15
Drug Delivery Systems

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15.1
Introduction

The majority of medicines contain a polymer within their formulation. Polymers play diverse roles in the pharmacy. For example, they act as wicking and disintegration components of tablets, enteric coatings, and modifiers of release kinetics, lubricants, wetting agents, solid dispersion phases, viscosity modifiers, penetration enhancers, and more. Biodegradable polymers, which undergo chain scission as part of their function and prior to removal from the body, play a more limited role than biostable polymers in medicines. Indeed, only two classes of biodegradable polymers, poly(α-hydroxy acids) and polyanhydrides, have been used in marketed products in the United States. Other classes of biodegradable polymers, for example, polyorthoesters, having undergone decades of improvement, are now in late-stage human trials.

The very limited number of polymer types that have been developed is symptomatic of the great challenge faced in developing new biodegradable polymers for pharmaceutical applications. Additionally, the lack of new biodegradable polymers joining the above classes also reflects the ability to modify the properties of poly(α-hydroxyl acids) and polyanhydrides using copolymer chemistry to match the mechanical and degradation profiles required for many drug delivery applications. One interesting characteristic of this field of research is that so many groups have based their research on a narrow range of polymer types over a long period that a major body of literature exists on the chemistry, biological interactions, and medical application of these polymers.

Despite the slow pace of development of new biodegradable polymers in the field of drug delivery, there is a need to accelerate research into new classes. Current polymers have important weaknesses, and the requirements for biodegradable polymers that can release proteins, gene products, and cells are exposing these weaknesses.

This chapter aims to provide an overview of the current state of knowledge of poly(α-hydroxyl acids) and polyanhydrides to highlight the complexity of biological interactions of even these relatively simple polymers. The chapter then looks at

Handbook of Biodegradable Polymers: Synthesis, Characterization and Applications, First Edition. Edited by Andreas Lendlein, Adam Sisson.

some examples of research into new classes of biodegradable polymers that address specific weaknesses in the current systems. The chapter does not attempt to cover the entire range of biodegradable polymers under development as drug delivery systems or to provide a complete history of the development of the poly(α-hydroxyl acids) and polyanhydrides, but the reader is referred to more comprehensive review articles throughout.

15.2 The Clinical Need for Drug Delivery Systems

Drug delivery systems modify the kinetics or the location of the escape of the drug from the medicine. Tables 15.1 and 15.2 provide generic reasons for using drug delivery systems.

For drug delivery systems containing biodegradable polymers, the major motivations for clinical use have been to deliver drugs that are required for long periods, are rapidly removed by metabolism or excretion, and are required at sites of administration that are difficult or impossible to reach with oral or conventional injection routes [1].

Cancer chemotherapy [2] and long-term replacement of human growth hormone [3] have been the major clinical foci for research on biodegradable polymer applications. Zoladex is the most successful (in terms of duration of clinical use and

Table 15.1 Use of a drug delivery system for kinetic control.

Dissolution of drug is too slow
Drug and/or formulation is physically removed from the site of action too rapidly
Metabolism or excretion of the drug is too fast
Drug is required intermittently
Administration is complex, invasive, and/or costly and therefore, dosing frequency needs to be reduced
Patient compliance (e.g., motivation to remember to take dosage) is poor and consequences of missing dosages are serious

Table 15.2 Examples of motivations to use a drug delivery system for location control.

Avoid side effects by minimizing exposure of other tissues
Concentrate drug at the site of action
Avoid rapid metabolism or excretion from the body
Accelerate drug transport across cell membranes
The route of administration is technically difficult (e.g., injection)

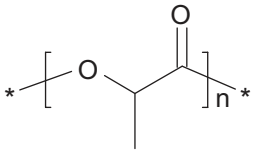
number of patients treated) biodegradable polymer-based formulation [4]. The primary clinical application of Zoladex LA is in the treatment of prostate cancer with the luteinizing hormone releasing hormone antagonist goserelin acetate. This drug blocks the downstream control of testosterone by the pituitary gland and thereby starves the tumor of a hormone that stimulates cancer growth. Goserelin acetate is a peptide molecule that can only be delivered by injection (it would be metabolized in the gastrointestinal track by enzymes). In addition, the drug needs to be constantly present in the blood stream for extended periods (e.g., 3 months). The polymer science underlying the release of drug from Zoladex, and the related product Lupron, is explored in Section 15.3.1.

Biodegradable polymer systems have also been employed for over a decade in the treatment of glioblastoma multiforme, an aggressive tumor within the brain [5–7]. In common with Zoladex, the systems used glioblastoma multiforme need to deliver drug over extended periods of time. Gliadel is a polyanhydride-based delivery system of the drug, 5-nitrourea, that concentrates the drug at the site of the tumor. In contrast to Zoladex, Gliadel provides local delivery of a toxic drug that must not be delivered to other sites in the body. The Gliadel product is placed at the site of the original tumor at the end of surgery to remove the primary tumor. Therefore, Gliadel achieves both temporal and spatial control of the release of a potent and toxic chemotherapy.

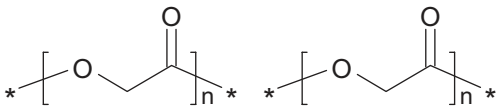
15.3 Poly(α-Hydroxyl Acids)

Polymers composed of lactic acid and glycolic acid dominate scientific literature on biodegradable polymers for drug delivery.

Polylactic acid:



Polyglycolic acid:



These polymers are synthesized by ring-opening polymerization of lactide and glycolide. In terms of nomenclature, the polymers are often termed polylactide, polyglycolide, and polylactide-*co*-glycolide as this reflects the monomer chemistry. However, the abbreviations PLA, PGA, and PLGA are more widely used than PL, PG, and PLG, and thus in this chapter polymer names including the acid term are used. It is very important to always specify the stereochemistry of the lactic

acid component (see Section 15.3.1) as it has a profound effect on the physical and biological behavior of these polymers.

The polymers in this family have been components of biodegradable sutures and orthopedic implants for many years providing a long history of use in the human body. PLGA systems possess many attributes that make them suitable for drug delivery applications in which a slow release of a drug within a device is required [8]. Principle attributes are given below:

1) **Ability to control the kinetics of polymer degradation**

   For detailed explanation of control, see review by Anderson and Shive [6] and papers of Vert *et al*. [7–13], for example, A summary of key features of methods of control are discussed below.

2) **Numerous routes to fabrication**

   Described in Section 15.6.4.

3) **Mechanical properties**

   Sufficient compressive and tensile strength for use in applications in which the delivery system will be under compression or tension during function. For example, the polymer class is used in orthopedic implants.

4) **Widely available at medical grade**

   Synthesized to high purity and following good manufacturing practice by a number of companies across the world.

The history of use of PLGA polymers provides a number of important lessons for the development of new classes of polymers. Despite the simplicity of the polymer chemistry of PLGA polymers, the broad use of these polymers in humans and animal models has exposed significant complexity in the behavior of these polymers *in vivo*. Section 15.3.1 highlights some of the complexity and draws heavily on the excellent review of Anderson and Shive [8].

15.3.1
Controlling Degradation Rate

There are two distinct steps in the breakdown and removal of a biodegradable polymer; degradation and erosion. Degradation is the chemical breakage of bone along the polymer backbone that results in a decrease in polymer molecular weight. Erosion is the loss of mass from the delivery system due to the dissolution of the products of degradation.

The kinetics of degradation and erosion are determined by chemical and physical properties of the drug delivery system. A major attraction of the poly(α-hydroxy acids) is the ability to use the ratio of lactic acid to glycolic acid in the polymer chain to control both sets of kinetics. The methyl group on the lactic acid monomer retards hydrolysis of the neighboring ester group compared with the glycolic acid

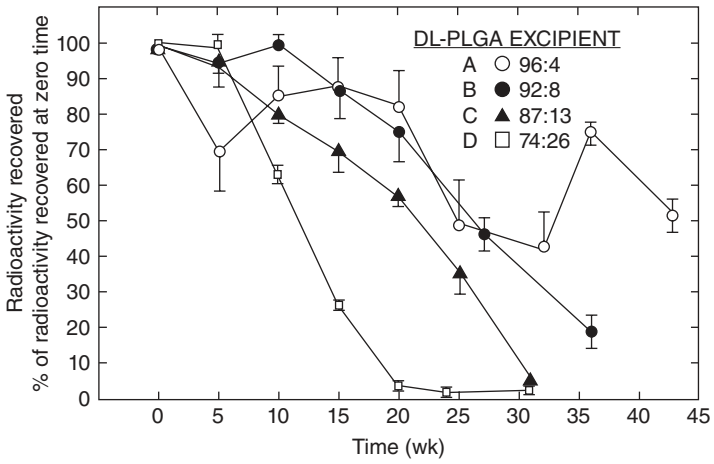


Figure 15.1 *In vivo* biodegradation of microcapsules is measured by Beck *et al.* by measuring radiolabeled P_{DL}LGA. Reproduced with permission from [10].

structure [9]. Hence, lactic acid containing homopolymers may take over one year to degrade and erode, while PGA may degrade and erode in one month. It is important to note that the exact period of time for degradation and erosion is not stated exactly because there are competing physical factors that can greatly accelerate or retard biodegradation. A study published by Beck *et al.* in 1983 demonstrates the effect of lactic acid to glycolic acid ratio on biodegradation and is reproduced in Figure 15.1 [10].

The next issue to be considered is the stereochemistry of the carbon-alpha to the ester [11, 12]. Clearly, both D and L forms of lactic acid exist, with L being the form used in nature. Lactic acid-based polymers are synthesized by the ring-opening polymerization of lactide. For drug delivery applications, both D,L-lactide and L-lactide are used. Hence, poly(D,L-lactic acid) (P_{DL}LA) and poly(L-lactic acid) (P_LLA) and both sterochemistries may be incorporated into PLGA copolymers. P_LLA and PGA are semicrystalline, while P_{DL}LA is amorphous. The degree of crystallinity affects the rate of water penetration into the drug delivery system and hence the rate of biodegradation. P_LLA may take more than 2 years to degrade *in vivo* if a semicrystalline morphology is allowed by the manufacturing route, while P_{DL}LA is removed in approximately 1 year. Li and Vert described a further complication in that the degree of crystallinity of quenched P_LLA (starting point amorphous due to quenching) and inherently amorphous P_{DL}LGA increased during degradation due to reorganization of the degradation products prior to, and delaying, erosion [13, 14].

