CHAPTER 1

INTRODUCTION

Traditional applications of synthetic polymers are mostly base on their relative inertness to biodegradation compared with natural macromolecules such as cellulose and proteins. Concerns about preventing or retarding attack on polymers by bacterial, fungi, insects and other animals provided the early incentive for the study of biodegradation of polymers. Now the use of synthetic polymers has accelerated to the extent that the disposal of the polymer products currently in use has become increasingly difficult. One of the important current incentives for the study of biodegradable polymers is their easier disposal. Moreover, biodegradable polymers are useful for application such as sutures, surgical implants, controlled-release formulations of drugs and agricultural chemicals [1].

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. The generally accepted definition of "polymer biodegradation" is: hydrolytic, enzymatic or bacteriological degradation processes occurring in a polymer which do not necessary proceed to a stage where the physical form of the polymer is altered [2].

Biodegradable polymers can be either natural or synthetic. In general, synthetic polymers offer greater advantages than natural materials in that they can be tailored to give a wider range of properties and more predictable lot-to-lot uniformity than can materials from natural sources. Synthetic polymers also represent a more reliable source of raw materials, one free from concerns of immunogenicity [2].

Polymers prepared from glycolic acid and lactic acid have found a multitude of uses in the medical industry, beginning with the biodegradable sutures first approved in the 1960s. Since that time, diverse products based on lactic acid and glycolic acid and on other materials, including poly(dioxanone), poly(trimethylene carbonate) copolymers, and poly(ε-caprolactone) homopolymers and copolymers have been accepted for use as medical devices [2]. These polymers are the most popular biodegradable polymers used in medicine since aliphatic ester bonds facilitate hydrolytic degradation by body fluid. Some examples of biodegradable polyesters currently used in medicine are listed in Table 1.1 [3].

Table1.1 Some biodegradable polymers used in medicine [3].

Polymer Name	Trade Name	Application	Chemical Structure
Poly(glycolic acid)	DEXON	SS	$-(O\text{-}CH_2\text{-}CO)_n-$
Poly(DL-lactic acid)	-	DRM	$-(O\text{-}CH(CH_3)\text{-}CO)_n-$
Poly(glycolide-co-lactic acid)	VICRYL	SS	$-(O\text{-}CH_2\text{-}CO\text{-}O\text{-}CH(CH_3)\text{-}CO)_n-$
Poly(δ-Valerolactone)	-	DRM	$-(O(CH_2)_4CO)_n-$
Poly(ε-caprolactone)	-	DRM	$-(O(CH_2)_5CO)_n-$
Poly(hydroxy butyrate)	BIOPOL	DRM	$-(O\text{-}CH(CH_3)\text{-}CH_2\text{-}CO)_n-$
Poly(p-dioxanone)	PDS	SS	$-(O(CH_2)_2O\text{-}CH_2\text{-}CO)_n-$

SS = Surgical Suture (absorbable)

DRM = Drug Release Matrix

1.2 The Need for Biodegradable Materials [4]

Biodegradable polymer 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 include the absorbable (or soluble) sutures. 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. Seventy to eighty percent of total collagen synthesis usually occurs within the first 3 weeks, the final 20 to 30 % require 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.

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 polymer chemist in that the optimal drug delivery profile is as variable as the drugs available for different treatments. The problem reduces to one of being able to load a biodegradable polymers 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 tissue of 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 become more important as the hydrophilicity of the drug molecule increase and its molecular weight decrease. Most biodegradable polymer by their very nature are hydrophilic, and once water has penetrated the matrix, the more hydrophilic the drug, the more easily it is removed.

1.3 The Requirements of a Biodegradable Material [4]

The initial requirement 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 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 desires period. The onset of loss of mechanical properties may be 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 preferable be water-soluble, small molecules and, where possible, naturally occurring metabolites. 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 microphage actively ingesting the breakdown products until mass loss is complete, at which time the capsule and attendant cells disappear.

1.4 The Use of Polymers as Surgical Sutures [5]

In recent years, polymer have found increasing use in the development of biodegradable implants for use in surgical applications, such as absorbable sutures and drug release matrices. Surgical sutures are sterile filaments used to hold tissues together until they heal adequately for self-support or to join tissues with implanted prosthetic devices. They are normally attached to needles for coaptation of the edge of wounds or surgical incision.

The sutures which are used in surgical applications can be devided into 2 main types: absorbable sutures and non absorbable sutures.

