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DEGRADATION OF POLYMERIC BIOMATERIALS

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Abstract

Environmental and processing factors affecting the biostability of medical devices made from traditionally "stable" polymers, such as isotactic polypropylene (PP) and ultrahigh molecular weight polyethylene (UHMW-PE), were analyzed and their undesirable degradation was related to performance of typical medical devices. Among the critical phenomena determining the biological performance of UHMW-PE and PP devices are oxidation during melt-processing and the propensity of the polymer chains to radiolyse and radio-oxidize. Polyesters and their biomedical devices, which can be designed to degrade predictably, are addressed with some focus on the less obvious determinants of performance.

Key Words: Absorbable polyesters, polyethylene, polypropylene, crystallinity, oxidation, polyoxalates.

Introduction

The growing clinical use of polymeric devices for short and long term applications has created a distinct need to study the factors affecting polymer degradation, and hence, device performance in the biological environment. One major area of interest pertains to the pre-use and in-use degradation of the polymeric materials due to environmental or processing factors. To avoid a fragmented treatment of this topic, it was decided to limit this report to families of polymers for which the subject of their degradation is well documented in literature but lacking an adequate, systematic analysis of the desirable and/or undesirable impact of chain degradation (Carlsson *et al.*, 1991). Sutures and prosthetic joint components made from isotactic polypropylene (PP) and ultrahigh molecular weight polyethylene (UHMW-PE), respectively, were chosen as model systems of long term implants with exceptional levels of biostability. In considering polymeric materials which are designed to degrade at predictable or controllable rates, polyesters based on hydroxy acids (used in suture materials) and experimental oxalate polymers were chosen for review. Depending on the type of polymer being addressed and whether degradation is controllable or uncontrollable, relevant factors and phenomena to be addressed include: (a) polymer manufacturing and purification schemes, (b) oxidative and photo-oxidative degradation during polymer processing, (c) radiation-degradation during sterilization and/or pre-implantation, and (d) *in vivo* mechanical and/or mechano-chemical degradation. The stabilization of implants which exhibit undesirable degradation as well as the design of more controllable systems having desirable degradation will be discussed.

Undesirable Degradation of Polypropylene

Fibrous forms of isotactic polypropylene are used in a number of critical, surgical products. These include monofilament sutures, surgical meshes for repairing hernias, and haptics for intraocular lenses. Because its chemical structure is characterized by the presence of a tertiary hydrogen, PP may readily undergo chain degradation through oxidation, photo-oxidation, radiolysis,

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and radio-oxidation. The latter three types of degradation can be most damaging to biomedical PP constructs. Radiolysis and radio-oxidation can be encountered when a PP construct is sterilized using high energy radiations, such as electron beams (e-beam) and gamma rays. One may also consider radiation sterilization of PP in an oxygen-free environment to limit the chain degradation by radio-oxidation, however, the presence of dissolved oxygen in the polymer will cause some level of radio-oxidation. On the other hand, photo-oxidation of PP can be encountered, primarily, if the undyed polymer is used as the haptics of an intraocular lens. The impact of chain degradation may not be easily assessed in short term *in vitro* testing at 37°C (or higher temperatures) but long term exposure can result in substantial loss in key mechanical properties (i.e., breaking strength and compliance). To control the polymer degradation during radiation sterilization and/or use as haptics, the addition of photostabilizers and/or antioxidants which can be in the form of organic dyes has been used with limited success. A second approach entailing the use of the so-called "chain mobilizers" was claimed to minimize the chain degradation during a typical radiation-sterilization cycle (Williams, 1991). Nevertheless, biomedical implants made of PP are usually recommended for sterilization by ethylene oxide (E.O.) and not high energy radiations.