When predicting the kinetics of degradation and erosion of PLGA polymers, it is necessary to consider the balancing contributions of polymer chemistry and crystallinity. For example, P_{DL}LGA (50:50) degrades and erodes more rapidly than PGA because the rate of penetration of water is the rate-limiting step rather than the steric hindrance to hydrolysis of the monomer structure.

A further complication in predicting and understanding the kinetics of degradation of this family of polymers is the effect of device size and architecture. Counterintuitively large device made from PLGA degrade more rapidly than microparticles in certain circumstances [15]. In addition, an important clue in the mechanism of accelerated degradation of large devices is the finding that large rods of PLGA often become hollow during degradation. These phenomena can be explained by the process of autocatalysis in which the acidic degradation products of PLGA hydrolysis accelerate local degradation. This localized catalysis is greatest within large devices due to the slow escape of the acid species. Hence, heterogeneous degradation kinetics occur across devices that have a diameter or width >300 μm.

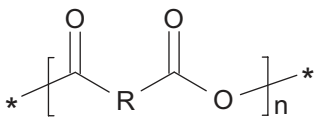
15.4 Polyanhydrides

The second class of biodegradable polymers approved for use in humans in a drug delivery application are the polyanhydrides. The product Gliadel has been used for the treatment of brain tumors (see Section 15.2). A comprehensive review has been published by Katti *et al.* [16].

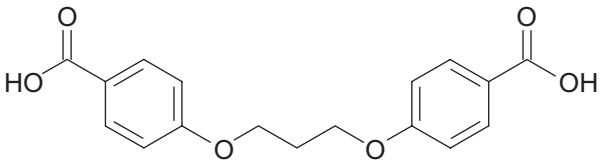
The motivation for using polyanhydrides over poly(α-hydroxy acids) is the need to restrict polymer erosion to the surface of the devise. As described in Section 15.3, the PLGA systems erode through a bulk mechanism for small particles and an autocatalytic hollowing mechanism for large rods. These mechanisms result in the encapsulated drug contacting with water for extended periods before the drug is released. Therefore, drugs that are sensitive to hydrolysis or other water-mediated instabilities could lose activity over time in the PLGA devices. A surface-eroding device would keep the drug dry prior to release. A further advantage of a surface-eroding system is the ability to control drug release kinetics via changes in surface area of the delivery system. For PLGA systems, the relationship between polymer degradation, drug release, and surface area is very difficult to predict (because bulk effects dominate and can be erratic due to physical breakup of the delivery system).

The Gliadel system is formed from a copolymer of the monomers bis(carboxyphenoxy)propane (CPP) and sebacic acid (SA). The structures of these monomers and the generic anhydride structure are shown below. Although no other polyanhydrides have been used in approved pharmaceutical products to date, the field of polyanhydride chemistry is active, and promising new structures are under investigation.

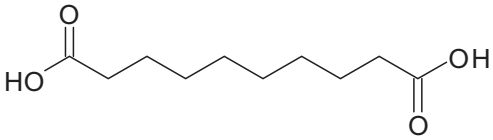
General PAA structure:



CPP:



SA:



Poly(bis-(carboxypheoxy) propane-*co*-sebacic acid) (PCPPSA) is designed to achieve surface erosion and to allow biodegradation kinetics to be controlled by the ratio of the monomers. The CPP component is hydrophobic and discourages water penetration into the device. The anhydride links between monomer are very labile and break rapidly in the presence of water. Hence, water penetration is slow that polymer degradation and chain scission is limited to the surface of the device. However, CPP has low water solubility and although degradation of PCPP at the surface is quick, erosion is very slow. Hence, SA is used within the polymer structure to accelerate dissolution of degradation products. Overall, the design of these copolymers is a balance between the need to restrict water penetration and to allow erosion to occur over clinically acceptable timescales. Figure 15.2 reproduces data from the paper of Leong *et al.* that quantified degradation kinetics for the PCPPSA system [17].

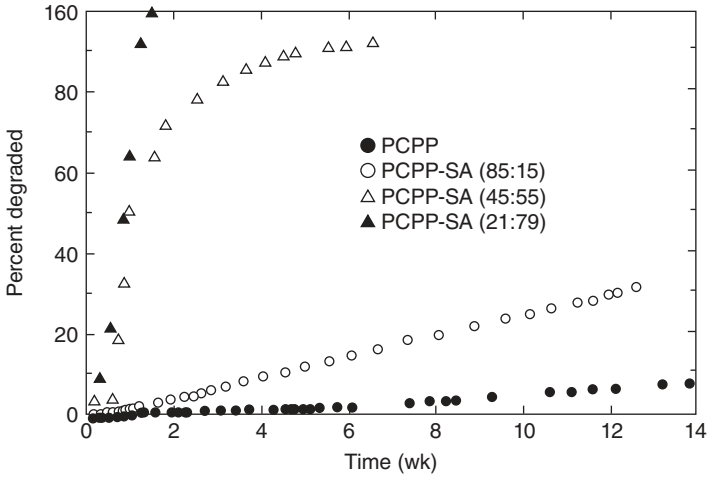


Figure 15.2 Degradation profiles of PCPPSA in 0.1 M pH 7.4 phosphate buffer at 37 °C. Reproduced with permission from [17].

15.5 Manufacturing Routes

The manufacture of drug and biodegradable polymer composites is not trivial. Both the poly(α-hydroxy acids) and polyanhydrides are water insoluble, indeed, that is an essential property that enables them to act as controlled release system. Hence, the polymer and drug phases of the delivery system will normally not share solvents that could be used to codissolve as a mobilization and mixing step in the manufacturing process. In the final product, a homogenous distribution of the drug within the polymer phase is likely to be required to generate a controlled and repeatable release rate for the drug. Therefore, it is essential that manufacturing routes achieve control of the size of the drug phases within the polymer phase and efficient dispersion of the drug phase.

A further complication in the manufacturing of these systems is the need to closely control the architecture of the finished product. For injectable formulations, a first requirement is that the drug delivery system can be expelled from the needle of syringe. For injections into the blood stream, or to sites where leakage into the blood stream will occur, the size of particle that can be used is further restricted to avoid blockage a fine capillaries in the blood system.

Emulsion-based processes are widely used to achieve the above properties in drug delivery systems. The drug can be dissolved in water and the polymer is dissolved in an organic solvent. Suspension of very small droplets of the aqueous drug solution within the organic solvent phase can be achieved within a water-in-oil (W/O) emulsion. If this W/O emulsion is suspended in a second water phase, then the droplet size of the organic solvent phase defines the maximum size of the final particle. Evaporation of the organic solvent in a stirred, open container creates solid particles containing the droplets of aqueous drug solution. Finally, sublimation of the water phase yields solid phase particles.

The above water-in-oil-in-water (W/O/W) emulsion system is widely used because it is adaptable to many polymer and drug combinations, including protein and nucleic-based drugs. However, there are numerous problems associated with the technique. In particular, the entrapment efficiency of the drug can be low as the drug can escape into the larger volume second water phase (outside of the organic solvent droplets). In addition, the formation of high surface area interfaces between the water and organic solvent phases may cause denaturing of protein drugs due to aggregation of loss of conformation.

A number of emulsion techniques have been described in the patent and scientific literature, which overcome shortcomings of the W/O/W technique. For example, Cleland *et al.* developed a human growth hormone delivery system using a novel cryogenic step in particle formation and demonstrated the importance of the manufacturing route to ensure integrity of protein drugs [18]. In addition, the manufacturing route eliminated the triphasic release profile that can hinder the use of PLGA-based microparticles. Morita *et al.* describe a useful method of creating solid dispersions of protein in polyethylene glycol (PEG) and then dispersing this composite in organic solutions of PLGA to create a solid-in-oil suspension.

This technique increases entrapment efficiency and removes any organic–water interface from the manufacturing environment [19].

An alternative to using an organic solvent to mobilize the polymer phase uses heat to melt the polymer. This has been used in the manufacture of Zoladex. The temperatures required to mobilize PLGA can be above 100 °C (depending on the composition and molecular weight) and so the technique is restricted for use with drugs that are stable at these elevated temperatures. Recently, Ghalanbor *et al.* have used hot-melt exclusion to load a protein, lysozyme, into PLGA. They demonstrated loading of up to 20% w/w of protein in the polymer with full retention of the protein enzymatic activity. The addition of PEG to the formulation eliminated the burst release of drug and drug release was controlled over a 80-day period [20].

The temperature of process of PLGA and many other polymers can be lowered to below 37 °C using CO_2 as a high-pressure processing medium. This technique relies on CO_2 depressing the glass transition temperature of amorphous polymers and lowering the viscosity of amorphous or crystalline polymer melts. High-pressure and supercritical-CO_2 processing have been described for microparticles, fibers, and highly porous scaffolds containing numerous types of protein drug [21–23].

15.6 Examples of Biodegradable Polymer Drug Delivery Systems Under Development

15.6.1 Polyketals

Polyketal-based drug delivery systems are under development for applications in which the acid degradation products from either poly(α-hydroxy acids) or polyanhydrides could cause detrimental side effects. Sy *et al.* have developed a poly(cyclohexane-1,4-diylacetone dimethylene ketal)-based delivery systems that can be used in the treatment of inflammatory diseases such as cardiac dysfunction [24].

This polyketal degrades in the presence of acid and generated neutral products. Sy *et al.* demonstrate that the encapsulation of a p38 inhibitor (SB239063) can improve the treatment of myocardial infarction.

15.6.2 Synthetic Fibrin

The biodegradable polymers discussed so far in this chapter have all used a simple water- or acid-triggered hydrolysis of a synthetic polymer backbone to lower their molecular weight and convert from water-insoluble to water-soluble forms.

