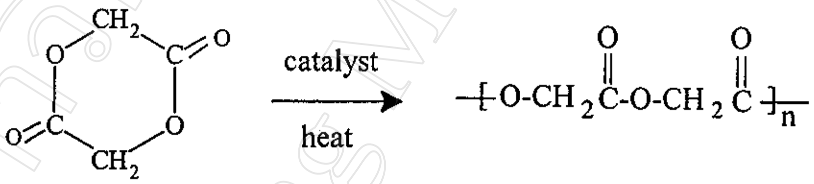


Fig. 3.1 Synthesis of poly(glycolide) (PG).

PG is a crystalline, biodegradable polymer having a melting point (T_m) of about 225°C and a glass transition temperature (T_g) of about 35°C. The heat of fusion of 100% crystalline PG is 45.7 cal/gram. Relative to other biodegradable polymers, PG is a highly crystalline polymer with crystallinity typically reported in the range of 35-75%. The molecular and subsequent crystalline structure of PG allow very tight chain packing and thus afford some very unique chemical, physical and mechanical properties to the material. In its highly crystalline form, PG has a very high tensile strength (10,000-20,000 psi) and modulus of elasticity (~1,000,000 psi).

PG biodegrades by hydrolysis of the readily accessible and hydrolytically unstable aliphatic-ester linkages. Final hydrolysis of PG results in glycolate, some of which is excreted directly in urine. Some glycolate may also be oxidized to glyoxylate which is then converted to glycine, serine and pyruvate. Pyruvate then can enter the Krebs cycle. The degradation time is just a few weeks depending on the molecular weight, degree of crystallinity, crystal morphology, physical geometry of the specimen, and the physico-chemical environment. Fig. 3.2 shows the *in vitro* degradation curve for PG fibers [13]. After 1 weeks, approximately 80% of the original strength was retained. The tensile strength falls to about 10% after 3 weeks.

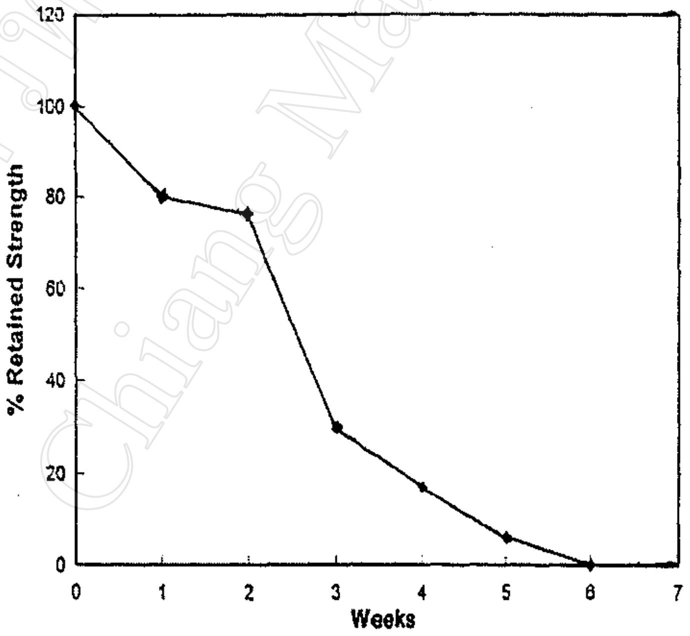


Fig. 3.2 *In vitro* degradation of polyglycolide [13].

3.2 Poly(lactide): PL

Although structurally very similar to PG, the polylactide (PL) are quite different in chemical, physical and mechanical properties because of the presence of a pendent methyl group on the alpha carbon. This structure causes chirality at the alpha carbon of PL; and thus, L, D, and DL isomers are possible. L-PL is made from L(-)-lactide and D-PL is made from D(+)-lactide while DL-PL is made from DL-lactide which is a racemic mixture of the L(-) and D(+) isomers and the meso form having both the D(+) and L(-) configuration on the same dimer molecule.

L-PL is a crystalline, biodegradable polymer having a melting point (T_m) of approximately 175°C and a glass transition temperature (T_g) of approximately 65°C. L-PL is generally less crystalline than PG, with crystallinity reported in the range of 35%. The polymer is very soluble in common organic solvents such as chloroform. In its more crystalline form, L-PL has a very high tensile strength slightly lower, although, similar to PG but a much lower modulus of elasticity.

