CHAPTER 1

INTRODUCTION

1.1 Biodegradable Polymers

In recent years, there has been a marked increase in interest in biodegradable polymers for medical applications. The term "biodegradable" refers to degradation induced by the vital activity of an organism, not simply the degradation of a material in a physiological environment. However, the term "biodegradable polymer" is now widely used to convey the meaning of a polymer that degrades in the human body [1]. The generally accepted definition of "polymer biodegradation" is: hydrolytic, enzymatic or bacteriological degradation processes occurring in a polymer which do not necessarily proceed to a stage where the physical form of the polymer is altered [2]. Linear aliphatic polyesters such as poly(glycolic acid), poly(L-lactic acid), poly(DL-lactic acid), poly(ε-caprolactone), polydioxanone and their co- and terpolymers are the most popular biodegradable polymers used in medicine since aliphatic ester bonds facilitate hydrolytic degradation by body fluids [3]. Some examples of biodegradable polyesters currently used in medicine are listed in Table 1.1.

Table 1.1 Some biodegradable polymers used in medicine [2].

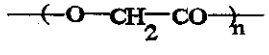
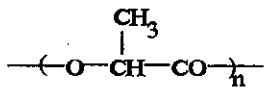
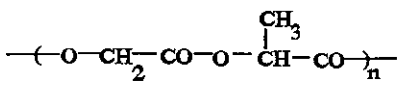
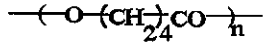
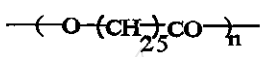
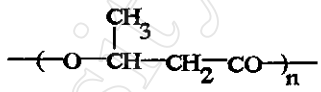
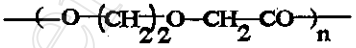
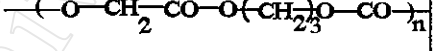
Polymer Name	Trade Name	Application	Chemical Structure
Poly(glycolic acid)	DEXON	SS	
Poly (DL-lactic acid)	-	DRM	
Poly(glycolic-co-lactic acid)	VICRYL	SS	
Poly(δ-valerolactone)	-	DRM	

Table 1.1 (continued)

Polymer Name	Trade Name	Application	Chemical Structure
Poly(ε-caprolactone)	-	DRM	
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

1.2 The Requirements of a Biodegradable Polymer [1]

The initial requirements in the selection or design of any biodegradable polymer are that it should possess the following properties:

1.2.1 Correct Balance of Mechanical Properties

The mechanical properties are largely controlled by the chemical structure, molecular weight, morphology and the glass transition temperature (Tg). The material should be selected or designed such that its Tg is outside the operating range of the body temperature in order that a discontinuity in properties does not occur in use. The Tg not only affects the modulus but also diffusion coefficients and hydrolytic stability.

1.2.2 Property-Loss Profile Appropriate to Application

The biodegradable polymer will exhibit a change in mechanical properties during its lifetime as it degrades and the property-loss profile must be such that the material remains useful over the desired period. The onset of loss of mechanical properties may be synchronous with, occur prior to or later

than the loss of molecular weight, depending on the mechanism of degradation. Mass loss usually occurs considerably later.

1.2.3 Degradation Products: Non-Toxic and Biocompatible

The degradation products are necessarily released into the adjacent tissue and therefore must be non-toxic and biocompatible. They should preferably be small, water-soluble molecules.

1.2.4 Minimal Tissue Reaction

The material must give minimal tissue reaction so as not to hinder the healing process or cause unnecessary additional pain to the patient.

1.2.5 Total Mass Loss within an Acceptable Period of Time

Total mass loss should occur within an acceptable period of time which, for an absorbable suture material, is usually considered to be within 6 months of implantation.

From the above requirements, the characteristics of a good absorbable suture can be summarized as follows [4-6] :

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

1.3 Mechanisms of Biodegradation [1]

There are four major mechanisms that can be utilized in the design of biodegradable polymers:

1.3.1 Solubilization

Solubilization is strictly applicable to polymers that are water-soluble. The degradation process involves diffusion of water into the polymer matrix, followed by continuous solvation and swelling until either fragmentation or dissolution occurs.

1.3.2 Ionization followed by Solubilization

Utilization of the ionization mechanism for bringing about solubility allows materials to be designed that are relatively hydrophobic prior to ionization. However, when these polymers are placed in an environment which causes them to become ionized, their surfaces absorb water, swell, and finally dissolve, causing the surface to erode.

1.3.3 Enzymatically Catalyzed Hydrolysis

Enzymes have more effect in naturally occurring sutures than in synthetic sutures. However, Williams et al [7] have shown that degradation rates in the latter can also be accelerated in the presence of certain enzymes at the pHs where they exhibit their maximum activity. They have reported, for example, that certain enzymes (such as esterase and carboxypeptidase) are able to influence the rate of hydrolysis in poly(glycolic acid).

