CHAPTER 3

BIODEGRADABLE POLYMERS

3.1 Biodegradation and Hydrolytic Degradation [17]

Hydrolytic degradation is possible in synthetic polymers containing ester, amide, urethane and carbonate links and in natural polysaccharides and proteins. Apart from the case of polymers with ester and amide structures in the side-groups rather than in the backbone, hydrolysis leads to a rapid loss of physical properties as a result of cleavage of the chains. Because of the hydrophobic character of most polymers, hydrolysis, even where feasible, may proceed slowly. Humid conditions and a pH of less than 7 will favour this type of degradation reaction.

Biodegradation of polysaccharides and proteins is induced by enzymes, which are complex proteins containing hydrophilic groups such as COOH, OH and NH_2. Enzymes are highly specific towards particular chemical structures.

Microorganisms may also be specific in their attack, but may be able to adapt to substrates such as synthetic polymers. Polymer structures sensitive to attack by microorganisms are aliphatic polyesters, polyethers, polyurethanes and polyamides. Two commonly used types of polyurethanes are poly(ester urethanes) and poly(ether urethanes). The former are more susceptible to biodegradation than the latter.

The various types of microorganisms have different requirements for effective action. Fungi require oxygen and quite acid conditions, pH 4.5-5, with an optimum temperature of about 35°C. Actinomycetes and bacteria prefer less acid conditions, pH 5-7, and will operate over a wider temperature range, the optimum being about 60°C. Whereas actinomycetes require oxygen, bacteria can operate in both anaerobic and aerobic conditions.

In addition to the functional group requirements noted above, it has been found that biodegradation is strongly influenced by chain length and branching. Short, linear chains are more susceptible. Polymers which are initially resistant to biodegradation may be become susceptible after the chain size has been reduced by photo-oxidation.

The susceptibility of various polymers to hydrolysis and biodegradation is summarized in Table 3.1.

Table 3.1 Susceptibility of unstabilised polymers to hydrolysis and biodegradation [17].

Polymer	Hydrolysis	Biodegradation
polyethylene	0	1
polypropylene	0	0
natural rubber	0	1
polystyrene	0	1
poly(vinyl chloride)	1	0
poly(vinyl acetate)	4	2
poly(vinyl alcohol)	0	3
poly(methyl acrylate)	1	1
poly(methyl methacrylate)	1	0
poly(ethylene terephthalate)	1	1
bisphenol A polycarbonate	1	0
polytretrafluoroethylene	0	0
polyamide (nylon-6)	2	2
polyurethanes	1	2-4
polypeptides	2	4
alkyd resins	1	0
epoxy resins	1	0
cellulose	2	3

Key : Susceptibility to degradation increasing on the scale 0 to 4

3.2 Biodegradable Polymers in Medicine

The development and applications of biodegradable polymers are closely connected with progress in different areas of human and veterinary medicine. This concerns especially the development of absorbable suture materials and other surgical and prosthetic aids, as well as matrix materials for parental long- term delivery systems for highly active drugs [18].

Some examples of biodegradable polyesters currently used in medicine are listed in Table 3.2. As seen from their structures, they are aliphatic in nature with relatively few main chain atoms separating successive ester groups. It is this high ester group concentration per unit chain length which gives the polymers the necessary hydrophilicity and hydrolysability for biodegradation to occur within an acceptable timescale.

Table 3.2 Biodegradable polymers used in medicine [19].

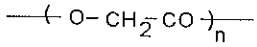
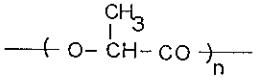
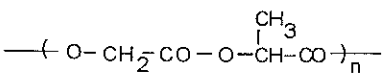
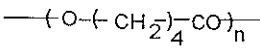
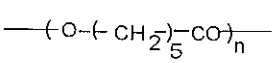
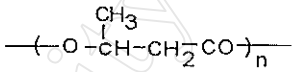
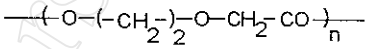
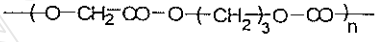
Polymer Name	Commercial Name	Application	Chemical Structure
Poly(glycolic acid)	DEXON	SS	
Poly(DL-lactic acid)	-	DRM	
Poly(glycolic-co-lactic acid)	VICRYL	SS	
Poly(δ-valerolactone)	-	DRM	
Poly(ε-caprolactone)	-	DRM	

