CHAPTER 2

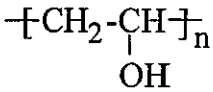
POLYMER BIODEGRADATION

2.1 Mechanism of Biodegradation [4]

There are four major mechanisms that can be utilized in the design of biodegradable polymers: solubilization, ionization followed by solubilization, enzymatically catalyzed hydrolysis and simple hydrolysis.

2.1.1 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. Since large molecular weight are involved, the degree of fluid flow at the interface is a prime factor in the dissolution process. Mechanical movement and flexing of device within the tissue bed, if excessive, will lead to fragmentation as the material swells and softens. An example of a solubilizable polymer is poly(vinyl alcohol).



poly(vinyl alcohol)

2.1.2 Ionization followed by Solubilization

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

"Gentrex" 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 take place.

2.1.3 Enzyme-Catalysed Hydrolysis

Enzyme-catalysted biodegradation is perhaps the classical mechanism by which implants are removed from the body, as prior to 1960, the only biodegradable material used in medicine was the absorbable suture, catgut. Catgut is inherently weak relative to synthetic sutures and the tensile loss profile is extremely unpredictable. The major constituent of catgut is collagen and mucopolysaccharides as minor components.

The mechanism by which catgut and collagen sutures degrade is by sequential attack by lysozomal enzymes. In muscle, the initial attack is by acid phosphatase, and this is sustained over the period where the major loss of strength occurs. Leucine aminopeptidase activity was demonstrated to be low initially but increase as the acid phosphatase activity declines; this is the major catalytic force during the absorption period.

2.1.4 Simple Hydrolysis

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. 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 7.40) and temperature (37°C)

Heterochain polymers, particularly those containing oxygen and/or nitrogen atom in the main chain, are generally susceptible to hydrolysis. Depending on the structure, this hydrolysis may be favored by either acid or alkaline conditions and, naturally, is much faster at elevated temperatures. Polymers which have been shown to degrade by simple hydrolysis *" in vivo"* are polyesters, polyamides (nylons and poly (amino acids)), and some polyurethane and cyanoacrylates.

2.2 The Phenomena of Biodegradation [4]

When inserted in the aqueous environment of the body, polymers may be considered to undergo four stages of degradation (Table 2.1).

Table 2.1 Four stages of polymer degradation *in vivo*.

Stage	Effect	Molecular Changes
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

2.2.1 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 pol(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, is 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.

2.2.2 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 system. 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.

2.2.3 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.

2.2.4 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.

Fig. 2.1 compares the typical property loss profiles for the polymer molecular weight, strength, and mass reduction changes which occur during suture absorption. From these profiles, the absorption process can be interpreted as comprising four distinct stages, as described in Table 2.1.

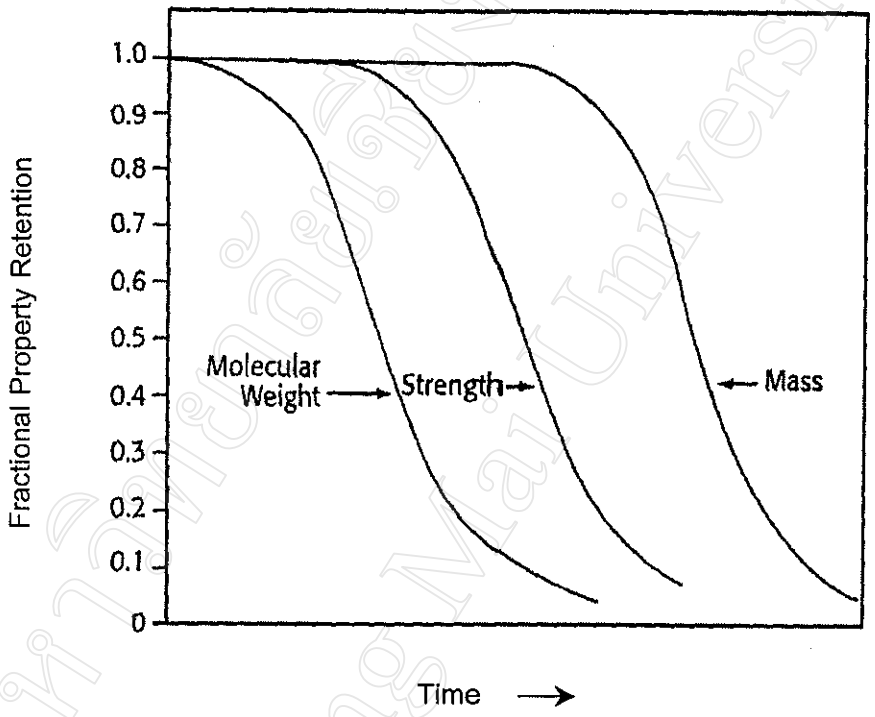


Fig. 2.1 Generic curves showing the sequence of polymer-molecular weight, strength, and mass-reduction over time [2].