A recent trend in the design of new biodegradable polymers for drug delivery has been to mimic enzymatic mechanisms of degradation used by our own bodies to remove extracellular matrix (ECM) and fibrin clots during tissue turnover or repair [25]. The need to employ this sophisticated method of controlling polymer

biodegradation has been created by the demands of regenerative medicine. Within one aspect of regenerative medicine, there is a need to deliver growth factors or angiogenic factors to a localized site within the body to control tissue formation. Potent molecules such as vascular endothelial growth factor, platelet-derived growth factor, and bone morphogenetic proteins have clinical potential and applications in the formation of bone and enhancing blood vessel formation (e.g., in diabetic foot ulcers). These factors are naturally occurring within our bodies and the body has evolved methods of tightly controlling the exposure of cells to these molecules. These molecules are bound within the ECM and are exposed to cells when the cells locally degrade the ECM to reveal the next growth factor molecule. The release of the factor is, therefore, demand driven and effective dosages have been shown to be orders of lower magnitude using this mechanism as opposed to chemically driven hydrolysis of PLGA.

The approach of using matrices from fibrin or synthetic versions of fibrin have been reviewed by Lutolf *et al*. [25]. The approach to design a fully synthetic version of fibrin has been described by, for example, Kraehenbuehl *et al*. [26]. They used PEG-based hydrogels in which PEG-vinylsulfone and a four-armed PEG-OH molecule were crosslinked to form a 3D hydrogel. The gel contained the peptide Ac-GCRDGPQGIWGQDRCG-NH_2. This peptide can be cleaved by enzymes matrix metalloproteinases that are secreted by cells as they remodel fibrin or other biological matrices. Hence, the hydrogel was degraded locally by cells.

15.6.3 Nanoparticles

The importance of drug delivery system architecture was highlighted in Section 15.5. Many sites of the body that require high localized concentrations of drugs are inaccessible to any particle in micron range. Therefore, nanoparticle technologies have been used in drug delivery for many decades.

Pioneering work in this field focused on the mechanism to avoid uptake of nanoparticles within the liver. The liver has a natural function to remove potential harmful foreign particles that have been coated with plasma proteins via a process termed opsonization. Early pioneering work by Davis and Illum demonstrated that polymer nanoparticles, including PLGA, could avoid extensive liver uptake if their surfaces were engineered to present high densities of PEG [27–30].

Building on this concept, Gref *et al*. developed a nanaoparticle system using a copolymer of PLGA and PEG [31]. The particles could be formed by the one-step phase separation manufacturing step and entrapped up to 45% w/w of the drug. The high density of PEG on the surface of the nanoparticles again altered biodistribution within mice. Five minutes after the administration, 66% of a dose of control particles (lacking PEG) were within the liver. This value dropped to less than 30% of the dose within the liver after 2 h for particles with a 20 kDa PEG component.

A recent study by Rothenfluh *et al*. demonstrated the ability to use nanotechnology and biological mimicry to create drug delivery systems that penetrate into

articular cartilage tissue [32]. This is an especially challenging site to target drug delivery systems into because the tissue lacks a blood vessel system and possesses a very dense ECM. This team demonstrated that particles of 38 nm penetrated the cartilage structure while particles of 96 nm could not. Surface engineering of the particles with the short peptide ligand WYRGRL targeted the nanoparticles to the articular cartilages, as opposed to other tissues, to achieve a 72-fold increase in particle deposition.

15.6.4
Microfabricated Devices

One of the most ambitious drug delivery systems composed of a biodegradable polymer has been described by Grayson *et al.* [33]. This paper shows that an elegant fabrication method for an old class of polymers can generate remarkable control of drug release. The motivation for the work by Grayson *et al.* was to mimic the body's ability to release molecules in a pulsatile manner. Many hormones, for example, are required for intermittent periods and do not function if the body is constantly exposed to them due to desensitization. In addition, many vaccines require multiple injections to rechallenge the body and generate immune responses.

Using PLGA polymers and a layered microfabrication technique, it was demonstrated that pulses of drug could be achieved. The device, shown schematically in Figure 15.3a, possesses pockets that act as drug containers. The pockets are capped with a membrane of PLGA and release of the drug is restricted by the presence of the polymer. Now, the length of time it takes for the cap to be removed is dependent on the molecular weight of the PLGA. As shown in Figure 15.3b, the use of four different molecular weights of PLGA as capping materials generated four pulses of release.

A further example of using microfabrication in drug delivery is the formation of biodegradable polymer microneedles for injection without the use of a hypodermic syringe. The Prausnitz group has created a minimally invasive drug delivery system composed of an array of polymer needles in the shape of cones with a tip radius of only 2.5 μm [34]. This array can penetrate the skin to a depth of 750 μm without causing any pain. The needles are loaded with drug/polymer microparticles that release into the sublayers of the skin over periods of many days. A major advantage of this system is the ability of the patient to self-administer the drug delivery system. In comparison, many implant systems (e.g., Zoladex LA) require insertion by trained staff. The biodegradable needles may be withdrawn when the patient removes the array patch with any needles that remain within the skin layers safely degrading.

15.6.5
Polymer–Drug Conjugates

A polymer–drug conjugate is formed when a covalent bond is formed between a polymer and drug. The physical properties of the molecule become dominated by

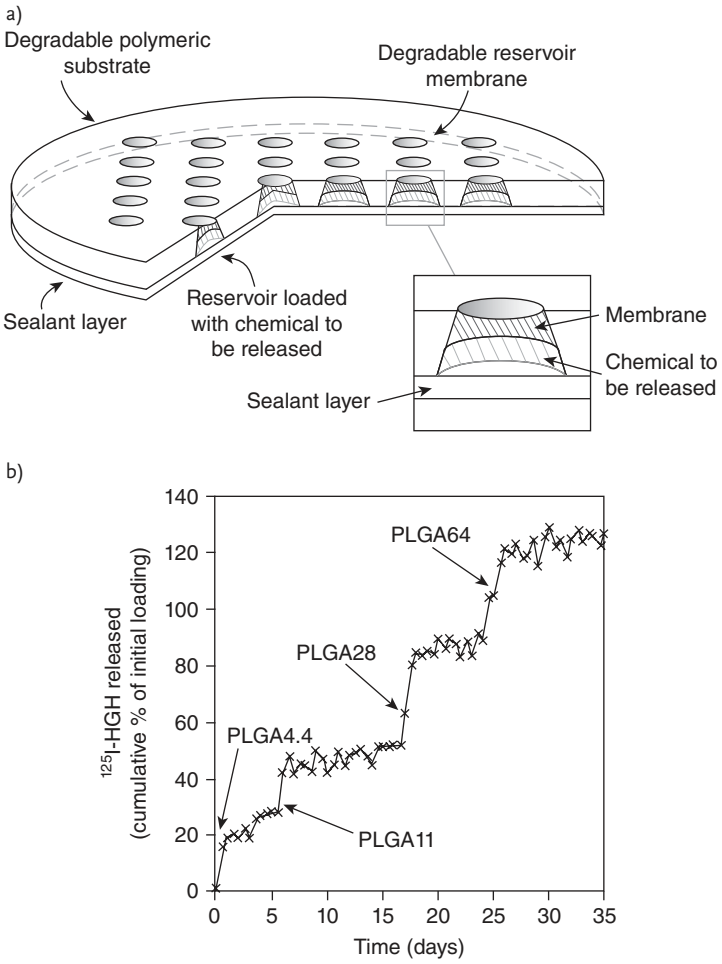


Figure 15.3 (a) Diagram of microfabricated device. The main body of the device is composed of a polymer that resists erosion until after the pockets have release their drug payload. Reservoirs or pockets of drug are capped with a membrane composed of PLGA. (b) Pulsatile release of human growth hormone achieved using PLGA of molecule weight of 4.4, 11, 28, and 64 Da. Reproduced with permission from [33].

the polymer and hence *in vivo* distribution, rate of liver excretion, and other properties that determine the time and location of drug action may be varied. Ringsdorf's initial vision for this class of polymer–drug conjugates has inspired numerous systems that have shown considerable promise in clinical trials [35, 36]. From a clinical perspective, the most important class of polymer–drug conjugates is formed using PEG. Numerous protein–PEG conjugates are used in drug therapy owning to the ability of the PEG to slow down the rate of protein metabolism and renal excretion and, hence, increase the half-life of biopharmaceutical [37].

However, PEG is not a biodegradable polymer and so we will not explore the mechanism of action of these conjugates further.

There are a number of polymer–drug conjugates that do contain biodegradable components. One key function of polymer–drug conjugates is their ability to release the drug once it has been carried into the cell by the polymer component. The high molecular mass of the polymer–drug conjugate results in an accumulation of the conjugate in certain types of tumors. This accumulation is caused by the enhanced permeability and retention effect, whereby many tumors possess leaky blood vessels that allow the conjugate to escape the blood system efficiency. In contrast, nontumor sites within the body have less-leaky blood vessels and so the drug does not enter tissues within which it would cause major side effects. Within the tumor site, the polymer–drug conjugate is taken up by cells and enters intracellular vesicles called lysosomes. The drug must escape the lysosome to have a pharmacological effect.

The Duncan group has described polymer–drug conjugates that preferentially release drug within the lysosome [38]. These lysosomotropic nanomedicinces use *N*-(2-hydroxypropyl)methacrylamide copolymer as the nondegradable backbone of the conjugate. This copolymer has been shown to be nontoxic and nonimmunogenic. The linkage between the *N*-(2-hydroxypropyl)methacrylamide copolymer and the anticancer drug is chemically broken within the lysosome when the pH falls. Hence, the drug remains as part of the conjugate until it has been successfully delivered to the target cell.