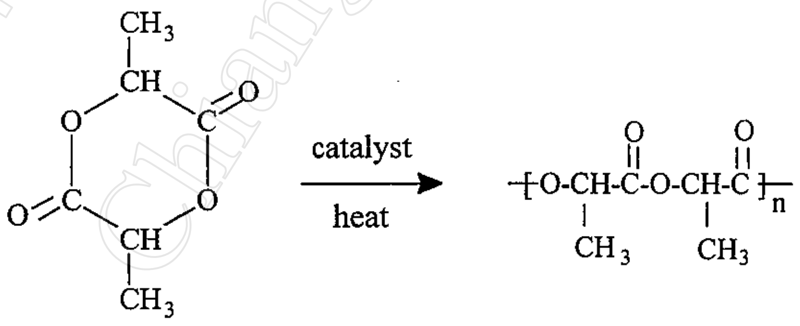


Fig. 3.3 Synthesis of poly(lactide) (PL) [8].

In an *in vitro* experiment performed at Linvatec, molded PL devices were soaked in buffered saline at 37°C for a number of months and the loss in tensile strength as a function of time was measured. Fig. 3.4 shows the change in tensile strength (as a percentage of the initial value) as a function of total elapsed degradation time. Initially, the tensile strength starts out at 100% and remains relatively high (about 75%) for approximately 20 weeks [13]

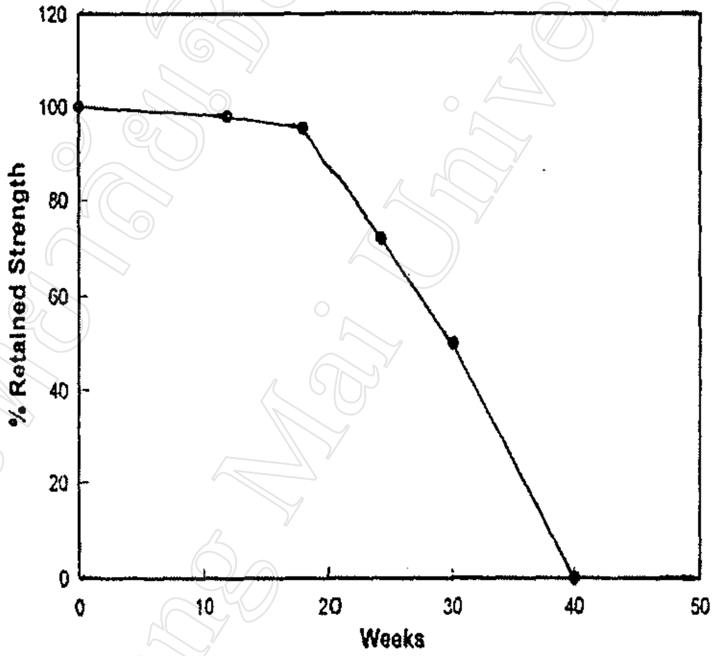


Fig. 3.4 *In vitro* degradation of poly(L-lactide) [13].

3.3 Polycaprolactone: PCL

The ring opening polymerization of ε-caprolactone (Fig.3.5) yields a semicrystalline, biodegradable polymer with a melting point of ~60°C and a glass transition temperature (T_g) ~-60°C. The repeating molecular structure of PCL homopolymer consists of five nonpolar methylene groups and a single relatively polar ester group. This structure gives PCL some unique properties. The mechanical properties are similar to polyolefin because of its high olefinic content, while the presence of the hydrolytically unstable aliphatic-ester linkage causes the polymer to be biodegradable. This combination also gives PCL the unusual property of being compatible with numerous other polymers and PCL polymer blends having unique properties have been prepared.

Biodegradation of the PCL homopolymer is considerably slower than the poly (α-hydroxy acid) such as polylactide because of the combination of its crystallinity and high olefinic character. The synthesis of PCL is shown in Fig. 3.5 [13].

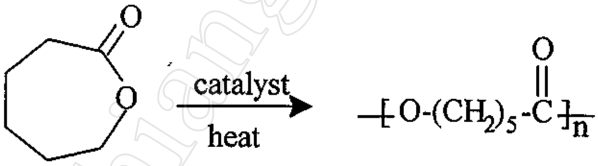


Fig. 3.5 Polymerization of PCL [13].

Sutures made from homopolymeric PCL were evaluated in a rabbit model by Barber and Click to determine their associated degradation rate. The results of this study are shown in Fig. 3.6.

