The Mechanisms of Oxidative Degradation of Biomedical Polymers by Free Radicals

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SYNOPSIS

Degradation is an essential factor in polymer biocompatibility. The physiological environment of the human body can be aggressive to polymers. Most implanted polymers suffer degradation and the kinetics and mechanisms of the processes can be significantly affected by various biologically active species, especially enzymes, lipids, peroxides, free radicals, and phagocytic cells. Iron enhances the toxicity of oxygen free radicals. Superoxide and hydrogen peroxide can interact to form the very toxic hydroxyl radical in the presence of iron. The data have shown that the hydroxyl radical is likely to be one of the main causes of polymer degradation in implantable devices. © 1994 John Wiley & Sons, Inc.

INTRODUCTION

Polymer degradation is becoming an important subject in the synthesis and use of polymers in medicine and surgery. Previous work[1-4] has indicated the potential role of enzymes, peroxides, free radicals, phagocytic cells, and lipids in the degradation of polymers, but no coherent theory is available and, therefore, no procedure exists for predicting, evaluating, or avoiding this degradation.

Generally, it is thought that the polymers known to degrade significantly within the body are susceptible to hydrolysis and that *in vivo* degradation can be reproduced by simple aqueous solutions *in vitro*. The early work on polymer degradation was concerned with the principles that enzymes could influence synthetic polymers,[5,6] that lipids may accelerate degradation,[7] that the degradation is influenced by the nature of the cellular environment,[8] and that applied stress contributes to the phenomenon.[9,10] Ratner et al.[11] studied polymer degradation and indicated that oxidative degradation takes place. Vascular prostheses of poly(ether urethane), such as Biomer, have suffered degradation when macrophage cells are able to gain access to the very fine fibers of the microporous structure.[12] Williams et al. demonstrated the degradation of poly(ethylene terephthalate) by macrophages in culture.[13]

The aims of our studies have been to determine which mechanisms of polymer degradation are operative *in vivo* and what are the mediators of these processes. Biodegradable polymers were chosen for the initial studies, in which they were incubated in various solutions. Since these polymers are hydrolyzed in aqueous media, the rates of hydrolysis could be compared in the presence or absence of oxygen free radicals. We present here a discussion of the rationale of the approach, an overview of the available information, and a description of the results from these initial studies.

Biocompatibility is defined[14] as the "ability of a material to perform with an appropriate host response in a specific application." The host response refers to the influence of the material on the tissue. The appropriate host response is ideally minimal where the material is designed to be ignored by the tissues or specifically functional if the material is designed to play a biologically active or pharmaceutical role rather than a simple mechanical or physical action. The host response is usually determined by the chemical reactivity of the material, which with polymers may be related to the leaching of additives,

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Journal of Applied Polymer Science, Vol. 51, 1389–1398 (1994)
 CCC 0021-8995/94/081389-10

catalysts, and other residues as well as the degradation of the polymer itself. Although the specific material requirements will differ according to the nature of the application, it is a fundamental requirement that the polymer should display adequate biocompatibility. This implies that, for permanent implant applications, the material should not degrade within the physiological environment, nor should it have any harmful effect on the tissue, and that for short-term degradable prostheses, the rate of degradation and the release of degradation products should be physiologically harmless.[1]

Thus, it can be seen that polymer degradation is an important factor in the suitability of polymers for medical and surgical use. Several high molecular weight polymers are well accepted by the body, being nontoxic, and only additives and breakdown products cause difficulties.[15,16]

Biodegradation is defined[17] as "the gradual breakdown of a material mediated by specific biological activity." All polymers are susceptible to degradation,[18] but the conditions under which it takes place and the kinetics of the reactions are extremely variable. The degradation processes can be divided into two types: First are those that involve the absorption of energy, which then causes the propagation of molecular degradation by secondary reactions. Second, there are hydrolytic mechanisms that may result in molecular fragmentation, usually in heterochain polymers where the process can be seen as the reverse of polycondensation.[19]

The conditions under which the first of these processes occurs include elevated temperature, especially with oxygen to give thermal oxidation, electromagnetic radiation, mechanical stress at elevated temperatures, and ultrasonic vibration. Naturally, the physiological environment within the human body does not offer any of these conditions to an implanted polymer. However, hydrolytic degradation is quite feasible in the aqueous extracellular fluid. Three conditions have to be met[1]: First, the polymer has to contain hydrolytically unstable bonds. Second, for any significant degradation to take place, the polymer should be hydrophilic. Third, the hydrolysis has to occur at a physiological pH, which is around 7.4.

The effects of degradation will vary, but, generally, there will be a change in average molecular weight, molecular weight distribution, crystallinity, and mechanical properties. Most implanted polymers suffer some degree of degradation within the human body and biological environment plays some active role in the process of biodegradation. Extracellular fluid components such as enzymes[20–22] and lipids[7] are able to influence hydrolytic degradation of certain polymers.