Undesirable Degradation of UHMW-PE

Ultrahigh molecular weight polyethylene has been used for about two decades in the production of prosthetic joint components (Black, 1978; Goodfellow, 1992). While these components have been successful in short term clinical use, recent findings revealed a functional failure of total arthroplasty associated with the use of UHMW-PE implants beyond 10 years (Kilgus *et al.*, 1991; Weightman *et al.*, 1991; Garcia-Cimbrello and Munuera, 1992). Undesirable performance of UHMW-PE was related, primarily, to creep and generation of wear debris which were, in-turn, suggested to have been associated in part with certain aspects of the polymer and device processing schemes, such as polymer degradation in reactive environments (Rose *et al.*, 1980; Eyerer and Ke, 1984; Eyerer *et al.*, 1987). For this reason, the study of factors affecting the crystallinity, thermal behavior, and thermo-oxidative properties of UHMW-PE was undertaken in our laboratory.

In recent studies by Deng and Shalaby (1993) and later by Deng *et al.* (submitted for publication), seven different grades of virgin UHMW-PE provided by Hoechst-Celanese were examined by thermal and X-ray diffraction methods in an attempt to uncover some of the factors affecting the polymer functionality as a prosthetic device. The examined virgin polymer samples were designated GX100, GUR202, GUR212, GUR402, GUR412, GUR405 and GUR415. Thermal data obtained through differential scanning calorimetry (DSC) are summarized in Table 1. The data in an air environment are the average of three samples and are listed as mean

± standard deviation (S.D.). Statistical analysis (ANOVA) showed that the melting temperature (T_m) and the heat of fusion (ΔH) measured in air are significantly different for different UHMW-PEs ($p < 0.001$). It appears that the T_m and ΔH measured in nitrogen are higher than those measured in air. As shown in Table 2, the percent crystallinity based on DSC measurements were consistent with those obtained by wide angle X-ray diffraction (WAXD). High values by DSC are paralleled by comparable values by WAXD. Since the amorphous portion of a polymer contributes to the X-ray diffraction pattern, the crystallinity by WAXD is slightly higher than that from DSC.

Analysis of virgin polymer samples in thermo-oxidizing environments (in excess of those which may be encountered during polymer processing) was sought to assess the relevance of the polymer manufacturing scheme to its thermo-oxidative properties. The DSC oxidative stability data in Table 3 suggest some dependence of thermo-oxidative stability of UHMW-PE (in air) on both particle size and molecular weight, and possibly the polymerization conditions (including the type of catalyst used).

The DSC data, complemented by the X-ray results discussed above, strongly suggest that different grades of virgin polymer vary in their crystalline content and display different thermal and thermo-oxidative properties. Such differences are expected to have substantial impact on the ability to convert UHMW-PE to prosthetic devices under ordinary processing conditions, without compromising their aging behavior. Physico-chemical defects, which may be created during processing of the exceptionally high molecular weight polymer, may cause long term undesirable degradation of the chains. This may lead to functional failure, as has been noted previously in clinical situations (Atkinson *et al.*, 1985).

Controllable/Desirable Degradation of Polyesters

The need to design polymeric chains with controllable degradation was acknowledged over two decades ago for biomedical applications. This was a result of surgeons' recognition of the importance of using synthetic absorbable sutures as a substitute for collagen-based ones, which elicit unacceptable tissue reactions (Kulkarni *et al.*, 1966; Lerwick, 1983; Shalaby, 1988). To this end, a number of lactone-derived polymers were successfully synthesized and converted to useful absorbable sutures and other forms of biomedical devices. The two base polymers used in the production of lactone-derived polyesters are polyglycolide (PG) and poly(*p*-dioxanone) (PD). The former is a high modulus, fast absorbing material while the latter is a moderately absorbing, more compliant system (Reed and Gilding, 1981; Williams, 1982; Lin *et al.*, 1993). Toward improving the properties of PG and PD (i.e., more compliant, radiostable, or faster absorbing materials), several types of PG- and PD-based copolymers were synthesized. PG

Degradation of polymeric biomaterials

Table 1. Differential scanning calorimetry data of virgin UHMW-PE samples.

