CHAPTER 1

INTRODUCTION

The widespread use of synthetic polymers in technology and in everyday life is an accepted feature of modern civilization. Polymers are now being used for almost every conceivable application and there is every indication that these uses will continue to increase in future years. However, there exists one important area in which the use of synthetic polymers has generally been cautious and limited - the area of medicine. Examples are in the applications of polymers in the biomedical field: artificial organs, prosthetic devices, surgical sutures, drug delivery systems, contact lenses, to mention but a few. The use of polymers in such applications brings together the specialized knowledge and research expertise of polymer scientists on the one hand and medical scientists on the other.

1.1 Biomedical Applications of Polymers : Sutures and Ligatures

The oldest medical writings are those recorded over 4,000 years ago by the Egyptians, who made reference to sinews and strings for ligatures and sutures. The Greeks were leaders in the field of medicine, and their techniques were later adopted by the Romans. Hippocrates described the use of sutures and ligatures, and Celsus, writing about sutures in his treatise "De Medicina Galen" in

the second century A.D., used silk and hemp cord for ligatures as well as strands of animal intestine to close the wounds of Roman gladiators.

John Hunter (1728-1793) and Philip Syng Physick (1768-1873) were the early English and American exponents, respectively, of sutures and their routine use in surgery. Physick, First Professor of Surgery at the University of Pennsylvania, has been credited with the development, in 1806, of absorbable ligatures using kid and buckskin.

Only in the past 50 years have the development and manufacture of suture materials been investigated in any detail. Synthetic absorbable materials, as well as other synthetic non-absorbable sutures, have been introduced only recently for use in surgery. Current refinements in the development of suture materials have yielded absorbable materials with plastic qualities that allow the formation of absorbable clips. Stapling techniques have also been introduced and developed within recent years. Many new devices are now available, including many specialized stapling instruments, as well as absorbable staples for the repair of internal organs. Future advances in the repair of surgical incisions, as well as in the healing of wounds, may include the use of specific biocompatible adhesives, as well as heat-sealing of knotted material to enhance the knot-breaking strength of ligatures and sutures.

Sutures can be classified as absorbable or non-absorbable, natural or synthetic, multifilament or monofilament. Basic suture materials are listed in Table 1.1

Table 1.1: Basic suture materials used in surgery.

Absorbable	Non-absorbable
Natural	Natural
Catgut	Silk
Plain	Cotton
Chromic	Metals (stainless steel, tantalum)
Collagen	
Synthetic	Synthetic
Polyglycolic acid (Dexon)	Poly(ethylene terephthalate), (Mersilene, Polydek, Tevdek, Ethibond, Tycron)
Polyglactin 910 (Vicryl)	Nylon (Ethilon, Dermalon, Braided Nurolon)
Poly-para-dioxanone (PDS)	Polypropylene (Prolene, Surgilene)
Polyglyconate (Maxon)	

1.2 The Need for Biodegradable Materials

A biodegradable polymer is a polymer that degrades in the human body . It has three major applications in medicine:

1) the temporary scaffold

2) the temporary barrier

3) the drug delivery matrix

The temporary scaffold has received the most attention and includes the absorbable (or soluble) suture. In this application, the natural tissue bed experiences a temporary weakness due to surgical trauma and requires artificial support. The healing wound has little strength during the first 6 days other than that of the coagulated protein-forming scab. The suture is used to hold both sides of the wound in close apposition until sufficient collagen synthesis has taken place to hold the wound together unassisted; movement of the healing surfaces results in thicker scarring. Seventy to eighty percent of total collagen synthesis usually occurs within the first 3 weeks, the final 20 to 30% requiring periods of 3 to 6 months. Although the suture is a clearly defined application, the availability of biodegradable polymers with the ideal combination of properties would broaden the scope of opportunities. Blood vessel, ureter, bladder, bile duct, and heart valve design could have added dimensions were it possible to use composite structures of biodegradable and non-biodegradable polymers. Were the biodegradable material tailored and fabricated correctly, tissue ingrowth might be controlled in such a way as to partially regenerate the natural structure. This in itself would be a major contribution to the field of prosthetic surgery,

since however satisfactory a prosthesis is, a major limitation is that of being non-repairing in the event of damage. The partially biodegradable composite is the potential answer to this problem.