It is anticipated that hydrolytically stable homochain polymers would be susceptible to degradation under the ambient conditions found in the body, but there is some evidence that other biological factors are involved in degradation mechanisms operative within the body.[23,24] Liebert et al.[24] suggested that trace amounts of metallic ions, enzymes, or other species could be responsible for the increased rate of oxidative degradation of polypropylene, taking into account that several enzymes have oxidative activity and certain cells release peroxide and other oxidative agents.

It has been indicated earlier that degradation rates can be influenced by various components of the tissue environment. Clearly, there are many different types of cells within this tissue and those cells with phagocytic ability are normally able to remove debris from the tissue by engulfment and digestion; therefore, the cellular digestion of implanted polymers should be considered. Kossovsky et al.[25] suggested that macrophages have been observed to cause pitting on the surface of silicone polymers by virtue of the peroxides released onto the surface, and Williams et al.[13] noted some degradation of labeled polyesters by macrophages *in vitro*.

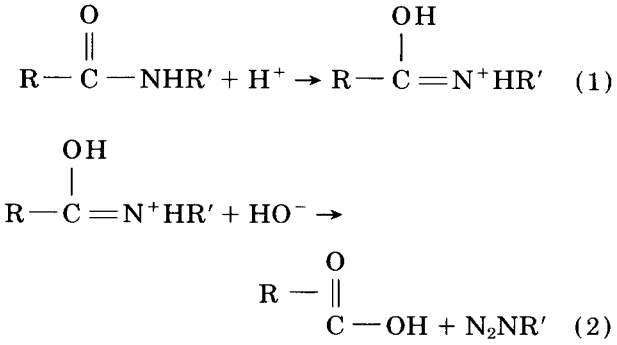
The physiological environment of the human body can be aggressive to polymers. Many suffer degradation and the kinetics and mechanisms of the processes can be significantly affected by various biologically active species, especially by enzymes, lipids, peroxides, free radicals, and phagocytic cells. The mechanisms of polymer degradation can generally be divided into hydrolytic and free-radical degradation.

HYDROLYTIC DEGRADATION

Heterochain polymers, especially those containing oxygen and/or nitrogen atoms in the main chain, are generally susceptible to hydrolysis. The hydrolysis, depending on the structure, may occur within either acid or alkaline environments and clearly is much faster above ambient temperatures. The aqueous environment of the body at 37°C is sufficiently hostile to degrade a number of polymers by hydrolysis. It is in this environment that enzymes and especially hydrolytic enzymes are most likely to have an effect. Among the polymers that have been shown to degrade by hydrolysis *in vivo* are cer-

tain polyamides, including nylons and polyamino acids, some polyurethanes, cyanoacrylates, and some polyesters, both aliphatic and aromatic.

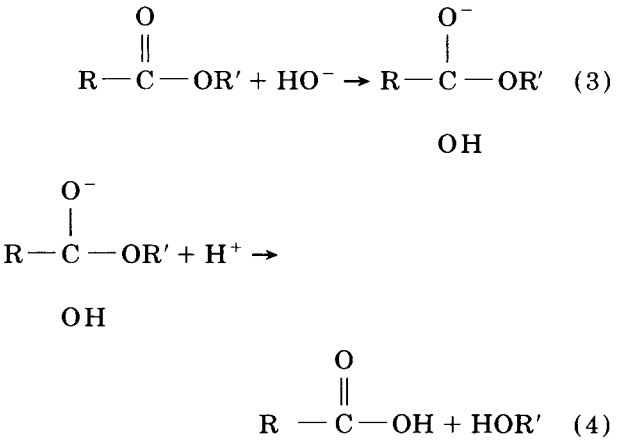
The hydrolysis mechanism of polyamides has been discussed by Gilding[18] and Zaikov,[26] the primary attack being that of the hydrogen ion on the oxygen atom of the carboxyl group [eq. (1)]:



(1)

(2)

Both acid and amine end groups are formed. The protonation reactions will vary depending on the pH of the environment. The influence of various constituents of the physiological environment on the kinetics and reaction products of polyamides have been studied.[6,8,27,28] The hydrolytic instability of the amide bond in synthetic amino acid polymers has been used in the synthesis of intentionally degradable soluble polymers for drug delivery.[29,30] The ester bond is readily hydrolyzed, resulting from the primary attack of the hydroxyl ion on the positive carbonyl C atom [eq. (3)]:

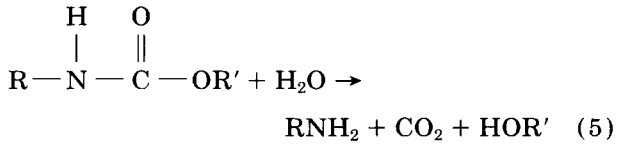


(3)

(4)

Generally, the aromatic polyesters are less sensitive to moisture than are the aliphatic polyesters due to greater hydrophobicity of the aromatic parts. The hydrolytic degradability of the ester bond has been used in clinical applications.[30–32] The effect of various biologically active species on the rate and kinetics of the ester hydrolysis has been reviewed.[1,19]