Table 3.2 : (continued)

Polymer Name	Commercial Name	Application	Chemical Structure
Poly(hydroxy butyrate)	BIOPOL	DRM	
Poly(p-dioxanone)	PDS	SS	
Poly(glycolic acid-co-trimethylene carbonate)	MAXON	SS	

SS = surgical suture (absorbable)

DRM = drug release matrix

3.3 Absorbable Surgical Sutures

The absorbable suture acts as a temporary scaffold while the process of wound healing takes place following surgery. It is a polymer which has the ability to biodegrade by hydrolysis under physiological conditions. The suture is used to hold both sides of the wound in close apposition until sufficient collagen synthesis has take place to hold the wound together unassisted. Seventy to eighty percent of total collagen synthesis usually occurs within the first three weeks, the final twenty to thirty percent requiring periods of three to six months [20]. The absorbable surgical sutures which have found commercial use are listed in Table 3.3.

Table 3.3 Natural and synthetic polymers used as absorbable surgical sutures [21].

Generic Name	Trade Name	Raw Material
Natural Collagens		
Plain gut	-	Submucosa sheep intestine
Chromic gut	-	Serosa of beef intestine + buffered chromicizing
Collagen (plain)	-	Beef flexor tendon
Collagen (chromic)	-	Beef flexor tendon + buffered chromicizing
Synthetics		
Polyglycolide	Dexon S	Homopolymer of glycolide
Polyglycolide	Dexon plus	Homopolymer of glycolide coated with polyoxamer 188
Polyglycolide	Dexon II	Homopolymer of glycolide coated with polycaprolactone
Polyglactin 910	Vicryl	Copolymer of lactide-glycolide coated with calcium stearate and polyglactin 370
Polydioxanone	PDS	Polymer of p-dioxanone
Polydioxanone	PDS-2	Modified PDS
Polyglyconate	Maxon	Copolymer of glycolide and trimethylene carbonate

The characteristic properties of a good absorbable suture can be summarized as follows: [22-24]

1. Good knot security
2. Superior tensile strength
3. Excellent handling characteristics
4. Minimal tissue reaction
5. Non-allergenic
6. Resistant to infection
7. Predictable absorption throughout the wound-healing process

3.4 Suture Monofilaments versus Multifilaments

Absorbable sutures may be fabricated as monofilaments or multifilaments; the latter are usually braided, but sometime twisted or spun, and may be coated with waxes, silicones, fluorocarbons, or other polymers to reduce capillarity and improve handling or functional properties [25]. Some of the properties and performance characteristics of multifilament and monofilament sutures are compared in Table 3.4.

Although "DEXON" and "VICRYL" multifilament sutures satisfy most of the requirements of the surgeon, some problems do still exist in their use. It has been in an attempt to alleviate these problems that two new monofilaments have since appeared on the market. Going under the trade names of "PDS" and "MAXON", they succeed in overcoming most of these problems as mentioned in Table 3.4.

However, because of their inherently greater stiffness and lower knot security than either "DEXON" or "VICRYL", "PDS" and "MAXON" have up until now been rather slow to gain widespread acceptance for general surgical use. Consequently, "DEXON" and "VICRYL" are still the most commonly used absorbable sutures at the present time.

Table 3.4 Comparison of the properties of multifilament and monofilament absorbable sutures relevant to surgery [26-31].

Multifilaments	Monofilaments
1. Tissue reaction can occur easily (see Note 1)	1. Tissue reaction much less pronounced (see Note 1)
2. Soft and flexible	2. Less flexible and rather springy
3. High coefficient of friction (see Note 2)	3. Low coefficient of friction (see Note 2)
4. Good knot security	4. Reduced knot security
5. Comfortable and easy to handle	5. Can be uncomfortable and difficult to handle
6. Rapid absorption (usually within 8-12 weeks)	6. Slower absorption (up to 6 months or longer)
7. Narrow temperature range for melt spinning	7. Wider temperature range for melt spinning

Note 1: In multifilament sutures, there are interstices formed by the relatively loose braid of the fibres which permit serum and blood to penetrate the suture and form a perfect refuge for bacteria. Therefore, multifilament sutures should not be used in an infected wound or in one likely to become infected

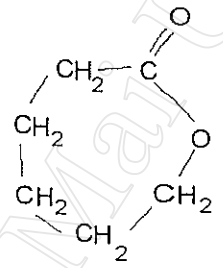
Note 2: The braiding of monofilaments causes the outer surface to be rough. This can make it difficult to pull the suture through delicate tissue without tearing the tissue in the process (i.e., causes tissue drag).