15.6.6
Responsive Polymers for Injectable Delivery

Responsive polymers undergo a phase change or gelation in result of a change in local environmental conditions. This concept has been used to great success in the development of block copolymers of PLGA–PEG–PLGA [39]. A product called ReGel is being developed for a range of drug delivery applications by exploiting the thermal gelation of this class of polymers. Gelation occurs at a temperature just below the body temperature. As a result, aqueous solutions of PLGA–PEG–PLGA are liquid at room temperature and may be injected through syringe needles into the body. Within the body, the system rapidly gels to form a delivery system that is retained at the site of administration. If a drug is included within the aqueous polymer solution, then it will be entrapped within the gel and released slowly due to retarded diffusion that accelerates as the PLGA component degrades. For example, ReGel has been used to release an anticancer agent, paclitaxel, for approximately 50 days [40].

15.6.7
Peptide-Based Drug Delivery Systems

The remarkable properties of biological molecules within living organisms have stimulated research into the replication of these properties in synthetic materials

[41]. Living systems use peptides and proteins to achieve many chemical and mechanical properties within cells. These properties can be generated in synthetic polymers built from amino acid monomers to form polymers with biodegradable amide linkages.

For example, Tirrell and coworkers have described artificial protein hydrogels with tunable erosion rates [42]. The hydrogels were formed from genetically engineered proteins and through aggregation of leucine zipper domains. The erosion rate of the hydrogel was controlled through changes in the amino acid sequence which in turn changes the network topology. This strategy generated hydrogels that are formed through physical crosslinks and possess highly predictable degradation properties.

15.7 Concluding Remarks

The poly(α-hydroxy acids) and polyanhydrides have undergone many years of research to generate the clinical products in use today. The versatility of these polymers encourages their use in a broad range of drug delivery systems in preclinical development. The weaknesses of these systems are apparent in the literature but the difficulty of replacing with new biodegradable polymer should not be underestimated. Promising new approaches are being reported based on systems that copy mechanisms of protein sequestering, thermal gelation, and cell-mediated release. Polymer–drug conjugates are being patiently optimized and clinical studies show promise in cancer chemotherapy. In addition, new fabrication techniques are opening new opportunities for established classes of biodegradable polymers.

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16
Oxo-biodegradable Polymers: Present Status and Future Perspectives

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16.1
Introduction

Synthetic and semisynthetic polymeric materials were developed for their versatility, easy processability, and durability – resistance to all forms of degradation as promoted by physical, chemical, and biological means or combinations thereof. Enhanced durability is achieved when required by including stabilizing additives (usually in combinations) and by processing under conditions that maximize the maintenance of molecular weight and functionality during fabrication and under subsequent service conditions. Macromolecular materials have been and are widely accepted because of their cost-effectiveness to provide a large variety of items that improve the comfort and quality of life in both modern industrial societies and developing countries. Moreover, the demand in the next two decades for polymeric materials is expected to increase two- to threefold primarily as a consequence of an increase in plastics consumption in developing countries, with an annual growth rate worldwide of 7–10%.

Plastics are ubiquitous because the various types that are commercially available collectively span a very wide range of useful properties. It is commonly claimed that approximately one-third of all commodity plastics are used for packaging purposes. The reason is that these materials are inexpensive, easy to fabricate, strong, tough, stretchy, have good barrier properties, and are reusable and recyclable, among other characteristics. The polyethylene (PE) shopping bag is an example of a common plastic article that is used in very large quantities because it does exactly what it is supposed to do at very low cost. It has supplanted the alternatives, for example, the brown paper bag, almost completely at checkout stations because it has overall superior properties and, most importantly, it is much less of an environmental burden to produce and transport [1, 2]. One criticism that is leveled at commodity plastics in short-lived applications, however, is that they persist too long after they are used and discarded. This is considered to lead to a serious plastic waste burden. The banning or taxing of PE shopping bags and analogous products is not the answer, however, because consumer

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requirements need to be met and there is no acceptable substitute. Therefore, innovative technology is required.

The design, production, and consumption of polymeric materials for commodity and specialty plastic items must surely contend with all the constraints and regulations already in place or predicted to deal with the management of primary and postconsumer plastic waste. This is certain to involve the formulation of environmentally sound degradable polymers. Technologies based on the recovery of free energy content through recycling and from incineration with heat recovery will be flanked by the increasingly attractive option of environmentally degradable macromolecular materials. These latter polymers should be considered as preferred replacements for conventional commodity plastics in those product segments for which recycling is not a practical option. The strategies that are nowadays receiving a great deal of attention at both fundamental and applied levels include the design of some bio-based polymers, the introduction of hybrid polymeric formulations, and the reengineering of well-established polymers of synthetic and natural origin.

16.2
Controlled – Lifetime Plastics

During the past 20 years, science and technology have been developed for polymers that can biodegrade after being used and discarded. Everything from shopping bags to agricultural mulch films to daily landfill covers to food packaging as examples can be made to disintegrate after disposal and to yield thereby molecular fragments that are susceptible to mineralization by naturally occurring microorganisms. The carbon in these polymers is returned to the biocycle, and there are no harmful residues. These are the oxo-biodegradable polyolefins, as defined below.

According to the ASTM definition [3], a biodegradable plastic is "*a degradable plastic in which the degradation results from the action of naturally occurring microorganisms such as bacteria, fungi and algae.*" Rather more informative is the ASTM definition [4] of the environmental degradation of a plastic: *"abiotic or biotic degradation process or both that occurs in a given environment and includes photodegradation, oxidation, hydrolysis and biodegradation. Living organisms affect biotic degradation processes and abiotic degradation processes are not biological in nature."* Two principal types of commercially viable biodegradable plastics have been developed and are finding a variety of applications in many mercantile segments and consumer products: (i) *oxo-biodegradable polymers* for which degradation is the result of oxidative and cell-mediated phenomena, either simultaneously or successively and (ii) *hydro-biodegradable polymers* for which degradation is the result of hydrolytic and cell-mediated phenomena, either simultaneously or successively. Both types of biodegradable polymer feature a two-stage sequential molar mass reduction in the environment with the first stage being abiotic. Since the objective is to reduce the amount of plastic with minimum effect on the environment, the second stage is

bioassimilation of the molecular fragments that are generated in the first stage. Abiotic mechanisms are generally regarded as too slow by themselves to be adequate in a variety of disposal environments.

There are several applications in which really quite rapid degradation of plastics after use is required. For example, plastics that end up in water- or sewage-treatment systems are an example of situations in which they need to lose integrity relatively rapidly so as to avoid plugging pumps, filters and the like. Hydrolytically unstable biodegradable plastics can provide an answer here. In many other uses (e.g., food packaging), however, hydrolytic instability is a disadvantage. Overall stability is required during shelf storage and use, but this should be followed by relatively rapid abiotic degradation within a specific time, depending on the disposal environment. The avoidance of the accumulation of plastic fragments requires that these be consumed through biodegradation by microorganisms in virtually all disposal environments. Effective biodegradation of such residues can be achieved when originally hydrophobic plastics acquire water-wettable (hydrophilic) surfaces and a relatively low molecular weight so that there is a significant number of molecular "ends" accessible at the surface. The science and technology of the development of commercially viable commodity plastics that can meet these criteria are the topics addressed in this chapter.

Of the current worldwide production of synthetic polymers, nearly 90% is represented by full-carbon-backbone macromolecular systems (polyvinyl and polyvinylidenics [5]), and 35% to 45% of production is for one-time use items (disposables and packaging).Therefore, it is reasonable to envisage a dramatic environmental impact attributable to the accumulation of plastic litter and other plastic waste from discarded full-carbon-backbone polymers, which are conventionally recalcitrant to physical, chemical, and biological degradation processes. The mechanism of biodegradation of full-carbon-backbone polymers requires an initial oxidation step, mediated or not by enzymes, followed by fragmentation with a substantial reduction in molecular weight. The functional fragments then become vulnerable to microorganisms present in different environments, with production (under aerobic conditions) of carbon dioxide, water and cell biomass. Figure 16.1 outlines the general features of environmentally degradable polymeric materials, which are classified as hydro-biodegradable and oxo-biodegradable. Typical examples of oxo-biodegradable polymers are PE, poly(vinyl alcohol) [6], natural rubber (poly-*cis*-1,4 isoprene) [7], and lignin, a naturally occurring structurally complex heteropolymer.

The prodegradant added to polyolefins to convert them to oxo-biodegradable status does not cause any oxidation or other degradation as long as antioxidants are present. Thus, the shelf life and use life of the plastics are maintained for a period that is controlled by the amount of antioxidant (or other stabilizing additives) present in the formulation. Once the stabilizers have been depleted, the prodegradant catalyses the oxidative degradation of the polymer, with the rate of degradation related to the concentration of prodegradant. By controlling the concentrations of these two classes of additive, one practically controls the "lifetime" of the plastic.

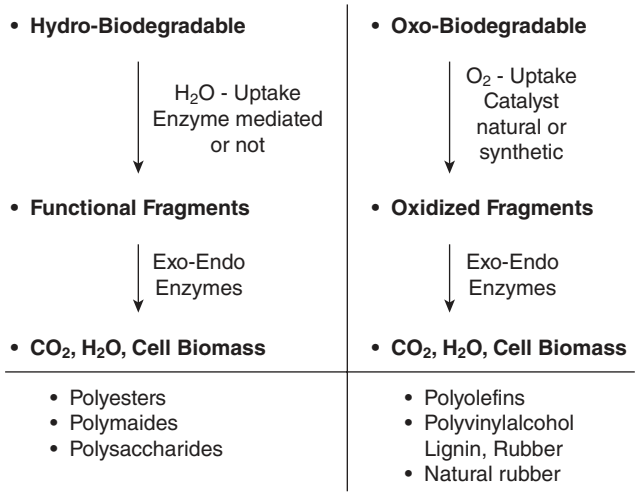


Figure 16.1 General features of the two classes of environmentally degradable polymers.