Polyurethanes contain both amide and ester groups. A wide variety of polyurethanes exist in which various groups are present in adjacent molecular chains. The susceptibility to hydrolysis depends on interactions between groups in adjacent chains, but an overall hydrolysis reaction can be written as

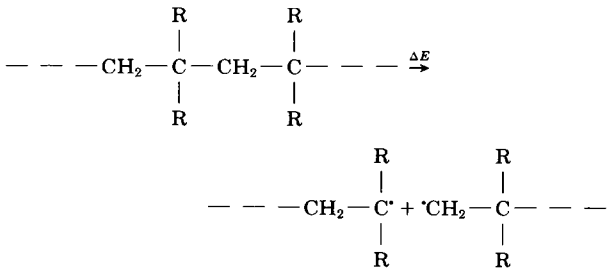


(5)

FREE-RADICAL DEGRADATION

Free-radical degradation on the absorption of energy is of great interest with respect to the hydrolytically stable homochain polymers such as some polyolefins (polyethylene and polypropylene), halogenated hydrocarbon polymers (polytetrafluoroethylene), polyacrylic acids and their esters [poly(methyl acrylate) and poly(ethyl acrylate)], and in some polyether urethanes and certain silicone polymers (polydimethylsiloxane), although its relevance to medical polymers has rarely been discussed.

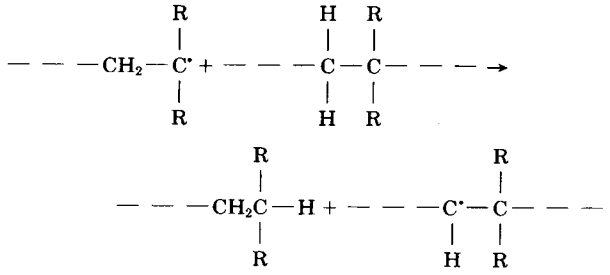
It is well known that this degradation process involves initiation, propagation, and termination stages. The initiation reaction takes place when energy is absorbed from an external source, causing the scission of a covalent backbone or cross-link:



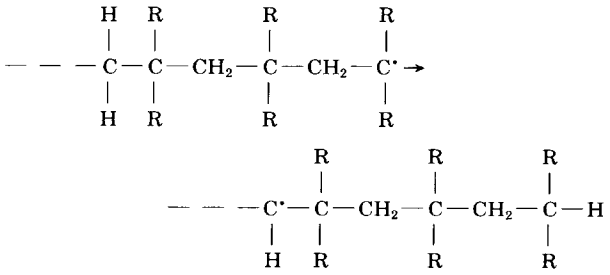
This is the preferred initiation route in homochain polymers as the C—C bond is the weakest bond. However, with polyethers and polyesters, the C—O bond is cleaved.

Propagation may take place by unzipping, such that the polymer is converted almost entirely to monomer or (and possibly simultaneously) by the radicals abstracting a neighboring H atom, so that

the radical is transferred to another chain or further down the same chain:



or



The mechanisms of propagation may be important in free-radical degradation of polymers in physiological environments in view of the variability of free-radical supply and diffusion.

Activation energies for the degradation of the hydrolytically stable homochain polymers used in surgery vary from 30 to 90 kcal mol^{-1} and such reactions generally require heat, UV light, or high-energy radiation, preferably in the presence of oxygen, to proceed. It seems certain from these conditions that no such degradation should take place within the human body. However, many of these polymers have suffered degradation *in vivo* and various biologically active species may possibly influence the rate, kinetics, and mechanism of their breakdown.

HYDROXYL RADICAL DEGRADATION OF MEDICAL POLYMERS

The implantation of medical devices, artificial organs, or biomaterials initiates a response by the body and mechanisms are activated to maintain homeostasis. The extent to which the homeostatic mechanisms are perturbed may lead to impairment of the functional capacity or permanent acceptance of the medical device, artificial organ, or biomaterial. Inflammation is defined as the local response of vascularized tissue to injury, e.g., created by the implantation process.

The biocompatibility of an implanted material is characterized by the morphological appearance of the inflammatory reaction to the material but the inflammatory response itself is a set of complex reactions of various kinds of cells whose densities, activities, and functions are controlled by various mediators.

The process of phagocytosis, in which cells ingest and attempt to digest extraneous matter, by both polymorphonuclear neutrophils and macrophages, is accompanied by a set of biochemical events, including a sharp increase in oxygen uptake followed by the formation of a number of highly reactive oxygen reduction products. This sequence of reactions is generally referred to as an "oxidative" or "respiratory" burst.[34-37] The primary reaction in the oxidative burst is the one-electron reduction of oxygen to superoxide (O_2^-) catalyzed by either NADPH oxidase or NADH oxidase and using NADPH or NADH as substrate:

$$2O_2 + NADPH \rightarrow 2O_2^- + NADP^+ + H^+$$

Superoxide radicals interact to form hydrogen peroxide (H_2O_2), this reaction being catalyzed by the cytoplasmic enzyme superoxide dismutase (SOD):

$$2O_2^- + 2H^+ \rightarrow H_2O_2 + O_2$$

During inflammation, oxygen-free radicals are formed, especially by polymorphonuclear leukocytes and macrophages.[38] The role of free radicals in inflammation is increasingly recognized.[39,40] Superoxide and hydrogen peroxide are reactive oxygen species primarily formed by phagocytozing cells. These species are relatively harmless on their own, but in the presence of iron or other transition-metal catalyst, a second generation of highly toxic radicals are produced such as hydroxyl radicals (HO•). The potent oxidant hydroxyl radicals are essential to the principal physiological function of phagocytes in the elimination of invading microorganisms.