1.4.1 Absorbable Sutures

An absorbable suture is a polymer which has the ability to biodegrade by hydrolysis. In human tissue, it usually degrades and absorbs within 60 days. There are 2 types of absorbable sutures:

a) Natural absorbable sutures; such as catgut (from female sheep's intestine).
b) Synthetic absorbable sutures; such as poly-α-esters, for example, poly(lactic acid) and poly(glycolic acid).

More recently, polyoxalates, polydioxanones and various copolymer modifications have added to the growing range of materials now available to meet the growing demands of medicine.

1.4.2 Non absorbable Sutures

Similarly, there are 2 types of non-absorbable sutures:

a) Natural non-absorbable sutures; such as silk and cotton.
b) Synthetic non-absorbable sutures; such as nylon, poly(ethylene terephthalate) and polypropylene.

Various sutures of all four types are listed in Table 1.2

Table 1.2 Suture materials used in surgery [5]

Absorbable	Non-absorbable
Natural Catgut Collagen	Natural Silk Cotton Metal (stainless steel, tantalum)
Synthetic a) Multifilament Poly(glycolic acid); DEXON Poly(glycolic acid-co-lactic acid); VICRYL b) Monofilament Poly-p-dioxanone; PDS Poly(glycolic acid-co-trimethylene carbonate); MAXON	Synthetic Poly(ethylene terephthalate) Nylon Polypropylene

1.5 Monofilament Versus Multifilament Sutures [6]

Synthetic absorbable sutures have the longest history in clinical applications among biodegradable polymers and still have the highest sales. There are two kinds of absorbable sutures when classified from the filament type:

1. monofilament,
2. multifilament or braided sutures.

Both have advantages and disadvantages.

1.5.1 Monofilament [5]

Monofilament sutures are single-stranded fibers which have no braiding or twisting. Their physical form can be shown as in Fig. 1.1. They are commonly prepared by a melt spinning process.

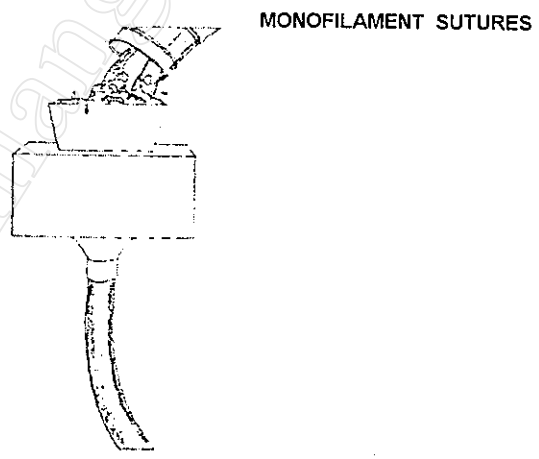

Fig. 1.1 The physical form of a melt-spun monofilament sutures.

1.5.2 Multifilaments

Multifilament sutures are composed of monofilament fibers which are braided or twisted together. Their physical form can be shown as in Fig. 1.2.

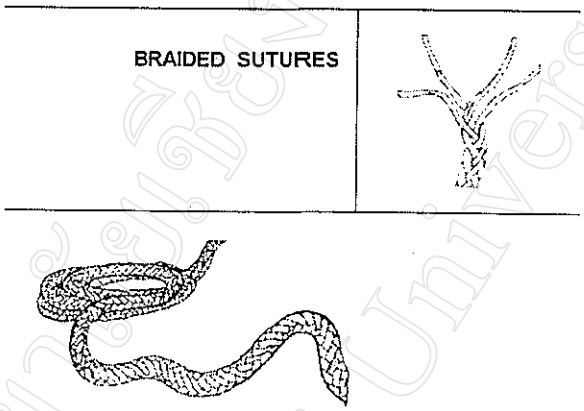

Fig. 1.2 The physical form of a braided multifilament sutures.

1.5.3 Comparison of Performance Characteristics in Surgery [5]

Monofilament sutures can be compared with multifilament sutures in surgery as shown in Table 1.3.

Table1.3 Comparison of the properties of monofilament and multifilament absorbable sutures in surgery.

Multifilament	Monofilament
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.Reduce 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)

Note1: In multifilament sutures, there are interstices formed by the relatively loose braid of the fibers which permit serum and blood to penetrated the suture and form a perfect refuge for bacteria. Therefore, multifilament sutures should not be used in an infected wound of in one likely to become infected.

Note2: The braiding of multifilaments causes their 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).