The temporary barrier, although less widely applicable than the scaffold, is of similar importance in the field of tendon, spinal, and open heart surgery. Surgical adhesions caused by blood clotting and later fibrosis between the sliding surfaces of the tendon, or between the cardiac wall and the pericardial sac, cause pain , debilitation, and major problems during subsequent surgery. A temporary barrier which would stop adhesions forming and remain in situ until all the fibrin had been phagocytosed (at about 2 weeks), degraded, absorbed, and excreted, would be a further invaluable aid to the surgeon.

A drug delivery matrix is no less a challenge to the innovative polymer chemist in that the optimal drug delivery profile is as variable as the drugs available for different treatments. The problem reduces theoretically to one of being able to load a biodegradable polymer matrix with as high a concentration of drug as possible, that is, 50 weight percent, and to have the matrix degrade at a predictable rate so that the release of the drug into the tissues of the target organ is controlled. The matrix is simply a vehicle which should disappear as rapidly as possible after the pharmacologically active agent has been delivered. In practice however, 20 to 25 weight % is the upper limit for drug loading and the

delivery mechanism is usually a combination of matrix degradation and drug diffusion. The role of diffusion becomes more important as the hydrophilicity of the drug molecule increases and its molecular weight decreases. Most biodegradable polymers by their very nature are hydrophilic, and once water has penetrated the matrix, the more hydrophilic the drug, the more easily it is removed. The role of the biodegradable polymer thus becomes one of water-proofing the drug, and one special configuration of the biodegradable matrix is microencapsulation.

1.3 The Requirements of a Biodegradable Material

The initial requirements in the selection or design of any biodegradable material are that it should have:

- correct balance of mechanical properties;
- property-loss profile appropriate to application;
- degradation products: non-toxic and biocompatible;
- minimal tissue reaction;
- total mass loss within an acceptable period of time.

The mechanical properties are largely controlled by the structure, and especially whether the material is crystalline or amorphous, and the glass transition temperature (Tg). Where possible, 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. Tg not only affects the modulus, but also diffusion coefficients and hydrolytic stability.

The biodegradable polymer has additional requirements because it 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. The products of degradation are necessarily released into the adjacent tissues and therefore must be non-toxic and biocompatible. The degradation products should preferably be water-soluble, small molecules and, where possible, naturally occurring metabolites. In such cases, there is the chance that the degradation products will dissolve in the extracellular fluid as they are formed and be excreted via the kidney and the lung. The tissue reaction around the film of a biocompatible, biodegradable polymer is usually the formation of a thin fibrous capsule with an internal lining of microphages actively ingesting the breakdown products until mass loss is complete, at which time the capsule and attendant cells disappear.

Most of the biodegradable polymers currently used in medical applications are listed in Table 1.2. As seen from their structures, they are mainly aliphatic polyesters.

Table 1.2: Biodegradable polymers used in medicine.

BIODEGRADABLE POLYMERS		
Polymer Name	Commercial Name	Structure
Poly(glycolic acid)*	Dexon (sutures)	$(-O-CH_2-CO-)_n$
Poly((DL-lactic acid)	–	$(-O-\underset{\displaystyle H}{\overset{\displaystyle Me}{C}}-CO-)_n$
Poly(glycolic-co-lactic acid)*	Vicryl (sutures)	$(-O-CH_2-CO-O-\underset{\displaystyle H}{\overset{\displaystyle Me}{C}}-CO-)_n$
Polyvalerolactone	–	$(-O-(CH_2)_4-CO-)_n$
Poly(ϵ-caprolactone)	–	$(-O-(CH_2)_5-CO-)_n$
Poly(ω-decalactone)	–	$(-O-\underset{\displaystyle H}{\overset{\displaystyle nBu}{C}}-(CH_2)_4-CO-)_n$
Poly(hydroxy butyrate)	Biopol	$(-O-\underset{\displaystyle H}{\overset{\displaystyle Me}{C}}-CH_2-CO-)_n$
Poly(hydroxy valerate)	–	$(-O-\underset{\displaystyle H}{\overset{\displaystyle Et}{C}}-CH_2-CO-)_n$
Polydioxanone **	PDS (sutures)	$(-O-(CH_2)_2-O-CH_2-CO-)_n$
Poly(glycolic acid-co-trimethylene carbonate) **	Maxon (sutures)	$(-O-CH_2-CO-O-(CH_2)_3-O-CO-)_n$