The mammalian cell has developed a system to combat the autooxidative damage due to attack by those oxygen-free radicals on membrane and cytoplasmic structures of the phagocyte itself. The main detoxification systems used to prevent this are superoxide dismutase (SOD), for the removal of O_2^- and glutathione peroxide and catalase, which destroy H_2O_2.

These highly reactive oxygen metabolites are generated upon contact of the cell plasma membrane with any of a number of surface-active materials or soluble substances that will induce phagocytosis or membrane perturbation.[36,41] Attachment of macrophages to large areas such as glass or polymer surfaces will trigger phagocytosis, i.e., toxic oxygen metabolite synthesis and lysosomal enzyme release. The increase in synthesis of superoxide anion and hydroxyl radical as well as released lysosomal hydrolases by activated macrophages will not only contribute to improved microbial activity of the macrophages, but also will augment any tissue injury due to the invading organisms. These highly reactive radicals generated by cellular mechanisms at or near the surface of implanted polymers may contribute to damage of the polymer surface in the same fashion as established polymer degradation reactions by reactive radicals.[24]

It is well known that iron enhances the toxicity of oxygen free radicals as shown, e.g., with EDTA or ADP–iron complexes.[42-45] Superoxide and hydrogen peroxide can interact to form the very toxic hydroxyl radical in the Haber–Weiss reaction as shown in eq. (6)[46]:

$$O_2^- + H_2O_2 \rightarrow HO^\bullet + HO^- + O_2 \quad (6)$$

$$O_2^- + Fe^{3+} \rightarrow O_2 + Fe^{2+} \quad (7)$$

$$H_2O_2 + Fe^{2+} \rightarrow HO^\bullet + HO^- + Fe^{3+} \quad (8)$$

However, the rate for this reaction is very low.[47] Iron, reduced by superoxide, is able to form hydroxyl radicals in a reaction with H_2O_2, the so-called Fenton reaction[48,49] as illustrated in eqs. (7) and (8). In fact, the Haber–Weiss reaction proceeds only through the catalysis by iron.

In vitro, O_2^- and H_2O_2 react together to form hydroxyl radicals $HO^\bullet$ in the presence of a micromolar concentration of iron,[50] and hydroxyl radicals have been thought to be responsible for many biological phenomena, such as radiation damage, alloxan-induced diabetes, microsomal ethanol oxidation, aging, lysosome peroxidation, phagocytic activity, and inflammation.[51]

It has long been known that the ferrous ion/hydrogen peroxide mixtures known as Fenton's reagent[48,49] produce a strongly oxidizing medium capable of oxidizing most organic compounds. The generally accepted mechanism for Fenton's reagent is that proposed by Haber and Weiss and involves initial reductive cleavage of the peroxy bond by ferrous ion (Fe^{2+}) to produce ferric ion (Fe^{3+}), hydroxide ion, and a hydroxyl radical[46] as indicated in eq. (8).

EXPERIMENTAL

Hydroxyl radicals were generated by the reaction of aqueous solutions of H_2O_2 with either ferrous sulfate

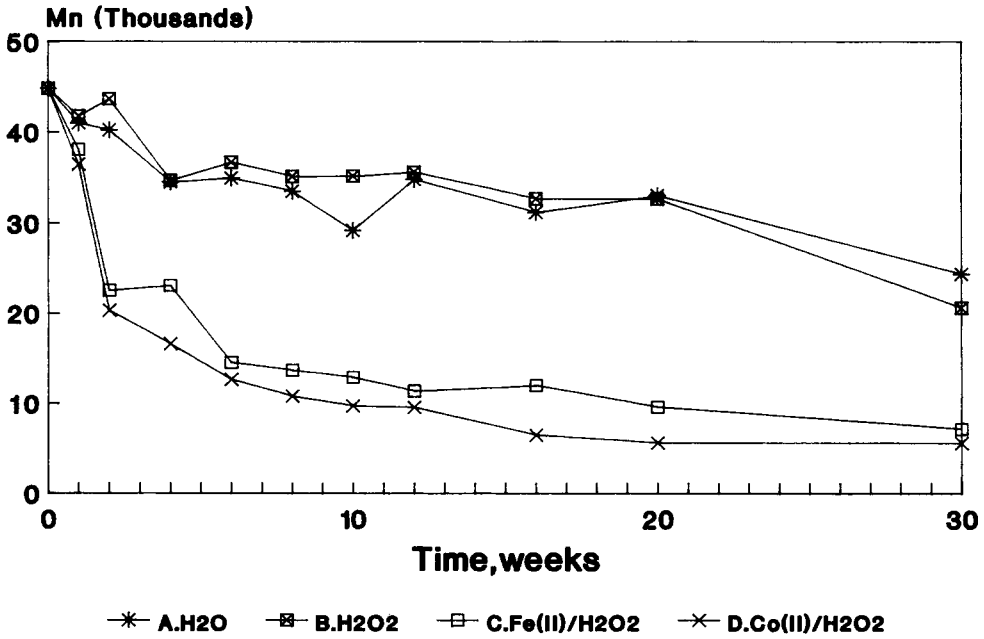


Figure 1 Molecular weight (M_n) of polycaprolactone in hydroxyl radicals, 37°C.