| Sample | Particle Size (μm) | T_m ($^{\circ}\text{C}$) | | ΔH (J/g) | | % Crystallinity* | |
|--------|------------------------------------|------------------------------|----------------|------------------|----------------|------------------|----------------|
| | | air ¹ | N ₂ | air ¹ | N ₂ | air ¹ | N ₂ |
| GX100 | 27 | 142.7 \pm 0.1 | 144.0 | 167.4 \pm 1.9 | 207.5 | 57.9 \pm 0.7 | 71.7 |
| GUR202 | 90 | 143.5 \pm 0.3 | 144.3 | 163.1 \pm 3.5 | 204.5 | 56.4 \pm 1.2 | 70.7 |
| GUR212 | 96 | 143.1 \pm 0.2 | 142.9 | 168.0 \pm 2.1 | 211.8 | 58.1 \pm 0.7 | 73.2 |
| GUR402 | 103 | 142.8 \pm 0.4 | 145.1 | 147.6 \pm 4.9 | 174.0 | 51.0 \pm 1.7 | 60.1 |
| GUR412 | 89 | 142.8 \pm 0.3 | 144.3 | 150.8 \pm 7.9 | 186.4 | 52.1 \pm 2.7 | 64.4 |
| GUR405 | 101 | 143.6 \pm 0.1 | 144.4 | 148.8 \pm 9.3 | 183.4 | 51.4 \pm 1.3 | 63.4 |
| GUR415 | 96 | 143.6 \pm 0.2 | 145.8 | 155.0 \pm 6.0 | 191.5 | 53.6 \pm 2.1 | 66.2 |

*Obtained from heat of fusion data using 289.3 J/g for 100% crystalline UHMW-PE.

¹Values are mean \pm S.D. (standard deviation).

Table 2. Comparative percent crystallinity data.

| Sample | Method | |
|--------------------------|--------|-------|
| | DSC* | X-Ray |
| GUR402 virgin powder | 60.1 | 63.3 |
| GUR405 virgin powder | 63.4 | 64.0 |
| GUR405 melt-crystallized | 46.2 | 61.8 |

*The DSC data were obtained for samples analyzed under nitrogen.

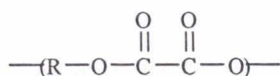
Table 3. DSC oxidation stability data of virgin UHMW-PE samples.

| Sample | Molecular weight (X 10 ⁶) | Average particle size (μm) | T_o * ($^{\circ}\text{C}$) |
|--------|---------------------------------------|---|--------------------------------|
| GX100 | 2 | 127 | 222.9 \pm 1.3 |
| GUR202 | 3 | 90 | 220.2 \pm 2.1 |
| GUR212 | 3 | 96 | 220.2 \pm 2.5 |
| GUR402 | 3 | 103 | 222.8 \pm 0.3 |
| GUR412 | 3 | 89 | 223.2 \pm 0.8 |
| GUR405 | 5 | 101 | 222.7 \pm 0.5 |
| GUR415 | 5 | 96 | 224.2 \pm 2.6 |

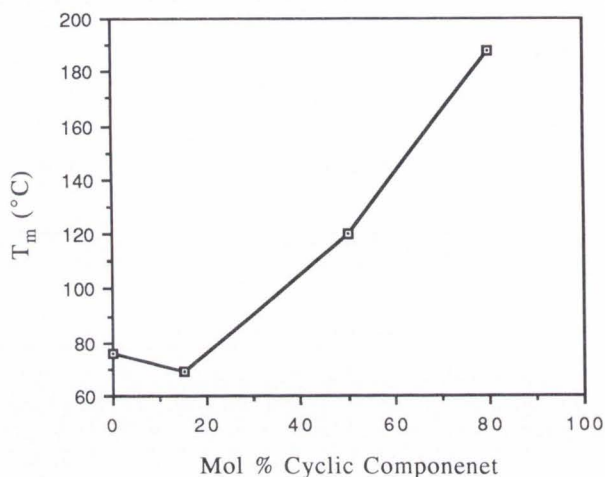
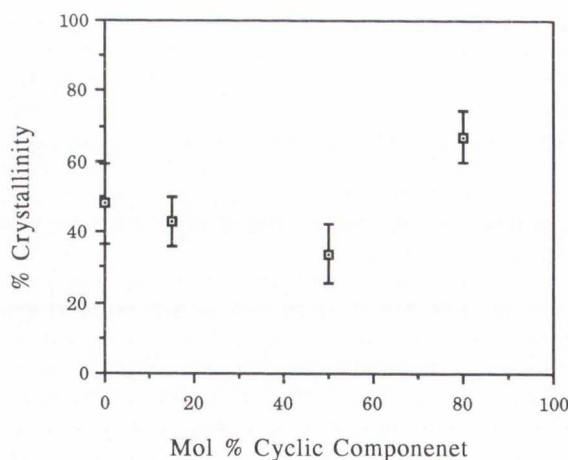
*Peak temperature of the oxidation exotherm.