NOTE: * = multifilament absorbable sutures

** = monofilament absorbable sutures

1.4 Surgical Sutures

Surgical sutures can be classified into two major groups:

(a) absorbable sutures

(b) non-absorbable sutures

Both kinds of sutures can be either synthetic or naturally occurring.

Absorbable sutures undergo rapid degradation in tissues and normally lose their tensile strength within 60 days; non-absorbable sutures, on the other hand, maintain their tensile strength for longer than 60 days. Previous research workers have reported that absorbable sutures therefore decrease the chance of stone formation, known to occur on suture materials in direct contact with the urinary stream. With non-absorbable sutures, a relatively high incidence of stone formation has been found.

1.5 Multifilaments versus Monofilaments

Multifilament sutures are monofilament fibers which are braided or twisted together. Hence, there are interstices formed by the relatively loose braid of the fibers 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. In this respect, monofilament sutures are preferable [1]. An 'in vivo' comparison of 'Maxon' and 'PDS' (monofilaments) with 'Vicryl' and chromic catgut (multifilaments) in fascial closure in rats has been reported [2]. The relative rates of tissue inflammatory response to these four different types of suture were as shown in Fig. 1.1.

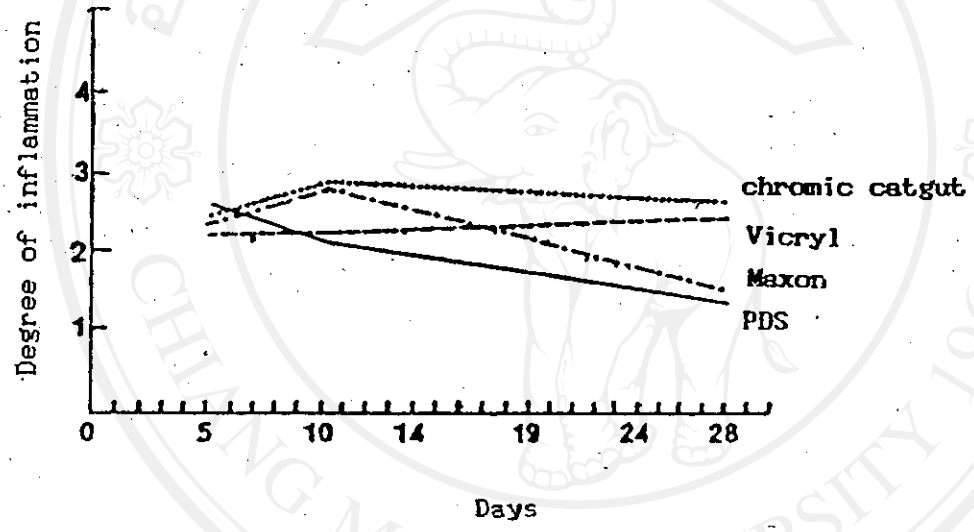

Fig. 1.1: Degree of wound inflammation at days 5,10 and 28 after surgery (fascial closure in rats) for chromic catgut, Vicryl, Maxon and PDS sutures [2].

From Fig.1.1, the degrees of tissue inflammation caused by the multifilament sutures were higher than those of the monofilaments. In the form of monofilaments, 'Dexon' and 'Vicryl' sutures are stiff and relatively inflexible. These polymers can be used as monofilament sutures only in the finest sizes. Consequently, because of their

stiffness, they are extruded into fine monofilaments and then braided. For multifilament sutures, their braided construction results in a coarse surface texture or high coefficient of friction. This has the disadvantages that it leads to difficulty in positioning knots and passing the suture through delicate tissue [3-5].