16.3 The Abiotic Oxidation of Polyolefins

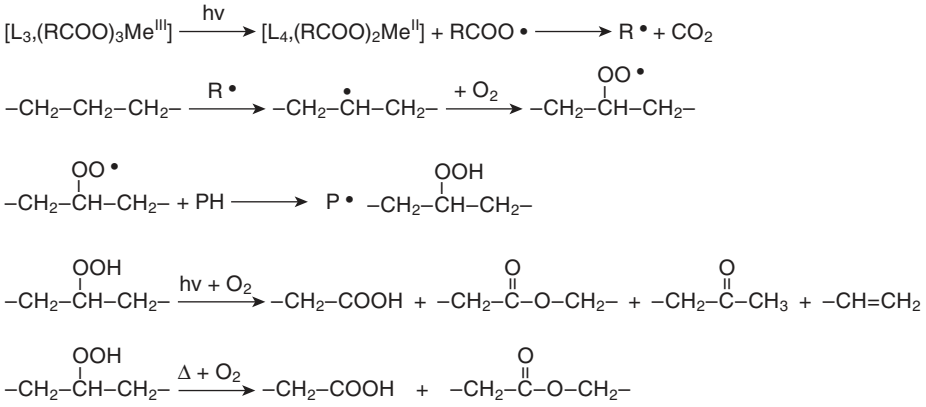
The knowledge [8–10] of the thermal and photolytic peroxidation mechanisms of PE and polypropylene (PP) constitutes the basis for the development of "reengineered" polyolefins susceptible to enhanced oxidation and fragmentation, when exposed to heat or light, with the aim of overcoming the intrinsic recalcitrance of polyolefins to biodegradation. It has been established that the beginning of the sequence of reactions leading to polyolefin peroxidation is the generation of sensitizing impurities during the processing of these thermoplastics [8]. It has been recognized that carbonyl [8, 11] and hydroperoxide [8, 12, 13] groups represent the major sensitizing impurities formed during the processing of PE and of PP. At this stage, the chemical structure of the polyolefins is considered to be the most important parameter capable of influencing the oxidative degradation processes. During subsequent use and disposal steps, the oxidation of both types of resin appears to be mainly affected by structural parameters, such as the degree of polymerization, chain conformation, degree of crystallinity, and geometry [13].

In the case of PE, the poor reactivity of the nonpolar C–C and C–H bonds markedly constrains the degradation processes by radical reactions. These are generally initiated by bond-breaking processes promoted by energy input in the form of heat, UV radiation, mechanical stress, or some combination of these. Since the susceptibility of saturated bonds to scission is dependent on bond energy, the initial homolytic bond scission reactions are largely restricted to structural defects, such as branch points and double bonds. The tertiary carbon–hydrogen bonds that alternate with methylene groups along PP chains are obviously vulnerable. Following initial bond breakage, a complex series of radical reactions may lead to the total degradation of the molecules.

16.3.1 Mechanisms

The overall sequence of reactions that are the basis of PE oxidation and of polyolefins in general has been elucidated during several decades of research, producing a large number of original papers and review articles. For example, it is widely accepted that the starting point of the process is the homolytic cleavage of C–C bonds in the backbone that occurs during polymer processing as a result of shear stresses during extrusion [14]. In the presence of oxygen (as in most industrial processes), the carbon-centered radicals are converted to peroxy radicals, and then to hydroperoxides by hydrogen abstraction from nearby tertiary sites. The high reactivity of hydroperoxides subjected to heat and/or UV light promotes a further series of reactions leading to chain scission (molar mass reduction) and the formation of several different oxidized groups. In the overall peroxidation process of PE, the decomposition of hydroperoxide groups is acknowledged to be the rate-determining step [13]. This initiates a radical chain reaction which is autoaccelerating, as shown in Scheme 16.1.

Even though the aim of this chapter is not to review the large amount of literature on polyolefin degradation, a general overview of the mechanism and kinetics of PE oxidation is useful for a better understanding of the environmental fate of PE. In this connection, the basic mechanism proposed by Bolland and Gee [15]–comprising the classic steps of initiation, chain propagation, and termination–should be considered as relevant (Scheme 16.1). As already mentioned, the key intermediates in the accepted mechanism are hydroperoxides, the decomposition of which produces further free radicals and the derived oxidation products. Many of the kinetic studies of thermooxidative processes of polyolefins are for polymers in the melt, and several mechanistic studies have focused on polymers in a solution. Considering that the practical uses of polyolefins are in the solid state, numerous studies have been devoted to the investigation of the kinetics of the thermal and photooxidation of polyolefin films and sheets. Oxidation products



Scheme 16.1 General mechanism of peroxidation and chain cleavage in polyolefins.

have been identified and several parameters, such as oxygen pressure, temperature, and sample thickness that influence oxidation processes have been considered in the investigations.

16.3.2 Oxidation Products

Fourier transform infrared (FTIR) spectroscopy is one of the most powerful techniques to be used in studying the kinetics of PE and PP oxidation in the solid state. Significant changes can be easily monitored in various regions of the spectra of films and sheets during thermal and photooxidation. In particular, the presence of hydroperoxides is recognized from absorption bands between 3400 and 3200 cm^{-1} and absorptions in the carbonyl region – specifically between 1780 and 1700 cm^{-1} – are used to evaluate the rate and extent of the oxidative degradation of polyolefins. In addition, the absorbance variation of double-bond deformation peaks as well as the absorption from carbon–oxygen single bonds can provide valuable information on the mechanism and oxidation products involved.

When oxygen concentrations are nonlimiting, during the initiation stage, it may be assumed that all the macroradicals as they are produced (e.g., by shear stresses) are instantly oxidized to peroxy radicals which, by intra- or intermolecular abstraction, are then converted to hydroperoxides. A fairly complex series of chain reactions involving the formation/decomposition of peroxy radicals/hydroperoxides constitutes the propagation step leading to oxidation product formation and chain scissions. It has been estimated that, in oxidized solid PE, more than 80% of the oxygen-containing products are represented by carbon chains bearing ketone or carbonyl groups [13]. Briefly their formation is generally attributed to the decomposition of hydroperoxides (in the case of ketones), whereas carbonyl groups are considered to be produced by peroxide decomposition. In addition, the conversion of alkoxy macroradicals by β-scission to produce a carbonyl group and a chain-end radical can occur. It has been ascertained that there is a straightforward relationship between the number of carbonyl groups formed and the extent of chain scission. Thus quantitative FTIR analysis can be used effectively to measure the extent of the abiotic thermal degradation of PE [16].

As a consequence of the radical oxidation processes and relevant chain scissions, a fairly high number of degradation products containing functional groups have been recognized in several investigations. In particular, two different classes represented by low-medium molecular weight fractions and volatile intermediates, respectively, can be detected during kinetic studies of the thermal and photooxidation of PE. As a result, the oxidation processes of PE and in particular of low-density polyethylene (LDPE) can be monitored effectively by gravimetric analysis showing the weight increase (oxygen uptake) as a function of the thermal aging time and temperature [16]. In a case study, carried out on an LDPE sample containing a thermal prodegradant, the time profile of weight variation showed a S-shaped profile, thus accounting for the exponential accumulation of oxidized low-medium molecular weight fractions, followed by the progressive weight

decrease owing to the loss of volatile intermediates. In several studies, low-medium molecular weight products containing carbonyl and hydroxyl groups have been identified [17]. It has been ascertained also that the amounts of these products account for at least 80% of the products containing ketone and carboxyl groups [13]. Carboxylic acids tend to accumulate during prolonged exposure times since other oxygen-containing products formed in the early stages of the degradation process, such as alcohols, aldehydes, and ketones, are susceptible to further oxidation to produce carboxylic acids. In classic studies [18, 19], most of the low-molecular-weight degradation products from both thermally- and photooxidized PE have been isolated and identified by solid-phase extraction coupled with gas chromatography/mass spectrometry. Accordingly, numerous semivolatile compounds have been identified [17] including alkanes, alkenes, ketones, aldehydes, alcohols, mono- and di-carboxylic acids, lactones, keto-acids, and esters. In addition, highly volatile organic products (C2–C6) have also been detected although in a very relatively small amounts. Among these, acetaldehyde represents the most important; its quantitative release profile has been monitored [13].

As discussed above, carboxylic and dicarboxylic acids have been found to be the most abundant products which are formed during both photo- and thermal oxidation. They tend to accumulate owing to their low propensity to oxidize further during prolonged aging. They presumably evolve from the oxidation of other functional groups, such as primary alcohols and aldehydes deriving from hydroperoxide decomposition followed by hydrogen abstraction or β-scission, respectively, particularly during thermal aging. Also, the photolytic cleavage of ketone groups by Norrish mechanisms can lead to the formation of carboxylic acid groups. Accordingly, dicarboxylic acids have been found to be the predominant products formed during the prolonged photoxidation of PE [20]. The presence of large amounts of carboxylic acids, as demonstrated qualitatively by FTIR spectroscopy, suggests the severe alteration of the PE matrix. Indeed, with the progressive accumulation of carboxylic groups as a function of exposure time, there is an accompanying variation in both the shape and the intensity of the absorption bands between 3800 and 3400 cm^{-1} that are associated with aliphatic carboxylic acids. Owing to their relative thermal stability (compared to photoinstability), ketone groups are considered as typically associated with the thermal degradation of PE. Other products, recognizable in the volatile and semivolatile fractions of PE oxidation products, such as keto-acids, have been identified during low-temperature thermal degradation, whereas lactones are usually generated under extreme conditions or after extensive degradation has occurred [18, 19, 21].

Since most of the oxidation products result in the first instance from the decomposition of polymer hydroperoxides, they are formed and trapped within the bulk solid, and only a small fraction can escape. In this connection, it has been noted that the estimation of the degradation products extractable with organic solvent(s) should both provide useful information about the level of oxidative degradation and help characterize the low-medium-molecular-weight oxidation products. Further information about the regioselectivity of oxidation can be obtained by analyzing the level of solvent extractable fractions and molecular weight and

polydispersity of a nonextractable polymer residue. The characterization of the oxidized fraction of PE soluble in a dichlorobenzene–methanol mixture showed that it contained a large amount of oxygen-containing functional groups attached to low-molecular-weight chain fragments, whereas the nonextractable portion of the polymer contained a relatively low level of oxidation [13].