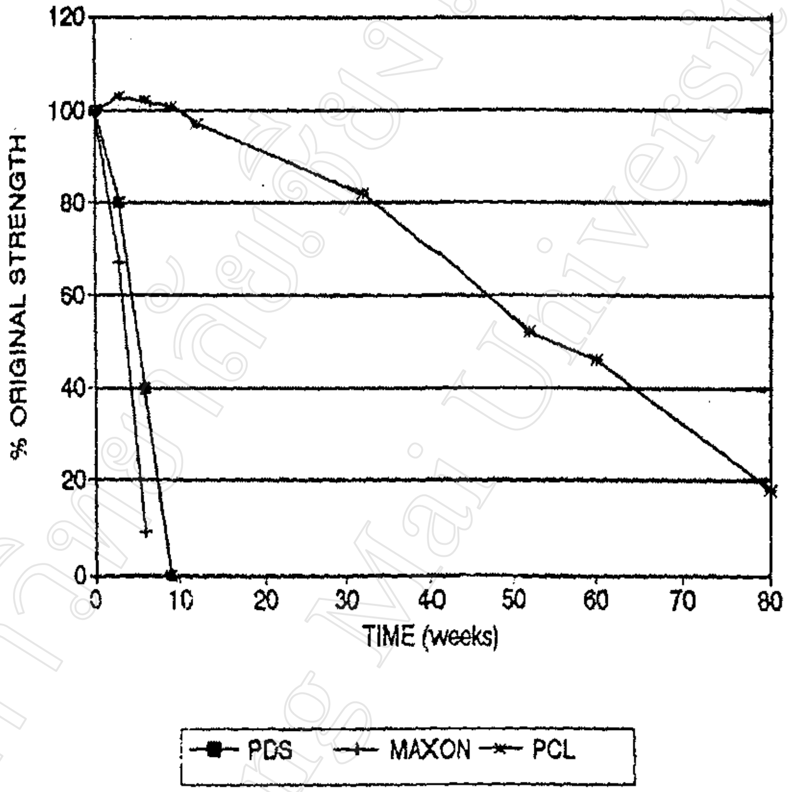
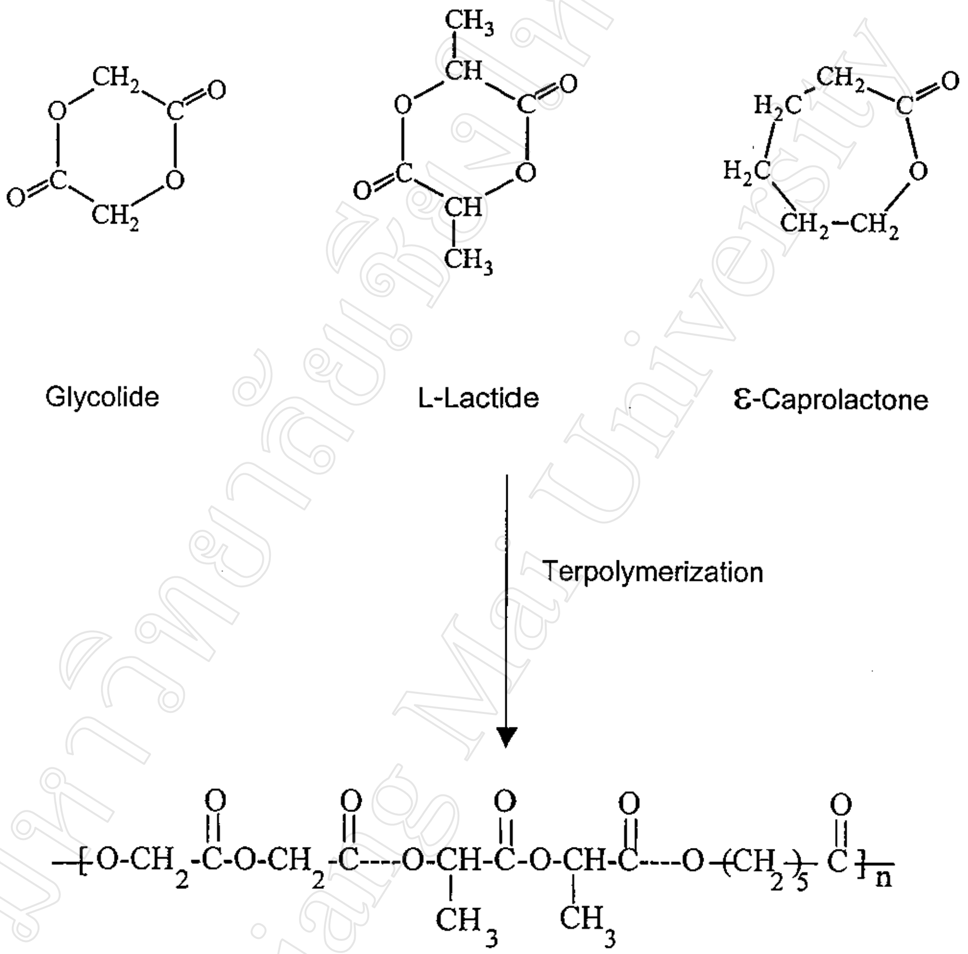


Fig. 3.6 *In vivo* degradation of absorbable sutures [13].