2.3 Testing for Biodegradation

The testing of materials for biomedical applications involves investigating the biocompatibility and/or the degradability of these materials. Test methods, test conditions and parameters relevant to the desire applications of the materials should be selected. Studies of biomedical polymer degradation are usually carried out in the sequence.

1. *in vitro* testing
2. *in vivo* testing
3. clinical trial

2.3.1 *In Vitro* Testing [11]

In vitro investigations are of considerable importance in evaluating the functionality and durability of a material. *In vitro* testing of polymers for biomedical applications often involves degradation in blood serum and degradation with isolated tissue. Such testing is similar in certain ways to test with microorganisms. The observed degradation might be a combination of enzyme-catalyzed degradations as well as nonemzyme-catalyzed degradations. *In vitro* degradation experiments are generally carried out before *in vivo* experiments to reduce the cost and time required for the latter.

The development of *in vitro* models of the physiological environment is of importance in the understanding of the basic mechanisms occurring *in vivo*. *In vitro* modeling, in principle, allows the physiological environment to be simplified. Degradation products can be isolated and obtained in relatively large quantities to enable complete characterization. This information, as a function of time, is the key to the elucidation of degradation mechanisms and kinetics.

To date, *in vitro* modeling has played a minor role in the development of biomaterials. However, from the commercial point of view the approach is crucial to the introduction of new products. Relative to animal testing, *in vitro* modeling is low cost, and allows larger statistical studies to be developed at a fraction of the cost of similar studies *in vivo*, which mean that smaller companies with lower resources may also contemplate advanced biomedical products. *In vitro* tests can never be a total replacement for animal testing; the animal must always be the primary reference. However, when a battery of *in vitro* tests have been shown to be equivalent to the *in vivo* situation, it allows itself to be applied more extensively to probing, production and storage problems than could ever be contemplated with the animal model both on human and economic grounds.

2.3.2 *In Vivo* Testing [3]

For biomedical applications, *in vivo* experiments must be carried out after *in vitro* testing. A polymer device is implanted for a certain period in an animal and is then explanted for analyses of chemical and physical changes. Degradation products released from the implanted device and excreted by the animal can also be analyzed.

2.3.3 Clinical Trials

Clinical trials are the last step in the evaluation of a new material for use in a given biomedical application. However, as the long-term effects and the complication are seen only in patients, as many interim examinations of the implant as possible at re-operations should be made, not only when complications with the implant arise. Permission to conduct clinical trials is subject to legal procedures and necessitates close collaboration between the polymer scientists (the inventors) on the one hand and the medical practitioners (the end-users) on the other.

2.4 *In Vitro* Biodegradation Studies

In this chapter only *in vitro* testing was presented. This was performed by immersing the sample in the phosphate buffer saline (PBS) solution at the physiological pH and temperature of 7.40 and 37°C respectively.

From the literature, various other *in vitro* condition have also been used. Blood plasma, Krebs solution, citrate-phosphate buffer, boric acid-borax buffer, etc., can be used as the immersion medium. To study the effect of temperature on the *in vitro* degradation, the degradation temperature can be varied [11].

In order to follow the *in vitro* biodegradation of synthetic homo and copolyesters studied here, the following properties were monitored;

1. Weight loss (absorption)
2. Polymer Morphology (T_m, ΔH_f)
3. Material surface
4. Tensile strength

2.4.1 Weight Loss

Weight loss resulting from the degradation of a polymer requires the breakage of chemical bonds. Once chemical bonds start to break, reactive chain ends and free radicals are created. Degradation can then proceed either by depolymerization or by random chain scission. The dominant degradation mechanism may depend significantly on the details of structure and composition, including the types of end groups terminating, the polymer chains, and the presence of structural defect, additive or impurities.

It was found that all existing synthetic absorbable sutures belong to aliphatic polyesters, simple hydrolytic main-chain scission have been suggested to be their biodegradation process. This process is known to start in the amorphous regions and then extend to the crystalline domains. The hydrolytic scission of tie-chain segments located in the amorphous regions would be reflected in the observed loss of tensile properties, while the weight loss must come from the destruction of the crystalline domains which are not permeable to water [12].

The weight loss as a function of time can be influenced by various factors. Bittner et al., [13] found that both mass loss and molecular weight decay were accelerated in alkaline and acidic pH in the case of ABA triblock copolymer of poly (lactide-co-glycolide). Dahlmann et al. [1] who had studied the *in vitro* degradation of polylactides and poly(glycolide-co-lactide) with different glycolide contents also found that the weight loss is effected by the structure of polyester.

2.4.2 Polymer Morphology

The morphology of the biodegradable polyester is an important variable in the hydrolytic degradation process. In this regard, the amorphous/crystalline property of the polymer play a role in controlling the hydrolytic degradation process. The amorphous phase of the polymer is much more accessible to water than the crystalline phase. Consequently, amorphous polyesters degrade faster than semi-crystalline polyesters.