The physical configuration and composition of the multifilament absorbable sutures have undergone two distinct changes to improve their handling characteristics. Firstly, the diameters of the filaments used in the multifilament sutures have been reduced significantly in size to decrease their stiffness. In addition, the surfaces of these synthetic sutures have been coated to decrease their high coefficient of friction. The coating on 'Dexon' sutures, for example, is an absorbable surface lubricant, polyoxamer 188.

A monofilament absorbable suture, polydioxanone (PDS), has recently been developed. This polymer is processed into small granules and melt extruded through appropriate dies into monofilaments of any desired sizes. Another synthetic absorbable monofilament suture is the glycolide-trimethylene carbonate copolymer suture, trade name 'Maxon'. Glycolide-trimethylene carbonate is a linear random copolymer made by reacting trimethylene carbonate and glycolide with diethylene glycol as the initiator and stannous chloride dihydrate as the catalyst. The strengths of these monofilament sutures is maintained 'in vivo' much longer than those of the multifilaments.

As mentioned previously, the multifilament absorbable sutures are normally not used in monofilament form because they are too stiff for general surgical use. However, 'PDS' and 'Maxon',can be used as monofilaments because they have ether (C-O-C) and trimethylene $\leftarrow CH_2 \rightarrow_3$ bonds in their chemical structures to make them more flexible. It is the biodegradation characteristics of these monofilaments which now forms the main part of this research work together with the design and synthesis of a new polymer for potential use as a monofilament suture.

1.6 Mechanisms of Biodegradation

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

(1) solubilization

(2) ionization followed by solubilization

(3) enzymatically-catalyzed hydrolysis

(4) simple hydrolysis

1.6.1 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. Examples of polymers that degrade by solubilizing are given below:

(a) Poly(vinyl alcohol) (PVA)

The type and degree of stereoregularity has a powerful effect on the solubility of PVA . The atactic isomer is more soluble than the isotactic isomer, whereas the syndiotactic isomer has an extremely low solubility. The effect of tacticity is exerted through the degree of interchain hydrogen bonding that can be brought into play. This has been shown to be particularly important when orientation and annealing is used. PVA has many applications; for example, PVA cross-linked by formaldehyde has been used in surgery, PVA cross-linked by anhydrides and diacyl chlorides have been studied for use as drug delivery matrices, and PVA itself is commonly used in creams and cosmetics as a water thickening agent.

(b) Poly(ethylene oxide) (PEO)

PEO is available in molecular weights commonly ranging from 200 to 6,000 and from 300,000 to 400,000. By adjusting the blend of high and low molecular weight components, it is possible to vary both the softening point and rate of solubility. This type of polymer has been used as the base for tablets, suppositories and creams.

1.6.2 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.

'Gantrex' resins provide examples of this type of biodegradation mechanism. They are copolymers of methyl vinyl ether and maleic anhydride. When these polymers are placed in a low pH environment, that is below the pKa, ionization of the surface layers takes place. These polymers are used for enteric coatings on tablets, while drugs that would be damaged by the acidic environment of the stomach can be encapsulated in this type of polymer, enabling them to undergo safe transit to the neutral duodenum or small intestine where the coating dissolves and releases the drug in an environment where it is active and able to be absorbed.

1.6.3 Enzyme-catalyzed Hydrolysis

Enzymes have more effect in naturally occurring sutures than in synthetic sutures. The major constituent of gut is collagen, with elastin and mucopolysaccharides as minor components. Collagen is digested by protease under acidic conditions. Salthouse et al [6] showed that the mechanism by which gut and collagen sutures degrade is by sequential attack by lysozomal enzymes.

Williiams et al [7] showed that degradation rates can be accelerated in the presence of certain enzymes at the pHs where they exhibit their maximum activity. They reported that certain enzymes (such as esterase and carboxypeptidase) are able to influence the rate of hydrolysis in poly(glycolic acid). Reed and Gilding [8] have shown that the 'in vivo' absorption of poly(lactic acid) has an enzymatic component to the total hydrolytic mechanism. There is about 18% greater loss in Mw at 4 months 'in vivo' than 'in vitro' in 0.2 M pH 7 phosphate buffer at 37°C.