1.3.4 Simple Hydrolysis [8]

Simple hydrolysis is the depolymerization process which can be seen as the reverse of polycondensation. Its occurrence is feasible in the aqueous extracellular fluid , although a number of conditions have to be met:

(a) The polymer has to contain hydrolytically unstable bonds.

(b) The polymer should be hydrophilic, otherwise the medium producing the hydrolysis will have very limited opportunity for gaining access to the hydrolysable bonds.

(c) The hydrolysis has to be able to take place at the physiological pH (around 7.40) and temperature (37°C).

Polymers which have been shown to degrade by simple hydrolysis in vivo are polyesters, polyamides and some polyurethanes and cyanoacrylates.

1.4 Absorbable Surgical Sutures

Sutures are sterile filaments used to close wounds and are made of either absorbable or nonabsorbable materials. An absorbable suture is one which is degraded in body tissues to soluble products and disappears from the implant site, usually within 2 to 6 months. A nonabsorbable suture is resistant to biodegradation, becomes encapsulated in a fibrous sheath, and remains in the tissue as a foreign body unless it is surgically removed (e.g., skin sutures) or excreted. Absorbable sutures may be fabricated as monofilaments or multifilaments. The first are single-stranded fibres which have no braiding or twisting; the latter are generally braided but sometimes twisted or spun and may be coated with wax, silicone, or other polymers to decrease capillarity and improve handling properties [9].

The newer monofilament sutures can be compared with the older multifilament sutures as shown in Table 1.2.

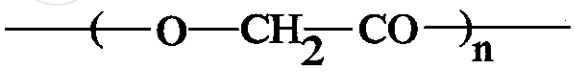
Table 1.2 Comparison of the properties of multifilament and monofilament absorbable sutures relevant to surgery [10-15].

Multifilaments	Monofilaments
1. Tissue reaction can occur easily	1. Tissue reaction much less pronounced
2. Soft and flexible	2. Springy and less flexible

Table 1.2 (continued)

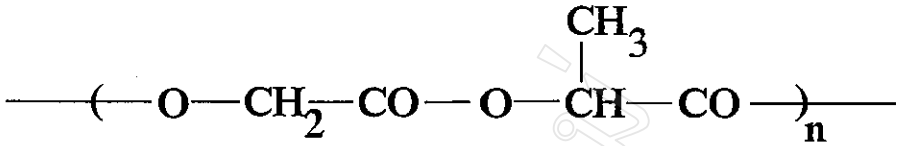
Multifilaments	Monofilaments
3. High coefficient of friction	3. Low coefficient of friction
4. Good knot security	4. Reduced knot security
5. Convenient and easy to handle	5. Less easy to manipulate due to their inherent springiness
6. Rapid absorption (usually within 8-12 weeks)	6. Slower absorption (up to 6 months or longer)
7. Narrow temperature range for processing	7. Wider temperature range for processing

Polyester fibres derived from the lower α-hydroxy acids, such as glycolic acid and lactic acid, were found to have suitable mechanical and biological properties for use as absorbable sutures. Thus poly(glycolic acid) (DEXON : Davis & Geck, American Cyanamid Co.) and poly(glycolic acid-co-lactic acid) (VICRYL : Ethicon, Johnson & Johnson) were introduced in the 1970s. Both are braided multifilament sutures that degrade in vivo by simple hydrolysis. The chemical structures of DEXON and VICRYL are as shown below:



DEXON (Davis & Geck, American Cyanamid Co.)

poly(glycolic acid)



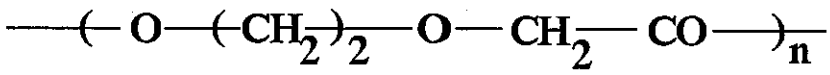
VICRYL (Ethicon, Johnson & Johnson)

poly(glycolic acid-co-lactic acid)

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: poly(glycolic acid-co-trimethylene carbonate) and polydioxanone, going under the trade names of MAXON and PDS respectively. They succeed in overcoming most of these problems. The chemical structures of MAXON and PDS are as shown below:

MAXON (Davis & Geck, American Cyanamid Co.)

poly(glycolic acid-co-trimethylene carbonate)



PDS (Ethicon, Johnson & Johnson)

polydioxanone

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, the older multifilaments, DEXON and VICRYL, are still the most commonly used absorbable sutures at the present time [16].