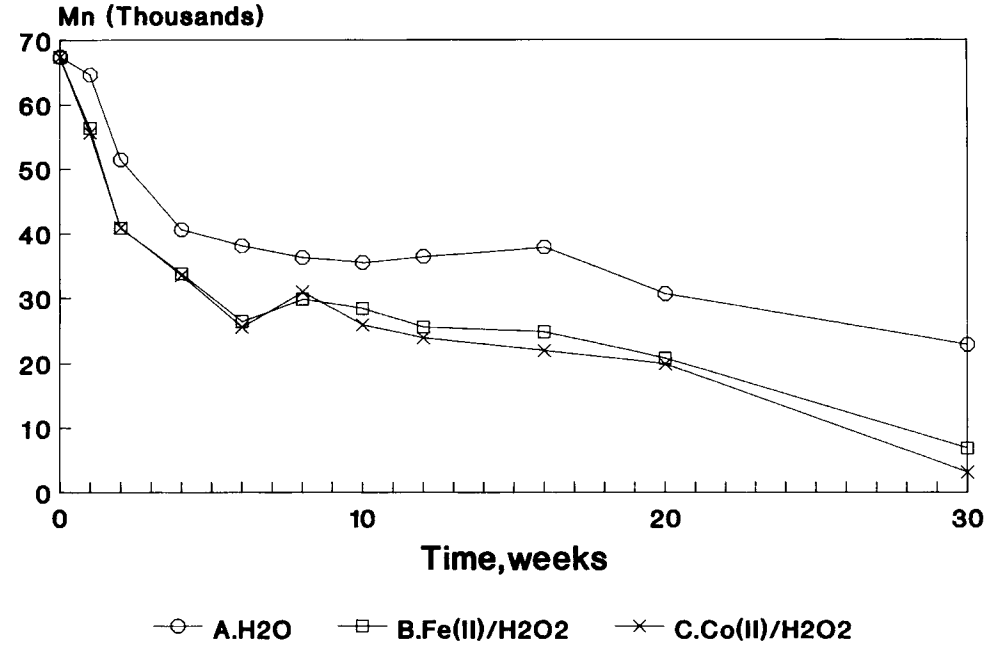
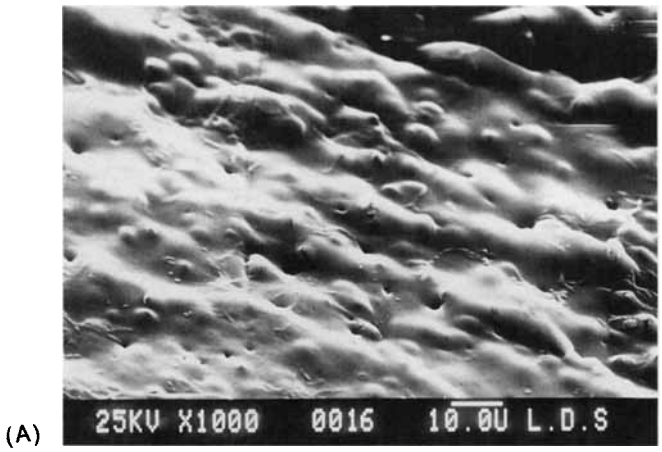


Figure 2 Molecular weight (M_n) of poly(DL-lactic acid) in hydroxyl radicals, 37°C.