1.6.4 Simple Hydrolysis [9]

Simple hydrolysis is the depolymerization process which can be seen as the reverse of polycondensation. It is feasible in the aqueous extracellular fluid. A number of conditions have to be met in this respect:

(a) the polymer has to contain hydrolytically unstable bonds;

(b) for any significant degradation to occur, 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 take place at the physiological pH (around 7.4) and temperature (37°C).

Heterochain polymers, particularly those containing oxygen and/or nitrogen atoms in the main chain, are generally susceptible to hydrolysis. Depending on the structure, this hydrolysis may be favoured by either acid or alkaline conditions and, naturally, is much faster at elevated temperature.

1.7 The Phenomena of Biodegradation [10]

When inserted in the aqueous environment of the body, polymers may be considered to undergo four stages of degradation (Table 1.3).

Table 1.3: Four stages of polymer degradation 'in vivo'.

Stage	Effect	Molecular Change
1	Hydration	Disruption of van der Waals forces and hydrogen bonds
2	Strength Loss	Initial cleavage of backbone covalent bonds
3	Loss of Mass Integrity	Further cleavage of covalent bonds to polymer molecular weight levels insufficient for mass coherence
4	Mass Loss (Solubilization)	Dissolution of low molecular weight species and phagocytosis of small fragments

1.7.1 Hydration

Hydration is variable in rate, degree and effect, and is dependent upon the nature of the polymer. Natural polymers such as collagen rapidly absorb appreciable quantities of water so that there is an almost immediate and significant reduction in strength compared to the unimplanted control. Synthetic materials, such as poly(glycolic acid), absorb little water and display negligible changes in physical properties during the hydration stage. This stage of absorption may be considered complete within minutes or hours after implantation unless, of course, the implant volume is so large that the diffusion of water into the mass simply takes longer. During this stage, few, if any, covalent bonds are broken. The primary effects result from disruption of secondary and tertiary structures stabilized by van der Waals forces and hydrogen bonds.

1.7.2 Strength Loss

The second stage of degradation is manifested by the irreversible loss of implant strength, usually as a result of covalent bond cleavage involving the polymer backbone. In the case of absorbable polyesters, the rate of strength loss is governed entirely by the rate of simple hydrolytic cleavage of the polymer backbone and is independent of any known enzyme systems. In this class of polymers, the strength loss rate is dependent upon temperature, pH and especially upon the degree of crystallinity of the polymer. More highly crystalline species may be expected to maintain their strength

for longer periods of time compared with those which are more amorphous. At the end of this second stage, most if not all of the original mass is still present.

1.7.3 Loss of Mass Integrity

This stage involves the beginning of the absorption or mass loss process. In what may be considered to be a continuation of the previous stage 2 covalent bond breaking, the polymer is degraded to a molecular weight level below that required for mass coherence and a friable or gelatinized mass which may fragment or partially solubilize results. It is during and after this stage 3 that the actual mass loss or absorption occurs.

1.7.4 Mass Loss (Solubilization)

The complete removal of polymer from the body tissue may be considered as the fourth and final stage of absorption. The polymer may lose mass simply by the solubilization of low molecular weight species into the extracellular fluid. Alternatively, small fragments may be removed from the implant site by phagocytes and eventually carried to the lymphatic system for completion of the solubilization process.

It is also possible that polymeric masses may be removed from implant sites without actual reduction in the chain length through solubilization processes involving side chain modification rather than backbone scission. Poly(vinyl alcohol) derivatives are an example of this.

1.8 Aim of This Study

The main aim of this project is to study the various structure-property requirements for a synthetic polymer to be used as an absorbable monofilament surgical suture. By carrying out comparative studies on existing commercial materials, it is hoped that ideas can be generated for the development of new materials with improved properties - in particular, enhanced flexibility.

The steps involved in this study are :

(1) physical characterisation of currently available commercial monofilament absorbable sutures ('PDS II' and 'Maxon');

(2) biodegradation studies 'in vitro' (both absorbable and non-absorbable);

(3) design and synthesis of new polymers which have potential for use as a monofilament suture.

It is hoped that the results of this study will provide some useful pointers towards the future development of a new monofilament suture for use in surgery.