copolymers with ϵ -caprolactone were made and converted to absorbable monofilament sutures for increased compliance (Shalaby and Jamiolkowski, 1987; Bezwada *et al.*, 1991). Shalaby and Koelmel (1984) have shown that incorporation of about 5% of morpholinedione in PD chains increased the absorption rate significantly without compromising the *in vivo* strength retention profile. To improve the radiation stability of PG, segmented glycolide copolymers were made with aromatic prepolymers to produce radiation sterilizable suture materials with exceptional physical and biological properties (Shalaby and Jamiolkowski, 1984; Bezwada *et al.*, 1985; Koelmel *et al.*, 1987). Shalaby *et al.* (1992) prepared polyglycosalicylate (PGS) in a study using absorbable polymers in conjunction with controlled drug delivery. This polymer is intended to release salicylic acid as it undergoes absorption.

A major concern with the lactone-derived polymers is the presence of monomers in processed or unprocessed polymers, depending on the thermodynamic stability of their chains. The presence of these monomers (and in many instances low molecular weight oligomers) in surgical implants may constitute a safety concern (Vert *et al.*, 1981; Shalaby, 1991; Illi *et al.*, 1992; Zhang *et al.*, 1993). Polymer purification and assessment of the effect of these impurities on the physicochemical and biological properties of these polymers are being pursued in our laboratory (Johnson *et al.*, 1992). Concerns about the purity of the lactone-based polymers have led Shalaby and Johnson (1994), as well as Shalaby and Jamiolkowski (1978; 1979a,b; 1980) to explore a family of oxalate-based polymers for use as absorbable coatings. Acyclic polyalkylene oxalates (Ox) can be made of linear chains (Fig. 1), where the R group represents (CH₂)₆ or a mixture of (CH₂)₄ to (CH₂)₁₂. These systems were synthesized by the condensation of diethyl oxalate with n-alkanediols. Their low melting temperatures were suggested by Shalaby and Jamiolkowski (1978) to allow for the formation of a liquid lubricant due to friction-induced heating during the tie-down and



alkylene oxalate unit

Figure 1. Alkylene oxalate unit.**Figure 2.** Melting temperatures of isomorphous copolyoxalates.**Figure 3.** Percent crystallinities of isomorphous copolyoxalates determined by X-ray diffraction.

sliding of two strands of sutures. This, in turn, provided minimum friction at the contact area between the sliding sutures. The tissue response in the gluteal muscles of Long-Evans rats to 10/90 P-LL/G [poly(l-lactide-co-glycolide); Vicryl] braided sutures coated with the various poly(alkylene oxalates) was reported to be minimal. Polyoxalates were synthesized in various forms using diols having carbon chains ranging from 3 to 16 methylene group; those based on C3 to C6 moieties were suggested for use as absorbable drug delivery systems. The absorbability of these polymers was shown to decrease,