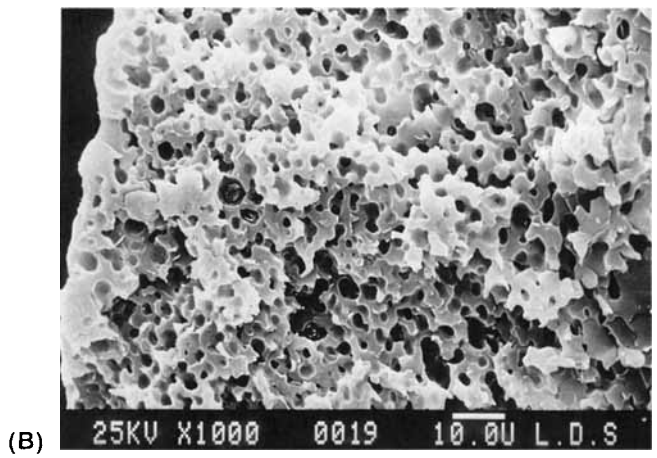
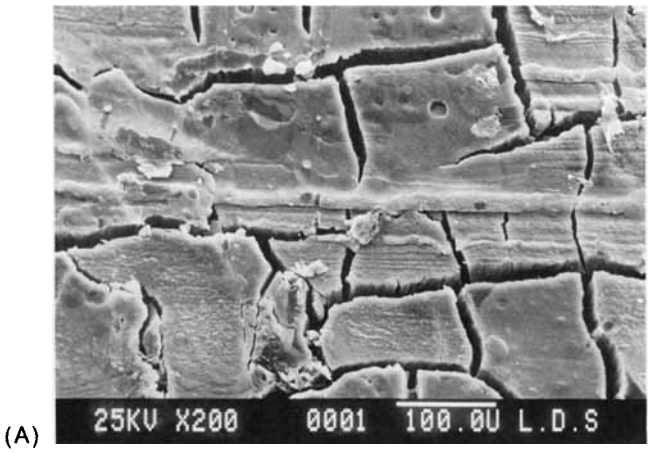


Figure 3 Scanning electron microscopy of (A) surface and (B) cross section of poly(DL-lactic acid) after 30 weeks of degradation in distilled H_2O.



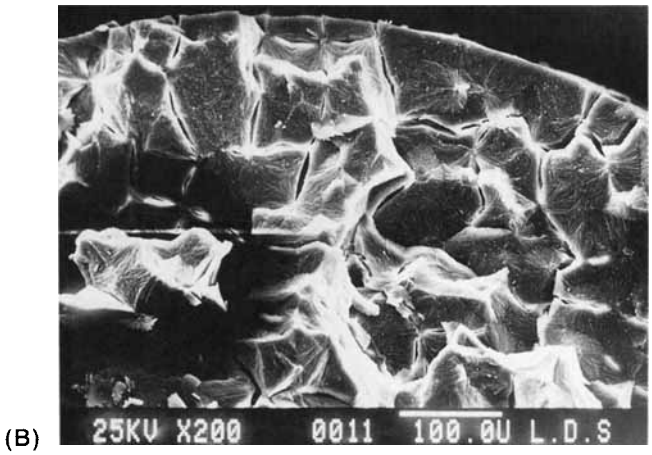
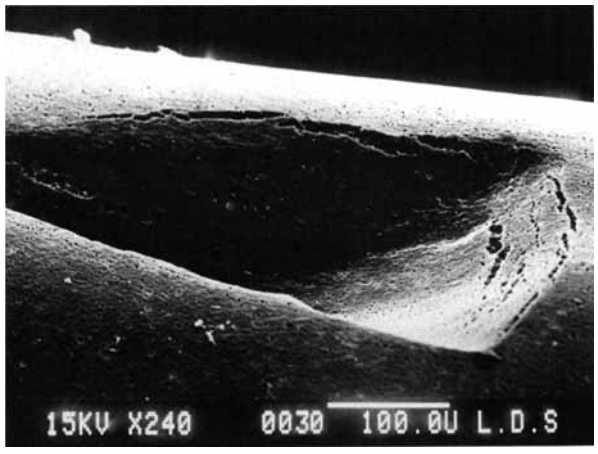


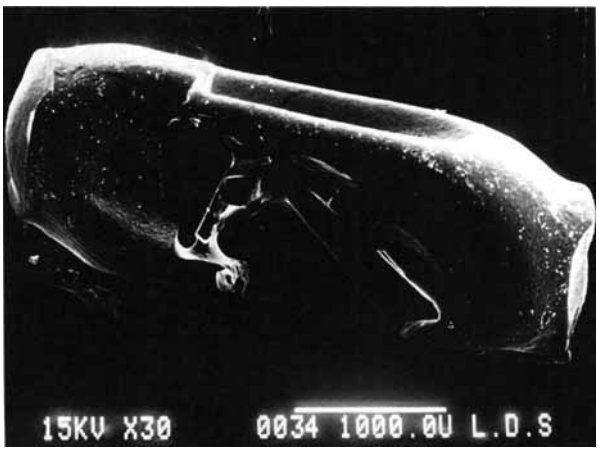
Figure 4 Scanning electron microscopy of (A) surface and (B) cross section of polycaprolactone specimen after 30 weeks of degradation in Co(II)/H_2O_2 solution.

($FeSO_4$) or cobaltous nitrate [$Co(NO_3)_2$] in deionized water. Optimum procedures were achieved to prepare both systems in order to use them as a standard technique for evaluation of the influence of HO• radicals on the oxidative degradation of various biomedical polymers. Polymer specimens were immersed in $Fe(II)/H_2O_2$ and $Co(II)/H_2O_2$ solutions and stored in a 37°C incubator over 30 weeks. Each medium was replaced twice a week to sustain the generation of fresh hydroxyl radicals.

Electron spin resonance spectroscopy (ESR) was used to check the presence of HO• radicals in both $Fe(II)/H_2O_2$ and $Co(II)/H_2O_2$ solutions. Gel permeation chromatography (GPC), differential scanning calorimetry (DSC), and scanning electron microscopy (SEM) were used to investigate the changes on the surface and in the bulk of the specimens in order to study the operative mechanism of degradation of these polymers.