1.6 Commercial Sutures

In the early 1970s, the introduction of synthetic absorbable sutures, DEXON (trade name of Davis & Geck) and VICRYL (trade name of Ethicon, Johnson & Johnson) was an important event. Both are braided sutures that degrade in *vivo* by hydrolysis. Although the handling properties were improved by coating DEXON with Poloxamer 188 and VICRYL with calcium stearate and a 70/30 copolymer of lactide and glycolide, the need for monofilament absorbable sutures still remained unfulfilled. In the 1980s, that need was satisfied when the MAXON (trade name of Davis & Geck) and PDS (trade name of Ethicon, Johnson & Jonhson) monofilament absorbable sutures became commercially available. In 1995, the MONOCRYL (trade name of Ethicon, Johnson & Johnson) was developed for use as an absorbable monofilament suture and seems to have better handling properties than MAXON and PDS. These monofilament products have longer in *vivo* life than the braided sutures (except for MONOCRYL) giving surgeons an additional choice to replace nonabsorbable sutures. These sutures, like ealier synthetic braided sutures, degrade by hydrolysis.

In addition to those commercial sutures, the search for new biomaterials is progressing at a fast peace, as judged from the number of patents that have been issued recently. Suture materials, based on monomers such as oxalate, succinate, and other copolymers having both amide and ester linkage in the polymer chain, have been patented for suture use. In this section only PDS II, MAXON and MONOCRYL are described.

1.6.1 Polydioxanone; PDS Sutures

An extensive research program has led to the discovery of a novel polymer which can be converted into a uniquely flexible monofilament suture of all size. It is known as polydioxanone suture marketed by Ethicon. It is prepared by ring opening polymerization of *p*-dioxanone, in the presence of a suitable catalyst (Fig. 1.3) [7]. The polymer should be processed at the lowest possible temperature to prevent depolymerization back to monomer.

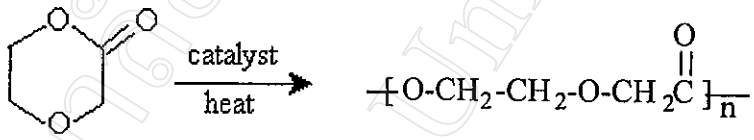

Fig. 1.3 Synthesis of poly(dioxanone) (PDS) [8]

Poly(dioxanone) has about 55% crystallinity with a glass-transition temperature of –10 to 0°C. Poly(dioxanone) demonstrated no acute or toxic effect on implantation. Recently, 'PDS II' has appeared on the market as an improved version of PDS. It is still the same polymer, poly(dioxanone), made by the same company, by with slightly improved flexibility. Poly(dioxanone) is a colorless, crystalline polymer. Violet colored polymer is produced by adding drug and cosmetic violet No.2 dye [4].

Table 1.4 summarized the physical properties of a typical size 00 poly (dioxanone) monofilament.

Table 1.4 Properties of poly(dioxanone) monofilament suture, size 00 [7].

Physical Property	Value
Diameter	13 mils
Straight tensile strength	80,000 p.s.i.
Knot strength	50,000 p.s.i.
Elongation to break*	30 percent
Young's modulus**	250,000 p.s.i.

* Per cent increase in suture length at breaking point.

** A measure of filament flexibility or pliability derived from stress strain characteristics; inversely proportional to flexibility.

p.s.i., Ponds per square inch.

Like poly(glycolic acid) suture, PDS suture is also a polyester which degrades by hydrolysis in the body. It loses 50% of its initial breaking strength after 3 weeks and is absorbed within 6 months, providing an advantage over DEXON or other products for low-healing wounds.

A comparison of the *in vivo* (rat) breaking strength retention of PDS and two multifilament, DEXON and VICRYL, is shown in Fig. 1.4.

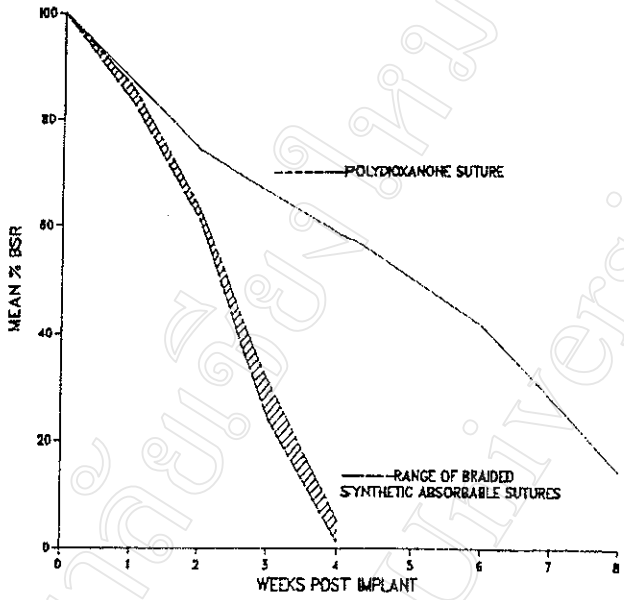

Fig. 1.4 Average breaking strength retention, BSR of monofilament poly(dioxanone) (PDS) suture following implantation in the subcutis of rats compared with the range of similarly derived data for multifilament (DEXON and VICRYL) sutures. Data expressed as average percentage of original, unimplanted strength [9].