3.5 Polycaprolactone (PCL) and Poly(lactic acid) (PLA) [32]

An interesting feature of polycaprolactone is that copolymerization of lactide into the molecule provides a material that is much more flexible than either poly(lactic acid) or polycaprolactone.

3.5.1 Polycaprolactone

Polycaprolactone is an example of a biodegradable polyester prepared by the ring-opening polymerization of a lactone. In this case, the lactone (ε-caprolactone) is a seven-membered ring in which a single ester moiety is linked together with five methylene units as shown below:



ε-caprolactone

Polycaprolactone is a hydrophobic, semicrystalline polymer ($T_g \approx -60°C$, $T_m \approx 63°C$) which is degraded very slowly *in vivo* to yield ε-hydroxycaproic acid. The low melting temperature of polycaprolactone could be an advantage in accelerating degradation in composting environments where temperatures often reach 60°C. However, problems may arise in applications where elevated storage or use temperatures may be experienced that could compromise mechanical integrity and performance.

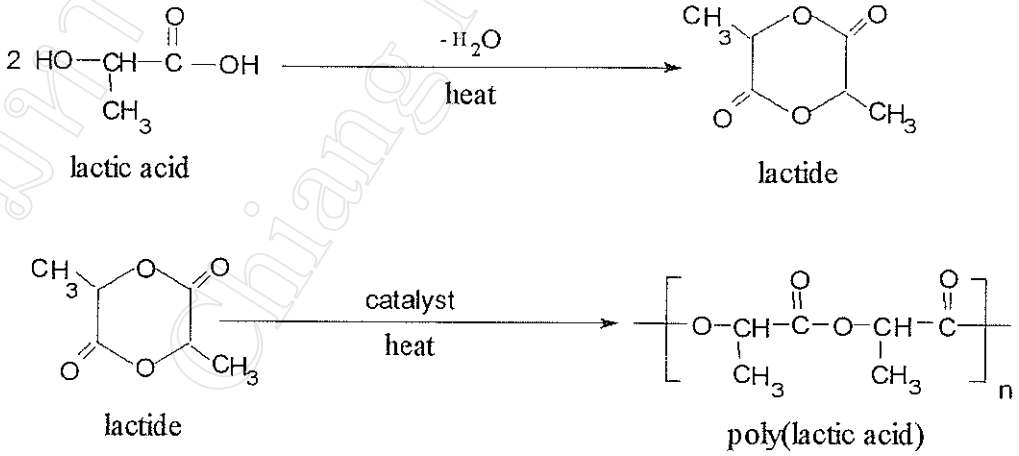
Polycaprolactone can be hydrolyzed and is biodegradable. As the molecular weight of polycaprolactone increases, the rate of biodegradation decreases. Biodegradation of polycaprolactone is initiated by nonenzymatic

ester hydrolysis. The final stage of biodegradation of polycaprolactone, however, was found to involve phagocytosis of polymer fragments by macrophages and giant cells and degradation within these cells by lysosome-derived enzymes. *In vitro* studies on polycaprolactone have established its sensitivity to microbial enzymes and, as expected, increased degradability of amorphous regions relative to the crystalline phase.

Current uses of polycaprolactone include orthopaedic casts, adhesive mold release agents and pigment dispersants. The permeability of polycaprolactone to various contraceptive steroids has made it an important candidate for development of drug delivery implants.

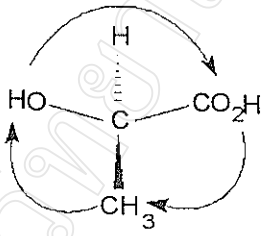
3.5.2 Poly(lactic acid)

Poly(lactic acid) is usually prepared via the following sequence of reactions.