16.3.3 Prodegradant Effects

In a recent study of ours [16] the amount of extractable fraction from thermally oxidized LDPE samples containing prodegradant additives was evaluated as a function of the level of polymer matrix oxidation as assessed by the carbonyl index (CO*i*) (Figure 16.2). In particular, it was shown that the amount of acetone-extractable material is positively correlated to the level of oxidation induced by thermal treatment in an oven, thus reaching fairly high levels corresponding to 25–30% of the original sample weight. The solvent-extractable fractions, as characterized by NMR and by FTIR, were heavily oxidized and had low molecular weights (0.80–1.60 kDa). Furthermore, it was also observed that the increase in oxidation level as related to CO*i* values was matched by an increase in the quantity of oxidized plastic having reduced molecular weight.

The large amount of numerous oxidation products, as well as their relative concentrations, are accounted for by the large number of interrelating elementary reactions, and these give rise to a rather complex scheme to describe the oxidation kinetics. In spite of the major interest in these complex series of chain reactions that has attracted a great deal of attention over the past 50 years, little agreement on the kinetic models and values of specific rate constants has been achieved, from either a theoretical or an experimental basis. One of the more contentious issues is that of whether the oxidation mechanism should be considered as a homogene-

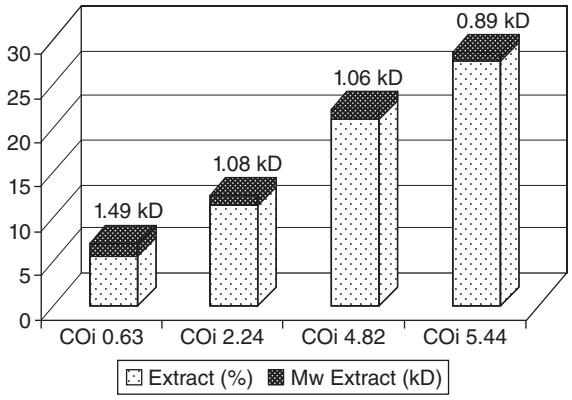


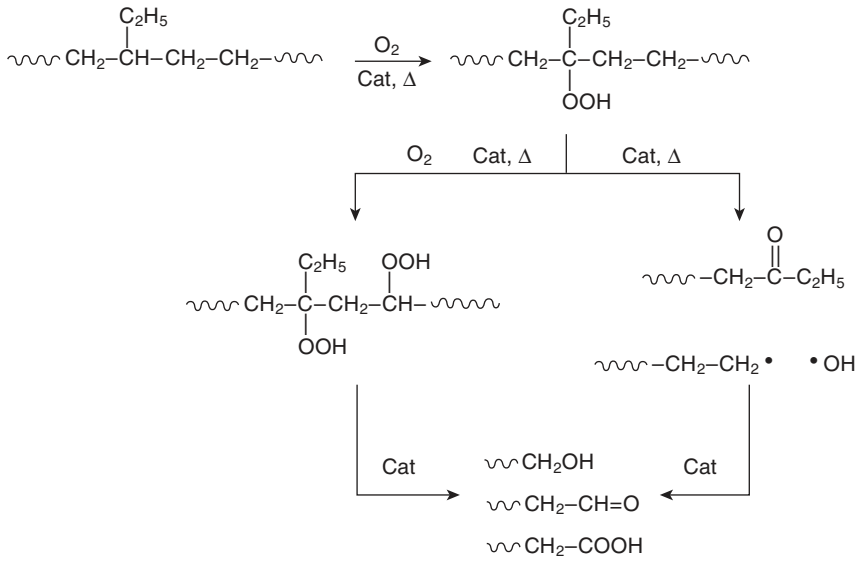
Figure 16.2 Percentage of fractions extractable with acetone and relevant molecular weight in thermally treated LDPE film at various levels of oxidation as determined by the carbonyl index (CO*i*).

ous phenomenon or as a heterogeneous process involving the spread of degradation from localized centers. This latter interpretation takes into account the semicrystalline nature of polyolefins, where amorphous regions, more susceptible to oxygen diffusion and oxidation, coexist with crystalline regions where oxidation events are hindered, largely owing to the negligible dissolved oxygen content.

Even though the aim of this chapter is not to review this topic, some basic simplified information on kinetic oxidation processes is useful to predict the ultimate oxo-biodegradation propensity of PE. In particular, the effect of physical parameters such as aging time, temperature, and radiation intensity may affect the subsequent extensive biodegradation step. Indeed, one of the most important requirements, in order to predict the oxidative behavior of polyolefin films, is the correlation between the experimental kinetics of oxidation and the chemical reactions that may occur in the bulk polymer. In several studies, therefore, it has been shown that the early stage of the thermooxidative degradation of PE, as monitored by the formation of carbonyl groups, is apparently in agreement with a typical auto-acceleration mechanism [22]. In the overall peroxidation of PE, the decomposition of hydroperoxide groups is therefore considered to be the rate-determining step [13]. Hence, additive molecules which are capable of enhancing hydroperoxide formation and decomposition to other radicals are active prodegradants since they accelerate the oxidation and cleavage of polyolefin chains.

16.4
Enhanced Oxo-biodegradation of Polyolefins

Major strategies to enhance the environmental degradation and biodegradation of polyolefins have been focused on copolymerization, blending, or grafting with functional polymers and other compounds as well as the addition of prodegradant additives. UV-absorbing carbonyl groups capable of accelerating the photooxidation process can be introduced by copolymerizing ethylene and carbon monoxide or vinyl ketones [23–26], the latter strategy being the technical process used in the production of Ecolyte polyolefins [25]. Another strategy to improve the environmental degradability of PE and PP films is the addition of prodegradant additives during processing [27]. It has been suggested, in fact, that this latter alternative may provide a more efficient control of the degradation rate, thus making the shelf life and use life of the polyolefins compatible with a very wide range of applications and disposal environments [14]. Most of the prodegradant additives used commercially are organic complexes of transition metals, those capable of yielding two metal ions differing in oxidation number by one unit. Several polymer-soluble metal carboxylates and acetylacetonates of Co^{3+}, Fe^{3+}, and Mn^{2+} are very effective photoprodegradants for polyolefins, capable of initiating the degradation process through metal salt photolysis to give the reduced form of the metal ion and a free radical. The anion radical promotes a fast hydrogen abstraction from the polymer with the subsequent formation of hydroperoxide. Afterward, the general radical oxidation reactions of polyolefins proceed with enhancement by the usual redox



Scheme 16.2 Radical chain reactions in polyolefins as promoted by transition metal ion prodegradants.

$$Co^{2+} + ROOH \longrightarrow Co^{3+} + RO^{\bullet} + OH^{-}$$

$$Co^{3+} + ROOH \longrightarrow Co^{2+} + ROO^{\bullet} + H^{+}$$

Scheme 16.3 Hydroperoxides decomposition as mediated by transition metal ions.

reactions between hydroperoxides and metal ions. Alternatively, prodegradant additives can induce the peroxidation process in polyolefins by absorbing energy as heat. In this case also, the activity derives from transition metal ions typically added to the final products in the form of stearates or acetylacetonates. The most commonly used cations are Mn^{2+} [28] and Co^{2+} [29]. Instead of Fe^{3+} complexes which are significant in photooxidation processes, Mn^{2+} and Co^{2+} are used to accelerate the radical reactions in polyolefin oxidation through the decomposition of hydroperoxides and peroxides induced by heat absorption [30] (Schemes 16.2 and 16.3). It must be emphasized that the transition metal salts catalytically induce the rapid decomposition of polyolefin hydroperoxides; very small amounts only are required to speed up the peroxidation of polyolefins by several orders of magnitude.

Another type of "photosenstizer" prodegradant for PE is Fe^{3+} dithiocarbamates or dithiophosphates. These compounds initially act as antioxidants by decomposing hydroperoxides by an ionic mechanism [31, 32] after which the ligands are destroyed and the free transition metal ions perform as a prodegradant. In this

way, in these compounds both antioxidant and prodegradant functionalities coexist. This characteristic has been used to finely control the lifetime before the photooxidation of PE commences. This is the basis of the Scott–Gilead technology [12] which led to the production and commercialization of controlled-lifetime photodegradable mulching films and analogous products, under the trade name Plastor. Nowadays, several agricultural plastic items based on oxo-biodegradable PE contain prodegradants comprising transition metal ions with organic ligands. They have been developed by several companies for sale as master batches (for blending on conventional equipment with normal resins) under different trade marks (TDPA, EPI Environmental Plastics Inc.), or end products (Envirocare, CIBA Specialty Chemicals).

Several studies have reported the significant reduction of molecular weight after thermal and photodegradation of PE samples containing prodegradants [20, 33] as well as the extraction, isolation and identification of oxidation products, including carboxylic acids, ketones, esters, and low-molecular-weight hydrocarbons [34, 35]. The overall rate and extent of the abiotic peroxidation of polyolefins are related to structural parameters such as chain defects and branching. The latter give rise to facile oxidation due to the susceptibility to hydrogen abstraction from tertiary carbon atoms through a vicinal hydrogen-bonded intermediate which can obviously be extensive in poly-α-olefins such as PP. The role of vicinal hydroperoxides is of particular importance in carbon chain cleavage and it leads to the release of small molecules carboxylic acids, alcohols, and ketones [20] even though random chain scission is considered to be the predominant process initially. Taking into account these considerations, it has been shown repeatedly that the decreasing order of susceptibility of polyolefins to peroxidation is: iPP > LDPE > LLDPE > HDPE [36, 37].

The ultimate environmental fate of "degradable" polyethylenes has to be recognized as the results of the combined action of abiotic factors and microorganisms. This has suggested the definition of "oxo-biodegradable" materials in keeping with the processes of biodegradation of lignin and natural rubber [11], for example, since the evaluation of the extent and rate of peroxidation of these materials represents a powerful tool for the prediction of their biodegradation. Several studies have therefore been carried out with the aim of determining the mechanisms of the photo- and thermal oxidation of polyolefins containing prodegradant additives. Nevertheless, most of these studies have been carried out under strictly controlled laboratory conditions, including accelerated conditions that cannot be considered as representative of natural environments. In fact, only a few investigations have been performed by assessing the synergistic effects of temperature, humidity, and sunlight exposure that are collectively involved in outdoor exposures. In the context of the general mechanism of the radical oxidation of PE (Scheme 16.1), the following parameters can be monitored during abiotic degradation testing of LDPE and LLDPE blown films: (i) weight variation; (ii) CO*i*; (iii) surface wettability; (iv) molecular weight changes; and (v) fractionation by solvent extraction. In particular, gravimetric analysis can be used effectively to understand the weight changes as a consequence of the oxygen uptake during the early stages of oxidation as well

as the weight loss due to volatilization of low molar mass fragments after prolonged thermal and photodegradation.