(A)



(B)

Figure 5 Scanning electron microscopy of the surface of poly(DL-lactic acid) specimen after (A) 20 weeks and (B) 30 weeks of degradation in $Fe(II)/H_2O_2$ solution.

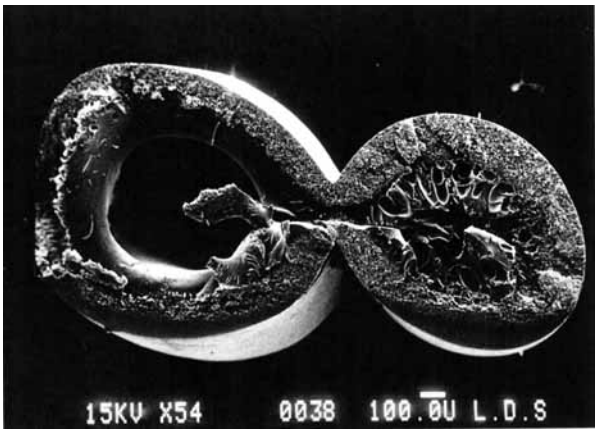


Figure 6 Scanning electron microscopy of the cross section of poly(DL-lactic acid) specimen after 20 weeks of degradation in $Co(II)/H_2O_2$ solution.

Polycaprolactone and poly(DL-lactic acid) are biodegradable aliphatic poly(α-hydroxy acids), which have found essential application in the field of human therapy due to their biocompatibility and resorbability. The hydrolytic degradation of these poly(α-hydroxy acids) in an aqueous environment was employed[52,53] as the control, over the period of incubation, to study the effects of hydroxyl radicals in aqueous solutions (Fenton's reaction) on the mechanism of degradation.

The values of number-average molecular weight (M_n) vs. the time of incubation in different media are shown in Figures 1 and 2.[52,53] Curves A and B in Figure 1 indicate clearly that the decrease of molecular weight values is due to hydrolytic degradation of the ester groups of both polymers resulting from the influence of aqueous and hydrogen peroxide solutions, respectively. A sharp decrease of molecular weight values, as demonstrated by curves C and D, indicates that this phenomenon is not only due to the hydrolytic degradation of the ester groups of both polymers but also to free-radical degradation. The presence of HO• radicals in media C and D shows that polycaprolactone and poly(DL-lactic acid) specimens have gone through mechanisms of both hydrolytic and free-radical degradation.

A significant difference in the rate of morphological changes has emerged from scanning electron microscopy (SEM) studies[52,53] after the treatment of polycaprolactone and poly(DL-lactic acid) specimens with distilled H_2O solution as shown in Figure 3 for the latter, in comparison with $Fe(II)/H_2O_2$ and $Co(II)/H_2O_2$ aqueous hydroxy radical solutions (Figs. 4–6) for both polymers. The presence of hydroxyl radicals in solutions [$Fe(II)/H_2O_2$ and

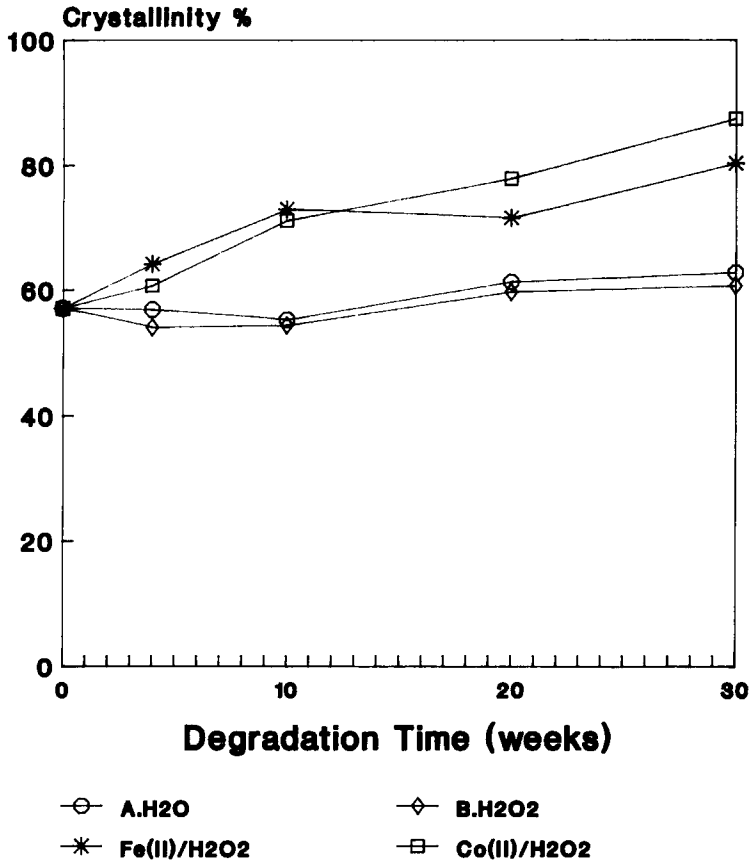


Figure 7 Effect of the hydroxyl radical systems with different degradation times on the crystallinity of polycaprolactone.