primarily, with increase in the methylene (or hydrocarbon) fraction of the polymer chain. High molecular weight oxalate polymers have been made and converted to monofilaments comprising extruded and oriented forms with the intent of producing absorbable sutures and surgical aids (such as fabrics for hernial repair). The filaments were described as soft, flexible and absorbable in animal tissue with minimal adverse tissue reaction. The absorption rates were characterized as slow for alkylene oxalate polymers with higher hydrocarbon fractions and rapid for lower ones. With the increase in hydrocarbon component of the polyester chains, melting temperatures of the polymers approached that of high density polyethylene (approximately 130°C), but most melted below 95°C. Such melting behavior was considered less than optimal for suture storage. Subsequently, the use of cyclic diols was considered as polymer precursors for higher melting alkylene oxalate polymers. Polyesters based on 1,4-*trans*-cyclohexanedimethanol (1,4-HDM) were synthesized and exhibited high melting temperatures. Polymers consisting of 1,4-HDM exhibited a higher hydrolytic stability than commercial absorbable polymers. For this reason, it was necessary to find polyesters with propensities for absorption that are intermediate between those of the acyclic alkylene and the cyclic 1,4-HDM oxalate polymers (Shalaby and Jamiolkowski, 1979b). Thus, the concept of isomorphic replacement was sought as a practical strategy to tailor-make cyclic/acyclic copolymeric chains and develop absorbable crystalline materials with a broad T_m range (including those which melt well above 100°C). More specifically, this entailed the copolymerization of 1,6-hexanediol and 1,4-HDM with the oxalate moiety. After characterization, it was surprising to find that a substantial level of crystallinity was attained throughout the entire range of copolymer compositions. Furthermore, the T_m s increased with increase in the cyclic fraction (above 20 wt% cyclic fraction) and displayed only one major melting transition. In the key patent on this technology (Shalaby and Jamiolkowski, 1979b), it was also noted that this family of isomorphic polymers was unusual in that all copolymers through the entire composition range of 5 to 95% of each isomorphic comonomer displayed levels of crystallinity comparable to those encountered in the parent homopolymers, namely between 40 and 60%, depending on the thermal history. These findings were confirmed in a study by Shalaby and Johnson (1994) (Figs. 2 and 3).

Most oxalate polymers and copolymers could be fabricated into compliant monofilaments having a range of *in vivo* strength retention and absorbed in animal tissue with minimal adverse reaction. As sutures, the isomorphic copolyoxalates were said to have acceptable initial tensile and knot strength and a high order of softness and flexibility. However, the *in vivo* strength of certain monofilaments decreased substantially within two weeks post-operatively (Shalaby and Jamiolkowski, 1979a, b). Recently, Johnson *et al.* (1992) prepared copolymers of hexamethylene oxalate and its isomorphic counterpart

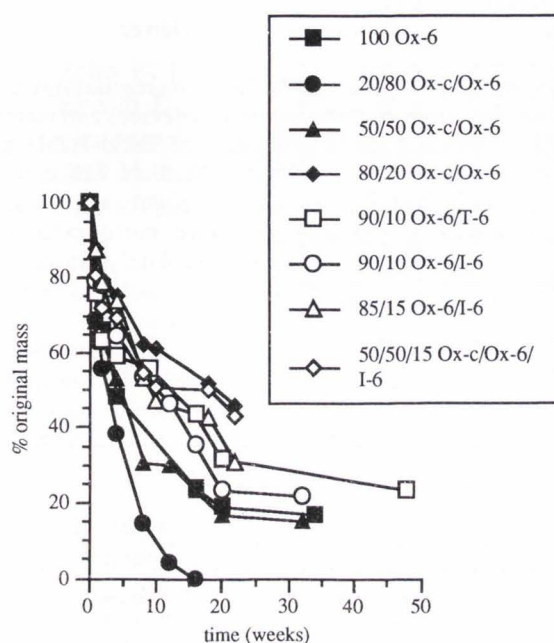


Figure 4. *In vitro* absorption profiles of all compositions at 37°C.

with aromatic diesters, which were intended to produce materials with improved *in vivo* tensile strength retention and/or radio-stability. Earlier reports on oxalate-based monofilaments by Shalaby and Jamiolkowski (1978, 1979, 1980) showed that there was a premature decay in the *in vivo* and *in vitro* tensile strength. Since those studies were conducted without systematic monitoring of the effect of leachable components, the early absorption profiles of these polymers was emphasized in the recent studies. Indeed a premature loss of mass was observed (Fig. 4), which may be associated with the previously observed phenomena of early loss of mechanical strength.

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Discussion with Reviewer

J.M. Schakenraad: The forthcoming regulations of ethylene oxide sterilization of medical devices and materials will necessitate the development of radio-stable polymers. Do the authors believe that they can construct polymeric materials which are absolutely radio-stable?

Authors: It is possible to make more radio-stable materials, but not to make absolutely radio-stable materials.