Another powerful tool for the qualitative and quantitative evaluation of the oxidation processes is the CO*i* as determined by FTIR spectroscopy. It has been reported repeatedly that most of the degradation intermediates from PE peroxidation contain carbonyl groups so that their concentration, as determined by CO*i* measurements, can be used to monitor the progress of degradation [22]. These determinations are usually carried out on test films by recording the ratio of the optical density of the carbonyl absorption bands in the range 1780–1700 cm^{-1} to the optical density of the band at 1463 cm^{-1} (CH_2 in-plane vibration – scissoring peak). In addition, FTIR analyses provide information on the presence and formation over time of oxidation products with absorption maxima at 1712 cm^{-1} (carboxylic acids), 1723 cm^{-1} (ketones), 1730 cm^{-1} (aldehydes), and 1780 cm^{-1} (lactones) [35].

16.4.1
Biodegradation of Polyolefin Oxidation Products

The determination of the wettability of film surfaces by contact angle measurements may provide useful information about the increasing polarity of film surfaces as a consequence of oxidation and the formation of functional groups. This information is also useful in order to predict the propensity for microbial attack on PE films, by recognizing that one of the reasons suggested to explain the intrinsic recalcitrance of PE to biodegradation is the hydrophobic character that hinders the adhesion and interaction of microbial cells. In terms of potential ultimate biodegradation (i.e., conversion to CO_2 and H_2O, mineralization), the assessment of molecular weight changes is of fundamental importance as well. Indeed, it has been suggested from a theoretical point of view that since PE is a nominally straight-chain hydrocarbon, it should be metabolized according to the biochemical pathway for linear alkanes. On the other hand, it has been established that there is a molecular weight upper limit for the utilization of *n*-alkanes as a carbon source by microorganisms. Haines and Alexander established that linear hydrocarbons with more than 44 carbon atoms (tetratetracontane) cannot be metabolized by soil microorganisms [38]. Recently, this dimensional limit has been extended to 0.72 kDa corresponding to 60 carbon atoms in a study using single bacterial strains [39]. In any case, these limits are thought to be related to the bacterial metabolism of *n*-alkanes that need the accessibility to methyl chain ends by extracellular oxidizing enzymes to start the biodegradation process. Thus, the rate and eventually the ultimate extent of biodegradation of solid *n*-alkanes is strongly affected by the availability of $–CH_3$ chain ends susceptible to enzymatic oxidation. It follows that the chain ends present at the surface of solid *n*-alkane decrease with an increase in molecular weight with extremely low values in the case of high-molecular-weight PE.

Finally, other information about the relationship between the levels of oxidation reached during the abiotic stage of degradation of "degradable" PE – the molecular weight reduction as well as the potential to be biodegraded in the environment – can

be effectively obtained by the fractionation of pre-aged specimens using solvent extraction. This procedure may also provide, especially if carried out by using solvents with different polarities, further information on the relative amounts of different classes (e.g., carboxylates, alkanes, etc.) of degradation products deriving from peroxidation and cleavage of PE chains.

16.4.2 Standard Tests

Further to the evaluation of the abiotic oxidation of "degradable" PE, the final step to be investigated in order to envisage the ultimate environmental fate of these materials is the estimation of the extent of biodegradation under different conditions. The requirement of two steps, abiotic and biotic, in the degradation mechanism of oxo-biodegradable plastic materials has recently led to the preparation and approval of ASTM D6954-04 "Standard guide for exposing and testing plastics that degrade in the environment by a combination of oxidation and biodegradation" [4]. This standard provides a framework to assess and compare the degree of degradation attainable under controlled thermal and photooxidation tests as well as the degree of biodegradation and ecological impacts in defined environments after abiotic degradation. Evaluations in ASTM D6954-04 are divided into three levels relevant to: (i) accelerated aging in standard tests for both thermal- and photooxidations and determination of the degree of abiotic degradation (Tier 1); (ii) measuring biodegradation (Tier 2); (iii) assessing the ecological impact after these processes (Tier 3). In order to implement Tier 1, the standard suggests the use of test conditions for thermal or photooxidation likely to occur in application and disposal environments for which the test material is designed. In other words, accelerated oxidation should be carried out at temperatures and humidity ranges typical of application and disposal conditions. Test materials resulting from the accelerated oxidation tests are therefore exposed to appropriate use or disposal environments (soil, landfill, compost) in standard respirometric (biometric) tests in order to assess the rate and the degree of biodegradation (Tier 2). Finally, any residues of the materials under test, deriving from both the abiotic oxidation stage and the biodegradation tests must be submitted to ecotoxicity tests to demonstrate their ultimate environmental compatibility (Tier 3).

As a case study, the oxo-biodegradation behavior of LDPE blown film containing proprietary prodegradant[1)] additives has been reported. In accordance with the general scheme of oxo-biodegradation, the study has been divided into two stages: (i) Tier 1 represented by the abiotic pre-treatment and structural characterization of the sample, and (ii) Tier 2 in which the ultimate biodegradation of the oxidized LDPE sample has been evaluated under different environmental conditions. Finally, the relationship between the degree of oxidation achieved during the abiotic oxidizing step and the propensity to biodegradation has been established. As repeatedly reported, the general mechanism of thermal or photooxidation is

1) Various patents assigned to EPI-Environmental Products Inc.–Vancouver, Canada.

Table 16.1 Structural changes recordable during the oxidation process of oxo-biodegradable polyolefins.

Parameters to be monitored during the preaging of LDPE		
Parameter	**Meaning**	
Weight variation	Increase: oxygen uptake	Decrease: loss of volatile intermediates
Carbonyl index by FTIR	Formation of cleavable oxidized groups in the main chain	Preliminary characterization of the oxidized functional groups
Wettability	Formation of an oxidized polar group at the surface	Increase: raise of the propensity to microbial colonization
Molecular weight	Evaluation of the degree of chain scissions	Decrease: raise of the propensity to microbial attack
Fractionation by solvent extraction	Estimation of the level of degradation	Characterization of oxidized intermediates

best described as an autocatalytic radical chain reaction leading to the oxidation and scission of polymer molecules, with the concomitant formation of oxidized low-molecular-weight fragments.

The parameters reported in Table 16.1 have been monitored during the preaging step carried out at 70 °C in an air convection oven. After an induction period, an appreciable weight increase according to a sigmoidal profile, attributable to the uptake of oxygen, is observed. Subsequently, as a result of prolonged treatment time, the sample weight starts to decrease owing to the loss of volatile (i.e., low molecular weight) degradation products. Since the carbonyl groups usually account for most of the oxidation products of the thermooxidative degradation of PE, the concentration of carbonyl groups on oxidation products, as determined from the CO*i*, can be used in monitoring the progress of degradation [40]. In line with the recorded weight increase, the CO*i* also shows a sigmoidal increasing shape. In addition, FTIR spectroscopy shows progressive broadening in the 1700–1780 cm^{-1} range for carbonyl groups with overlapping bands corresponding to carboxylic acids (1712 cm^{-1}), ketones (1723 cm^{-1}), aldehydes (1730 cm^{-1}), and esters (1740 cm^{-1}) during the aging period, thus indicating the formation of different oxidation products as aging progresses, as reported previously [41].

The increase in surface wettability during the oxidation of PE film containing prodegradant is an important indicator of the loss in hydrophobic character of this plastic. It has been shown that a few days of thermal treatment at 70 °C is sufficient to cause a dramatic decay in the contact angle of the LDPE film surface as hydrophobicity decreases. In addition, as a result of thermal oxidation, bulk density increases and film disintegration is observed, by floating the test film in tap water.

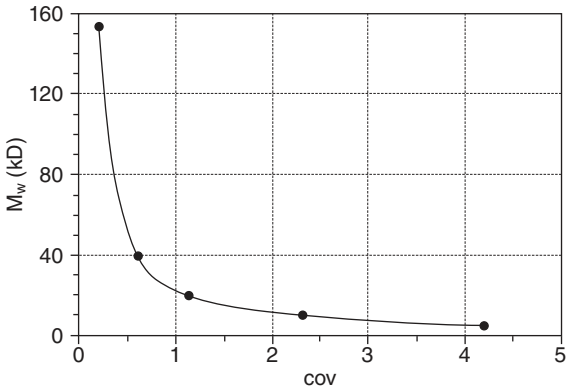


Figure 16.3 Molecular weight versus carbonyl index (CO*i*) relationship in LDPE film sample thermally treated in air in oven at 70 °C.

The disintegration of film samples occurred within 28 days, with film debris tending to sink to the bottom of the vessel. In parallel with the advancing oxidation process as monitored by CO*i*, weight changes and wettability increase during thermal degradation; a dramatic decrease in the molecular weight of the test sample has been recorded after a few days of oven aging. The progressive shift toward lower molecular weights as the CO*i* increases with the aging time can be observed by HT-GPC analysis. The relationship between the M_w and CO*i* can be expressed by a mono-exponential trend (Figure 16.3). Accordingly, CO*i* values may be used in order to predict the M_w decrease as a function of the level of oxidation. Moreover, the recorded trend is in agreement with a statistical chain scission mechanism, as suggested for the thermal- and photodegradation of polyolefins [13].

The feasibility to separate oxidized LDPE films into high- and low-molecular-weight fractions using a relatively simple extraction procedure with acetone has also been demonstrated [16]. In particular, the level of oxidation, as related to the carbonyl index, illustrates the increase in the amount of the solvent extractable fraction in parallel with a significant decrease in molecular weight. Accordingly, from heavily oxidized test samples, more that 25% by weight of acetone extracts can be obtained, thus also showing a very low *M*w (0.85–1.05 kDa) (Figure 16.2). These data once more confirm that LDPE containing prodegradant additives can be effectively oxidized and massively degraded to low molar mass fractions which, owing to their wettability and polar functionality, become vulnerable to microorganisms.