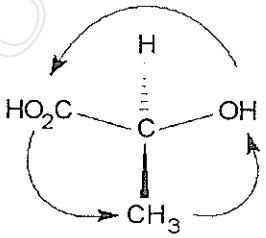


Although lactic acid can be polymerized directly to poly(lactic acid), much higher molecular weight polymer is obtained by first converting the lactic acid into lactide, the cyclic diester. The ring-opening polymerization of lactide is typically catalyzed with the use of stannous octoate.

The optical isomerism of lactic acid has an important influence on monomer metabolism and polymer properties. This type of isomerism results from the fact that one of the carbon atoms (known as the asymmetric center) has four non-identical groups attached to it and thus is non-superimposable on its mirror image (the optical isomer). There are 2 configurations. These configurations are also commonly known as D- and L-lactic acid respectively, as shown below.



D - Lactic Acid
R - Configuration



L - Lactic Acid
S - Configuration

Pure L- and D-lactic acids can be obtained by fermentation or culture techniques, whereas synthetic lactic acid is a racemic mixture, referred to as DL-lactic acid, which is an equal mixture of D- and L-lactic acid molecules. DL-lactic acid is thus optically inactive.

Poly(lactic acid) is typically available as either poly(L-lactic acid) (used in absorbable sutures) or poly(DL-lactic acid) (used in drug delivery applications), although poly(D-lactic acid) has recently become available. The differences between these polymers result primarily from differences in crystallinity. Poly(L-lactic acid) and poly(D-lactic acid) are semicrystalline polymers whereas poly(DL-lactic acid) is totally amorphous.

Fibre spinning in suture form allows a greater degree of control over polymer morphology since the filaments can be stretched during the crystallization process. This provides a dramatic improvement in tensile strength relative to unoriented filaments. Optimization of the deformation rate and drawing temperature of poly(L-lactic acid) has yielded fibres with a tensile strength of 2.3 GPa. In comparison, solution spinning gave a lower fibre strength of 1.2 GPa. In both cases, the polymer chains were oriented by drawing which resulted in the formation of crystal structure in alignment with the fibre axis. In any case, successful melt processing of poly(lactic acid) requires that the polymer be substantially free of water, monomer, oligomers and catalyst to minimize loss of molecular weight during extrusion.

Table 3.5 Some of the physical, mechanical and barrier properties of polycaprolactone (PCL) and poly(lactic acid) (PLA) [32].

Properties	PCL	L-PLA	DL-PLA
Glass transition temperature (°C); T_g	-60	50 - 59	53
Melting temperature (°C); T_m	55-65	130 - 196	-
Decomposition temperature (°C); T_d	250	245	255
Tensile strength (MPa)	21 - 31	50	-
Elongation at break (%)	600 - 1000	3	-
Oxygen permeability (cm^3/m^2 day)	115	500	-

3.6 Scope and Objectives of This Project

The main objective of this research project is to produce monofilament fibres of consistent quality for potential use as absorbable sutures. The speciality materials to be used in this study are novel biodegradable polyesters which are currently being developed as past of an wider ongoing research programme in biomedical polymers. Fibres will be produced using a newly-acquired small-scale melt spinning apparatus. The work will also involve the use of a combination of thermoanalytical and mechanical techniques to determine the optimum processing temperatures and to characterize the microstructure and properties of the fibres formed. Finally, if fibres of acceptable quality can be produced, their *in vitro* biodegradabilities revelant to their intended application will also be studied.

This project will be divided into 2 distinct parts:

Part 1: Melt Spinning of Commercial Polypropylene

Here the main purpose is to become accustomed to the use of the small-scale melt spinning apparatus using a commercial polypropylene sample of which the fibre-forming characteristics are well-known. This will also include a study of various processing variables on the properties of the fibres obtained.

Part 2: Melt Spinning of Synthesized Poly(L-Lactide-co-ε-Caprolactone)

Using the knowledge and experience gained from Part 1, a prototype suture material synthesized as part of another research project [33] and made from a random copolymer of L-lactide and ε-caprolactone will be melt spun and its properties tested. As mentioned above, this will also include a study of the changes in copolymer microstructure (morphology) during processing.