3.4 Terpolymers of Glycolide, L-Lactide and Ɛ-Caprolactone

The major class of synthetic biodegradable polymer is aliphatic poly(ester). PCL provides a very good permeation for steroids, good flexibility and also PCL is easy to process. However, its long degradation time (3-5 years) is usually a disadvantage for medical applications as drug delivery system. PL and PG behave in the opposite way [15]. PL and PG are typically examples of aliphatic polyesters, which are of good properties for biomedical applications mainly in degradable and absorbable sutures, implants, artificial skin grafts, and drug release systems. The great advantage of these synthetic biocompatible and absorbable materials is that their degradability is due to simple hydrolysis of the ester backbone in aqueous environments such as the body fluids. Furthermore, the degradation products are ultimately metabolized to carbon dioxide and water or are excreted via the kidney [16].

To combine the flexibility of PCL with the good degradability of PL and PG, random terpolymers of l-lactide, glycolide and Ɛ-caprolactone have been synthesized and studied. The chemical structures of this terpolymers are as shown below:



Poly(L-lactide-*ran*-ε-caprolactone-*ran*-glycolide)

3.5 Terpolymer Characterization

A random terpolymer of L-lactide, ε-caprolactone and glycolide was selected for this research project. This PLCG terpolymer was not synthesized as part of this project but as part of the ongoing research work within the Chiang Mai Polymer Research Group (see Note). It was used for melt spinning as obtained direct from the synthesis reaction. The 0.2% by mole of stannous octoate was used as the initiator for the ring opening reaction. The copolymerization was conducted at 140°C for 72 hours. This random terpolymer, (PLCG), was then characterized by various analytical techniques.

The characteristics for the PLCG obtained from various analytical techniques were concluded as shown below:

Comonomer composition = 68:21:11 (LLA : ε-CL : GA)
Intrinsic viscosity; $[\eta]$ = 0.81 dl/g
Number average molecular weight; $\overline{M}_n$ = 29000
Weight average molecular weight; $\overline{M}_w$ = 62000
Polydispersity; $\overline{M}_w / \overline{M}_n$ = 2.16
Melting temperature; T_m (onset) = 86.7°C
T_m (peak) = 117.7°C
Heat of fusion; ΔH_f = 7.43 J/g
Degradation temperature; T_d = 242.0 - 439.9°C

Note : The ***Biomedical Polymers Research Unit*** is a network research unit of the ***National Metal and Materials Technology Center*** (MTEC)

3.6 Fiber Processing and Fiber Characterization

3.6.1 Fiber Processing

In any fiber forming processes, the morphology and molecular orientation within the fiber at the microscopic level can be controlled by the processing method and condition used. This, in turn, controls the fiber properties at the macroscopic level. In this study, melt-spinning, off-line hot drawing and annealing were used in the production of monofilament fibers of PLCG and these processing methods were done by the biomedical polymers research unit.

In this study, the PLCG random terpolymer were melt-spun with a small-scale melt spinning apparatus [17] and the processing conditions used to produce monofilament fiber were described below:

Spinning Temperature = 120°C
Ram Speed = 2.0 mm/min
Take-up Speed = 0.6 m/min
Hot-drawing Temperature = 53°C
Draw Ratio (λ) = 5
Annealing Temperature = 40°C
Annealing Time = 24 hours

After drawing and annealing the PLCG fiber, the average diameter was about 0.39 mm.

3.6.2 Fiber Characterization

In this research project, Differential Scanning Calorimetry was used to study the thermal properties of the PLCG monofilament fiber. All of the DSC measurements were carried out over the temperature range of 35-200°C using a heating rate of 10°C/min under a flowing nitrogen atmosphere.

The melting temperature, T_m, and heat of fusion, ΔH_f, for PLCG random terpolymer fiber were found to be:

$$\boxed{\begin{aligned} T_m^{*} &= 107.00^{\circ}\text{C} \\ \Delta H_f^{**} &= 17.14\ \text{J/g} \end{aligned}}$$

T_m^{*} = melting point, taken as the peak temperature of the melting range

ΔH_f^{**} = heat of fusion $\propto$ % crystallinity

3.7 Aim of This Study

The main aim of this research project is to follow the changes in various properties during the *in vitro* biodegradation of the commercial sutures MONOCRYL, MAXON and PDS II and to compare them with those of a newly synthesized monofilament fiber. The new synthetic absorbable monofilament fiber of particular interest is a random terpolymers of L-lactide, ε-caprolactone and glycolide, PLCG, which has been purpose-designed for potential use as an absorbable suture. The property changes with time will be followed by a combination of complementary analytical techniques which should enable the overall *in vitro* biodegradation process to be described.