16.4.3
Biometric Measurements

The second stage in the assessment of the environmental fate of "degradable" polyolefins is the evaluation of the ultimate biodegradation of them under different test conditions aimed at reproducing disposal or accidental littering environments.

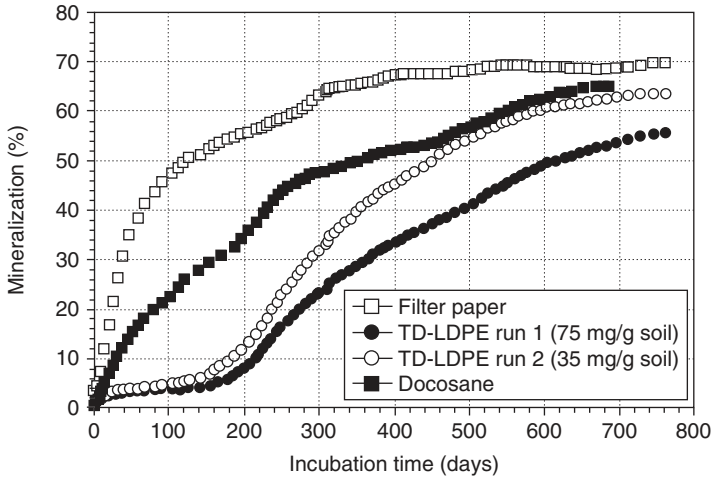


Figure 16.4 Mineralization profiles of thermally oxidized LDPE films and cellulose in a soil burial respirometric test.

In this connection, by using the materials retrieved from different abiotic degradation tests, several biometric respirometric tests have been carried out. The aim was to assess the susceptibility to mineralization under test conditions representative of soil, compost, and river water environments of LDPE that had reached different degrees of oxidation during the abiotic degradation stage.

Highly reproducible results have been obtained from several biodegradation tests carried out in soil burial biometer flasks aimed at assessing the biodegradation behavior of thermally oxidized LDPE film samples [42]. In all cases, the mineralization in soil of thermally oxidized samples does not show appreciable lag phases but it tends to a first plateau at about 5–7% mineralization in a few weeks (Figure 16.4). After that, a prolonged stasis (4–6 months) in the microbial conversion to CO_2 of the carbon in the samples has been observed repeatedly before further and markedly exponential increases in the biodegradation rate. Fairly high (55–65%) degrees of mineralization are observed after 18–24 months of incubation at room temperature. This two-step biodegradation behavior of thermally oxidized LDPE samples has been observed also in mature compost biodegradation tests. Therefore, in contrast to previous studies [41, 43] showing only limited and slow conversion to CO_2 of UV-irradiated LDPE samples, samples with no preaging and additive-free LDPE samples in natural soils, very large degrees of mineralization have been recorded although these were obtained over a relatively long time frame ranging between 22 and 30 months [42].

The first exponential phase, occurring during the first days of incubation in the biodegradation of thermally oxidized LDPE in soil, could be attributed to the fast assimilation by soil microorganisms of low-molecular-weight oxidized intermediates whose formation on the film surfaces has been demonstrated by the increased

wettability observed during the abiotic stage of degradation. The ready biodegradability of these compounds has been suggested previously because they disappear once oxidized samples are incubated in the presence of hydrocarbon-degrading microorganisms such as *Arthrobacter paraffineus* [20, 40, 44, 45]. Additional support for this hypothesis is obtained from the FTIR characterization of the LDPE films exposed for a few months to soil microorganisms during biometric tests. Indeed, a significant reduction of the absorbance in the carbonyl region with respect to the values recorded at the beginning of the test has been observed repeatedly. In contrast, the number of double bonds in the carbon–carbon polymer chains was found to increase during the soil burial experiments, with a corresponding dramatic change in the fingerprint region of the IR spectra of the LDPE samples. These observations suggest that, during the soil burial tests, preoxidized LDPE samples undergo an ongoing degradation process, mediated by both abiotic and biological factors, which leads to the formation of large amounts of oxidized molecular fragments capable of being assimilated as carbon sources by soil microorganisms. This might explain the two-step biodegradation behavior that has been observed repeatedly for preoxidized PE films in soil.

The effect of different levels of oxidation as reached during the preaging (e.g., thermal degradation) step on the biodegradation propensity has also been evaluated in respirometric tests carried out in an aqueous medium in the presence of river water microbial populations. The complex biodegradation profile characterized by the presence of alternating plateau and exponential phases has been observed in this case also, which suggests that this behavior can be considered as typical of the biodegradation of oxidized LDPE. A straightforward relationship between the level of oxidation as determined by CO*i* and the biodegradation behavior of thermally oxidized LDPE samples has been observed also in biodegradation tests carried out in an aqueous medium [46]. In this experiment, heavily oxidized fractions of thermally degraded LDPE films as well as LDPE films having medium and high CO*i* values were supplied as the sole energy and carbon source in a mineral salt medium to a microbial consortium obtained from a river water sample. During incubation for 140 days at room temperature, degrees of mineralization ranging between 10% and 50% were recorded in the case of thermally oxidized LDPE samples having CO*i* values between 4.6 and 20.7, respectively (Figure 16.5). Negligible mineralization was observed in the case of lightly oxidized LDPE with a CO*i* value of only 2.3. These data also suggest, therefore, that readily biodegradable oxidized LDPE samples can be obtained, depending on the level of oxidation reached during the abiotic pretreatment.

16.5
Processability and Recovery of Oxo-biodegradable Polyolefins

The use of activating additives of the types described above does not affect the processing characteristics of conventional polyolefin resins. These are “run” on the usual equipment at normal speeds. The products are indistinguishable from

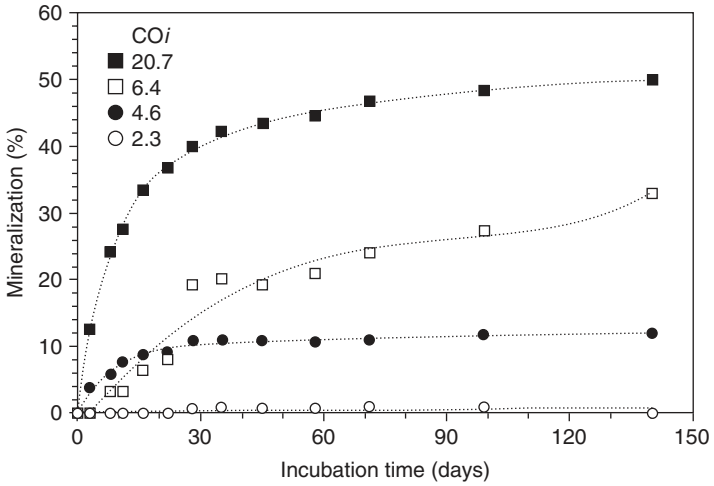


Figure 16.5 Mineralization profiles of thermally oxidized LDPE materials having different levels of oxidation in aqueous respirometric tests.

the same products made without the prodegradant additives. The oxo-biodegradable technology adds yet another desirable characteristic to the long list of useful properties for which the polyolefins are well known. This technology also provides environmental benefits at nominal extra cost that consumers would like to support but are usually reluctant to pay much of a premium for.

In many countries there are formal as well as informal programs for recycling postconsumer plastics. The recycling of used plastics can be a significant challenge, [47] but it is an important part of striving for a sustainable society. It is significant therefore to note that EPI's TDPA–PE materials, in spite of being oxo-biodegradable, can be recycled with regular PE recycling operations. This is because the prodegradants involved are not just simple oxidizing agents. The former do not affect the properties of the plastic until something else, for example, heat or UV light, initiates oxidative degradation, and this will not occur until all the antioxidants are consumed.

16.6 Concluding Remarks

For a number of decades, the polyolefins have been among the most useful and versatile materials. This is because they have a wide variety of desirable properties and are relatively inexpensive. In order to provide for years of reliable service, especially outdoors, it has been necessary to determine the kinetics and mechanisms by which polyolefins lose their useful properties over time, that is, to elucidate the details of oxidative degradation. On the basis of this fundamental

information, highly effective stabilizers (e.g., radical scavengers, peroxide decomposers, UV absorbers) have been developed; they are used extensively in a wide variety of commercial formulations.

More recently, the demand for polyolefin products having a shorter lifetime has arisen, primarily in single-use packaging applications but also for a variety of agricultural products and in hygiene applications. As a result, oxo-biodegradable polyolefins have been invented and developed. These "clever" products are based on the following principles. (i) The actual requirement is for polyolefins having controlled lifetimes, that is, shelf life/use life combinations that can be varied between a few months and several years, depending on the formulation. (ii) In order to achieve such controlled lifetimes, it is required to enhance the rate of oxidative degradation – after the polyolefin articles have been used and discarded – by several orders of magnitude. This cannot be done simply by adding an oxidizing agent or by omitting the addition of stabilizers. It is being done by adding transition metal/fatty acid salts in catalytic quantities to conventional polyolefin resins prior to product fabrication. These salts catalyze the decomposition of hydroperoxide groups attached to the polymer molecules, but only after stabilizing additives in the resins have been depleted. (iii) Polyolefins are resistant to biodegradation by naturally occurring microorganisms, but their degradation products are biodegradable. (iv) The combination of abiotic oxidation and biodegradation provides for the required shelf life/use life values and sufficiently rapid bioassimilation to avoid the buildup of discarded plastics in a variety of environments. The oxo-biodegradation of suitable polyolefin formulations when buried in soil occurs at rates which permit the retention and use of as-produced biomass; (v) no toxic byproducts are produced in either the abiotic or subsequent biotic degradation of oxo-biodegradable polyolefins.

In the immediate future, it is expected that oxo-biodegradable polyolefins will become available for even more eco-compatible products and applications.

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