An example of an increase in the rate of hydrolysis arising from a reduction in crystallinity is provided by the copolymers of glycolic acid and lactic acid. This copolymers are degraded more rapidly than polyglycolic acid because of a reduction in the crystallinity; the 1:1 copolymer, which is totally amorphous, is hydrolyzed most rapidly.

It is expected that the degree of crystallinity will influence chemical and physical properties, such as swelling behavior and hydrolytic sensitivity of the polymer and, consequently, its rate of biodegradation.

The level of crystallinity of the sutures always increasing initially with hydrolysis time, reaches to a maximium, and then decreases thereafter. Fig. 2.2. illustrates this change in the level of crystallinity *in vitro* environment.

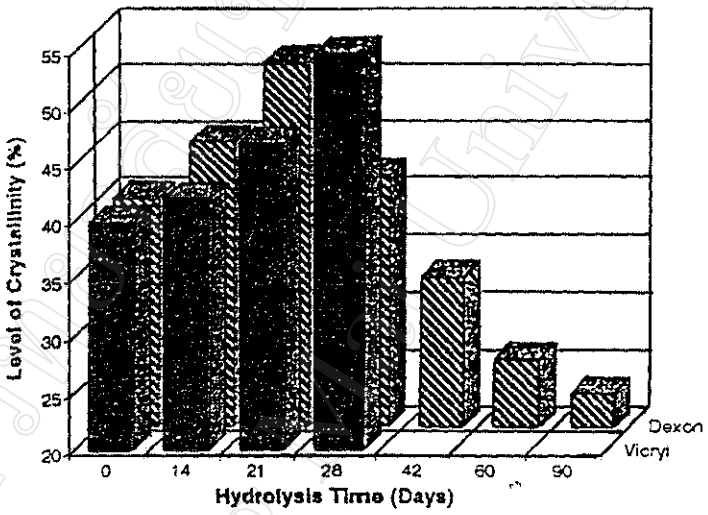


Fig. 2.2 The level of crystallinity of synthetic absorbable sutures upon *in vitro* hydrolysis in phosphate buffer [12].

The data in this figure indicate that the time where the peak level of crystallinity locates varies with the type of suture materials. The location of the peak could be used as an indicator by Chu to predict the rate of hydrolytic degradation and for examining the effects of various intrinsic and extrinsic factors on absorbable suture degradation.

Secondary crystallization was suggested to be the cause for exhibiting the maximium pattern of crystallinity with hydrolysis time. With the hydrolytic degradation in the amorphous regions during the early stage of hydrolysis, main-chain scission result in lesser degree of entanglement of long-chain molecules in these region. Therefore, the remaining undegraded chain segments in the amorphous regions acquire to an ordered state. Further crystallization is induced and an increase in crystallinity is expected and was indeed observed. The degree of crystallinity reaches a maximium and starts to decrease as hydrolysis proceeds to the second stage and destroys the crystalline lattice.

2.4.3 Material Surface

Surface morphological changes during degradation were followed after defined time intervals by means of scanning electron microscopy. Tomihata et al. [6] found that there is no morphological change on the P(LA/CL) suture surface in the course of hydrolysis within 2 weeks, but small cracks were formed on the surface vertically to the direction of fiber drawing when *in vitro* hydrolysis was allowed to take place for 32 weeks. Such regularly repeated crack formation was also observed for PDS II, MONOCRYL and MAXON [6]. Lin et al., [14] suggested that the accelerated weight loss coincided with a surface morphologic change observed by SEM. SEM micrographs showed that there was no visible surface crack or any surface alteration on PDS sutures before 90 days (corresponding to less than 9% weight loss). However, circumferential cracks started to appear in a regular manner at 120 days and followed by subsequent detachment of surface layer from the underneath fiber at 150 days. Other investigators reported that the appearance of longitudinal surface cracks on PDS sutures occurred as early as 28 days *in vitro* hydrolysis in Tris buffer, and that a combination of esterase and γ-irradiation accelerated the formation of these surface cracks on PDS sutures. The observed surface cracks were not unique to PDS suture fibers.

2.4.4 Tensile Strength

Along with the loss of molecular weight, the tensile properties and mass of absorbable suture also decrease with hydrolysis time. PDS and MAXON sutures, exhibited much longer tensile strength and mass retention than DEXON and VICRYL sutures. Monofilament MONOCRYL suture loses its tensile strength considerably faster than PDS and MAXON. Along with its faster loss of tensile strength among the three absorbable monofilament sutures, MONOCRYL loses its mass faster too [12].

Reed et al. Found that DEXON suture maintain 80% of the initial tensile strength for two weeks. From the practical view point this is important as a wound has little strength above that of coagulated fibrin up to 1 week, but is rapidly reinforced by collagen synthesis between 1 and 3 weeks. The observed asyncronization of tensile and mass loss profiles indicates that the degradation process may be complex. It also found that temperature has a dramatic effect on the rate of loss of tensile strength and mass.