1.6.2 MAXON Sutures [9]

Poly(glycolic acid) absorbable sutures (PGA), have been used routinely in general and in many surgical specialities. These sutures degrade in tissues by hydrolysis which breaks the filaments of the sutures into small fragments. The fragments are phagocytized by the enzymatic action of the mononuclear and the multinuclear cells. The strength of PGA and PGA-like sutures is significantly stronger for longer periods of time in the host than conventional catgut sutures. However, PGA is stiff and inflexible. To overcome this problem an extensive research and development effort was

undertaken to develop polymeric structures which would yield flexible, strong and absorbable monofilament sutures. This goal was met by incorporating a softer component into the PGA matrix: This produce a material which was capable of easy manipulation and the formation of secure knots. The new suture is made from a copolymer of glycolide and trimethylene carbonate. It has been given the trade name of MAXON (Devis and Geck).

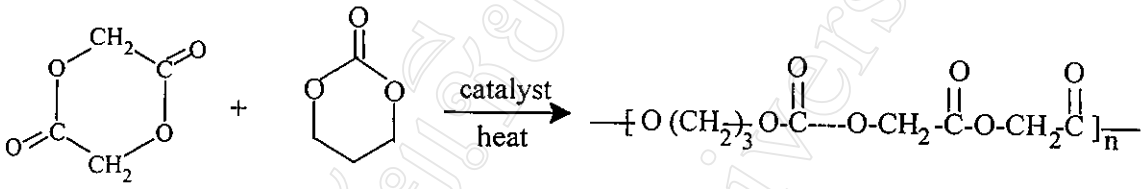

Fig. 1.5 Synthesis of poly (glycolide-co-trimethylene carbonate) (MAXON).

MAXON is a linear copolymer made by reacting trimethylene carbonate (TMC) and glycolide with diethylene glycol as an initiator and stannous chloride dihydrate as the catalyst. The two constituents are combined in the ratio of approximately 2:1 in a random copolymer type structure [4], as shown in Fig. 1.5.

The MAXON sutures are available in the natural clear color or green (colored by green DG #6). The dye is added at the level of no greater than 0.3 per cent. Clear or green sutures are cut into required lengths and appropiate needles attached.

The out of package strength in pounds per square inch (psi) of MAXON sutures taken from the packages was greater in knot and straight-pull than polypropylene or nylon sutures.

Comparisons of MAXON with PGA braided synthetic absorbable sutures are shown in Fig. 1.6. Percent retention of both materials was quite high and similar at 14 days. Thereafter, PGA sutures lost strength fairly rapidly. The strength retained of MAXON sutures was much greater and persisted at reasonable levels for six weeks.

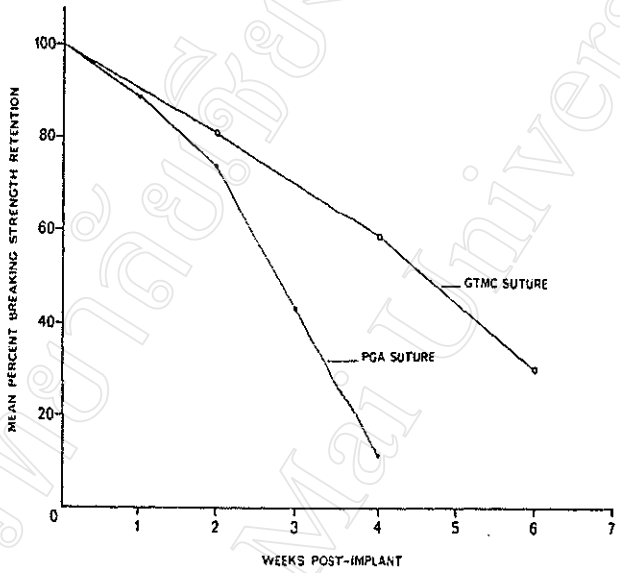

Fig. 1.6 Comparison of poly(glycolic acid) (PGA) braided sutures and MAXON. The mean retention of strength as a percentage of package values after implantation into the subcutaneous tissues of rats is shown.