Co(II)/H_2O_2] indicate that polycaprolactone and poly(DL-lactic acid) specimens have gone through not only hydrolytic degradation but also free-radical degradation. The total collapse of the poly(DL-lactic acid) specimen after 30 weeks treatment of Co(II)/H_2O_2 aqueous hydroxyl radical solution removed the opportunity for a clear micrograph.

Figure 7 presents the crystallinity changes of polycaprolactone specimens at different degradation times as deduced from differential scanning calorimetry (DSC). It seems that the incubation of these specimens in aqueous solution at 37°C resulted in the degradation of the amorphous phase, which led to more mobility and crystallization.

Different rates of crystallinity level change between the H_2O and H_2O_2 in comparison with Fe(II)/H_2O_2 and Co(II)/H_2O_2 solutions, with incubation time, were also evident (Table I). The general increase in the degree of crystallinity of polycaprolactone specimens in aqueous solutions is attributed to the hydrolytic degradation of ester groups.[54] The greater rates of crystallinity change in the hydroxyl radical systems is probably due to chain cleavage caused by hydrolytic as well as much more reactive free-radical degradation mechanisms.

Table II presents the changes of the glass transition temperature (T_g) values of poly(DL-lactic acid) specimens at different degradation times as

Table I Effect of the Hydroxyl Radical Systems with Different Degradation Times on the Degree of Crystallinity of Poly(caprolactone) (PCL)

Degradation Time (Weeks)	Crystallinity % of PCL[a]			
	H_2O	H_2O_2	Fe(II)/H_2O_2	Co(II)/H_2O_2
0	57.1	57.1	57.1	57.1
4	56.9	54.1	64.2	60.7
10	55.3	54.4	73.0	71.2
20	61.3	59.7	71.6	77.9
30	62.8	60.7	80.3	87.4
Overall change	+10%	+6%	+41%	+53%

[a] Standard deviation ±3%.

Table II Effect of the Hydroxyl Radical Systems with Different Degradation Times on the Glass Transition Temperature, T_g, of Poly(DL-lactic acid)

Degradation Time (Weeks)	Glass Transition[a] (°C)		
	H_2O	$Fe(II)/H_2O_2$	$Co(II)/H_2O_2$
0	55	55	55
4	51	50	49
10	51	50	48
20	51	50	48
30	51	50	48

[a] Standard deviation ±3%.

deduced from DSC. Poly(DL-lactic acid) is totally amorphous, and before degradation, DSC reflected only a glass transition, T_g, at about 55°C, in agreement with the amorphous morphology. After 30 weeks incubation with distilled water, the T_g decreased to 51°C (Table II) due to the plasticizing effect of absorbed water. It was noted that the decrease of T_g of poly(DL-lactic acid) incubated with $Fe(II)/H_2O_2$ and $Co(II)/H_2O_2$ hydroxyl radical aqueous solutions, are 50 and 48°C, respectively. Different rates of reducing the T_g values could be attributed to not only the plasticizing and hydrolytic effects of water but also to chain breakdown caused by hydroxyl radical degradation, i.e., an increase in the free volume.

CONCLUSIONS

The data have demonstrated[52,53] that the hydroxyl radical is likely to be one of the main causes of degradation in some medical polymers. Indeed, it is one of the most reactive chemical species known. For example, it is pointless to try to demonstrate hydroxyl radical reactions *in vitro* in solutions containing Tris buffer, since HO• attacks this buffer rapidly and a Tris-derived radical is produced.

Reactions of HO• can be classified into three main types: hydrogen abstraction, addition, and electron transfer. Radicals produced by reactions with HO• are usually less reactive, however, since HO• is such an aggressive species. It is assumed that the reaction of HO• with these poly(α-hydroxy acids) proceeds through hydrogen abstraction. Hydrogen atoms adjacent to carboxyl, carbonyl, and other electron-withdrawing groups are more easily abstracted by free radicals.[55-57] Thus, polycaprolactone and poly(DL-lactic acid) have a relatively labile hydrogen on the carbon alpha to the ester group. Thus, hydrogen abstraction in these polymers tends to be site-specific:

$$R_1-(-O-CH(R_2)-COO-)_n-R_3 + HO^\bullet \rightarrow R_1-(-O-C^\bullet(R_2)-COO-)_n-R_3 + HO-H$$

In vivo, the HO• radicals can be generated by transition-metal ions, peroxide, and superoxide species during the respiratory burst of phagocytic cells in acute or chronic inflammation sites. The reactivity of HO• radicals is so great that, if they are formed in living systems, they will react immediately with whatever biological molecule in their vicinity, producing secondary radicals of variable reactivity.

The work reported here was carried out with the support of a Rolling Grant from the U.K. Science and Engineering Research Council.

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Received March 3, 1993
Accepted April 25, 1993