1.5 Copolymerization of Glycolide with Other Cyclic Monomers [17]

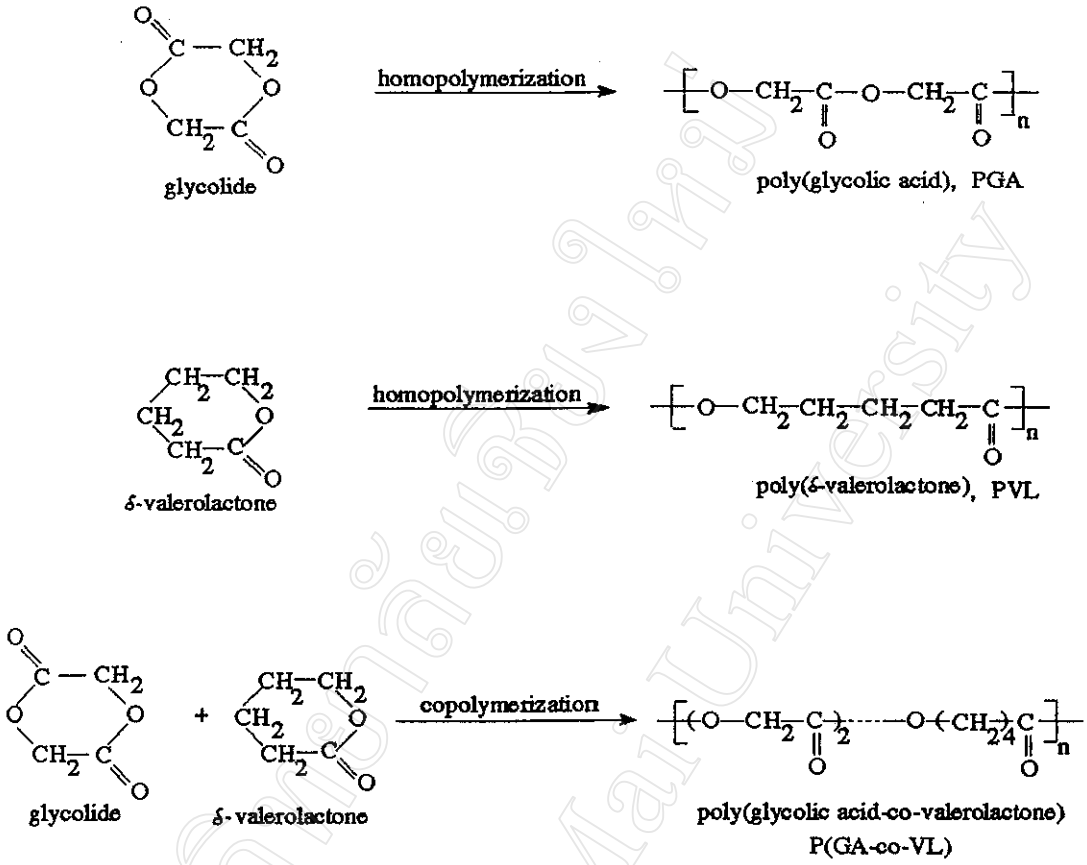
Glycolic acid is a component of the metabolism of numerous organisms and thus possesses an extremely low toxicity. Furthermore, its polyester, poly(glycolic acid), and its copolyesters with other cyclic ester monomers have extremely low immunogeneities and are biodegradable even in the human body. Owing to these advantageous properties, poly(glycolic acid) and other cyclic copolyesters have found increasing use in various pharmaceutical and medical applications, such as drug delivery systems and surgical sutures.

Poly(glycolic acid), synthesized from glycolide as the monomer, is a highly crystalline material with a relatively high melting range (200-220^{o}C) so that any processing in the melt entails the risk of thermal degradation. Due to the combination of its chemical structure and high crystallinity, poly(glycolic acid) is insoluble in all common organic solvents, so that processing from solution is not feasible. Hence, the incorporation of more flexible comonomers should be a suitable means of modifying the properties of poly(glycolic acid) in the directions of a lower melting range, lower melt viscosity and better solubility.

Examples of cyclic esters which may used as comonomers with glycolide include β-propiolactone, β-butyrolactone, δ-valerolactone and ethylene carbonate.

1.6 Aims of This Study

The main aim of this research project is to follow the changes in various properties occurring during the <u>in vitro</u> biodegradation of some new biodegradable polyesters. The polyesters of particular interest are the homopolymers and copolymers of glycolide and δ-valerolactone, as shown below:



Prior to this, the polymers will be synthesized and then characterized in terms of their chemical structure, morphology and probable molecular weight range. Wherever possible, the polymers will be melt spun into monofilament fibres. It is hoped that the results obtained will lead to a greater understanding of the structure-property relationships involved in the overall biodegradation process.