1.6.3 MONOCRYL Sutures

Synthetic absorbable sutures are available as braided constructions or as monofilaments. Braid absorbable sutures are made either from polyglactin-910, a 90:10 copolymer of glycolide and lactide, sold by Ethicon, under the trade name VICRYL, or from polyglycolide, sold by Davis and Geck under the trade name DEXON. Except for fine sizes, the monofilaments derived from these polymer are relatively stiff and mainly braided sutures are produced from polyglactin 910 and its variants. However, there are some concerns with braided sutures that relate to tissue drag and trauma. Other concerns with braided sutures include the possible potential of infection through the interstices of the braided structure.

To eliminate some of the concerns of braided sutures, absorbable monofilament sutures, PDS II and MAXON have been introduced. Even though some advances have been made with these monofilament, monofilament do not handle as well as braids. To overcome these problem, a major research program was initiated which led to the development of MONOCRYL (poliglecaprone25), the most pliable synthetic absorbable monofilament suture marketed. These monofilaments are derived from a segmented copolymer of ε-caprolactone and glycolide. This complex polymeric system contains soft segments of a random copolymer of ε-caprolactone and glycolide which provide good handling characteristics, and hard segments of polyglycolide which provide high strength (see Fig. 1.7).

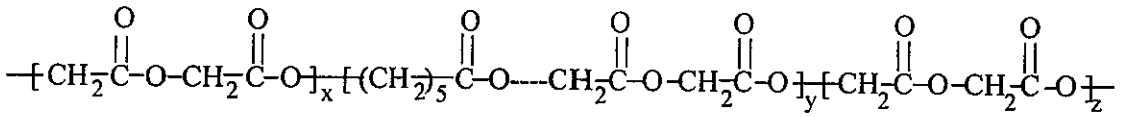

Fig. 1.7 Molecular structure of MONOCRYL [10].

The overall optimium composition of this copolymers was about 25 mol% ε-caprolactone and 75 mol% glycolide repeating units. The copolymer composition of glycolide:ε-caprolactone in the middle block was about 55:45 mol%.

The physical properties of size 2-0 MONOCRYL suture are compared in Table 1.5 to the following commercial absorbable sutures: VICRYL, PDS II and Chromic Gut.

Table 1.5 Physical property comparison of size 2-0 absorbable sutures [10].

Material	Diameter (mils)	Straight-pull Strength (psi)	Knot-pull Strength (psi)	Elongation (%)
MONOCRYL	15.03	91,100	45,700	39
PDS II	13.93	70,700	48,400	51
Chromic Gut	15.70	46,700	23,200	22
VICRYL	13.74	103,000	54,000	24

The breaking strength retention profiles of size 2-0 MONOCRYL, PDS II, VICRYL and Chromic Gut suture are compared in Fig. 1.8 [10].

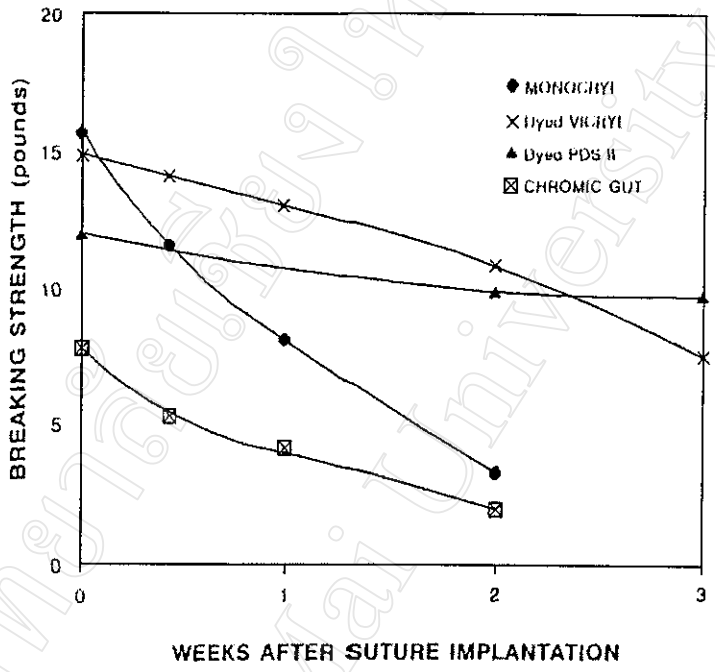

Fig. 1.8 Average breaking strength of size 2-0 MONOCRYL, VICRYL, PDS II and Chromic Gut sutures as a function of implantation time in the subcutis of rats.