A Comparison of the Efficacy of Various Antioxidants on the Oxidative Stability of Irradiated Polyethylene

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Published online: 20 September 2014
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Abstract

Background Ultrahigh-molecular-weight polyethylene (UHMWPE) is subjected to radiation crosslinking to form highly crosslinked polyethylene (HXLPE), which has improved wear resistance. First-generation HXLPE was subjected to thermal treatment to reduce or quench free radicals that can induce long-term oxidative degeneration. Most recently, antioxidants have been added to HXLPE to induce oxidative resistance rather than by thermal treatment. However, antioxidants can interfere with the efficiency of radiation crosslinking.

Questions/purposes We sought to identify (1) which antioxidant from among those tested (vitamin E, β -carotene, butylated hydroxytoluene, or pentaerythritol tetrakis [methylene-3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate]) causes the least reduction of crosslinking; (2) which promotes the greatest oxidative stability; and (3) which had the lowest ratio of oxidation index to crosslink density.

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Methods Medical-grade polyethylene (PE) resin was blended with 0.1 weight % of the following stabilizers: alpha tocopherol (vitamin E), β -carotene, butylated hydroxytoluene (BHT), and pentaerythritol tetrakis [methylene-3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate] (a hindered phenol antioxidant [HPAO]). These blends were compression-molded into sheets and subjected to electron beam irradiation to a dose of 100 kGy. Equilibrium swelling experiments were conducted to calculate crosslink density. Each PE was subjected to accelerated aging for a period of 2 weeks and Fourier transform infrared spectroscopy was used to measure the maximum oxidation. Statistical analysis was conducted using analysis of variance with Fisher's protected least significant difference in which a p value of < 0.05 was used to define a significant difference.

Results The least reduction of crosslinking in antioxidant-containing HXLPE was observed with HPAO, which had a crosslink density ($n = 6$) of 0.167 (effect size [ES] = 0.87; 95% confidence interval [CI], 0.162–0.173) mol/dm³ compared with 0.139 (ES = 1.57; 95% CI, 0.132–0.146) mol/dm³ ($p = 0.020$) for BHT, 0.131 (ES = 1.77; 95% CI, 0.123–0.139) mol/dm³ ($p = 0.004$) for β -carotene, and 0.130 (ES = 1.79; 95% CI, 0.124–0.136) mol/dm³ ($p = 0.003$) for vitamin E, whereas pure HXLPE had a crosslink density of 0.203 (95% CI, 0.170–0.235) mol/dm³ ($p = 0.005$). BHT-PE had an oxidation index of 0.21 (ES = 13.14; 95% CI, 0.19–0.22) followed by HPAO-PE, vitamin E-PE and β -carotene-PE, which had oxidation indices of 0.28 (ES = 9.68; 95% CI, 0.28–0.29), 0.29 (ES = 9.59; 95% CI, 0.27–0.30), and 0.35 (ES = 6.68; 95% CI, 0.34–0.37), respectively ($p < 0.001$ for all groups). BHT-PE had the lowest ratio of oxidation index to crosslink density of the materials tested (1.49, ES = 1.94; 95% CI, 1.32–1.66) followed by HPAO-PE (1.70, ES = 1.52; 95% CI, 1.61–1.80), vitamin E-PE (2.21, ES = 0.52;

95% CI, 2.05–2.38), and β -carotene-PE (2.69, ES = -0.43; 95% CI, 2.46–2.93) compared with control PE (2.47, 95% CI, 2.07–2.88) with β -carotene ($p = 0.208$) and vitamin E ($p = 0.129$) not being different from the control.

Conclusions BHT-modified HXLPE was found in this study to have the lowest oxidation index as well as the lowest ratio of oxidation index to crosslink density compared with vitamin E, HPAO, and β -carotene-modified HXLPEs. More comprehensive studies are required such as wear testing using joint simulators as well as biocompatibility studies before BHT-modified HXLPE can be considered for clinical use.

Clinical Relevance BHT is a synthetic antioxidant commonly used in the polymer industry to prevent long-term oxidative degradation and has been approved by the FDA for use in cosmetics and foodstuffs. It may be an attractive potential stabilizer for HXLPE in total joint replacements.

Introduction

Ultrahigh-molecular-weight polyethylene (UHMWPE) is one of the most commonly used bearing surfaces in total joint arthroplasty [3]. Polyethylene (PE) is subjected to gamma or electron beam radiation crosslinking to a dose of 50 to 100 kGy to form highly crosslinked polyethylene (HXLPE). HXLPE has been shown to have an improved wear profile compared with conventional PE in both laboratory [16, 18] and clinical studies [13]. However, residual free radicals from the radiation process become trapped in the crystalline regions of HXLPE and increase the risk of long-term oxidative degeneration [26]. First-generation HXLPE was subjected to either remelting or annealing to reduce free radical content [12]. The former is more effective in quenching free radicals but alters the crystallinity more than the latter. Although this helps reduce oxidation, the process of irradiation as well as heating the polymer causes reduction in resistance to fatigue crack propagation [2, 17, 22]. Most recently, antioxidant additives have been combined with HXLPE to help avoid thermal treatment and thus preserve its initial as-crosslinked mechanical properties [4–6, 19, 24, 28]. Vitamin E and a hindered phenol antioxidant (HPAO) have been approved by the FDA for use in HXLPE to help limit long-term oxidative degeneration and are in clinical use today [8, 10].

One of the key issues with the use of antioxidants in HXLPE is that they are typically blended with UHMWPE before radiation crosslinking [7, 21, 23]. The free radicals generated during irradiation necessary for crosslinking are quenched by the antioxidants and thus crosslinking is reduced [21]. This may be prevented by diffusion of liquid

antioxidants such as vitamin E or alpha-tocopherol into UHMWPE after irradiation [19, 24] but this is not ideal because the diffusion requires thermal treatment and it often requires a separate process to control the spatial uniformity of vitamin E [19]. This inhibition of crosslinking when the antioxidant is blended before radiation can potentially reduce the wear properties of HXLPE. It thus is suggested that the ideal stabilizer will be one that minimally reduces crosslinking while maximally improving oxidative resistance. A few hindered amine light stabilizers have been shown to prevent reduction of crosslinking while inducing oxidation resistance in UHMWPE; however, their biocompatibility has not yet been adequately studied for implant applications [7].

This study aims to investigate the comparative effects of the following antioxidants on HXLPE: vitamin E, β -carotene, butylated hydroxytoluene, and pentaerythritol tetrakis [methylene-3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate] (an HPAO) (Fig. 1). Except for β -carotene which has two reactive heterocyclic ends that can trap peroxy radicals [15], the other three are sterically hindered phenols with one reactive phenolic end that converts peroxy radicals to hydroperoxides [11]. We sought to identify (1) which antioxidant from among those tested (vitamin E, β -carotene, butylated hydroxytoluene, or a hindered phenol antioxidant) causes the least reduction of crosslinking; (2) which promotes the greatest oxidative stability; and (3) which had the lowest ratio of oxidation index to crosslink density.

Materials and Methods

Medical-grade GUR 1020 resin (PE) (Celanese, Florence, KY, USA) was soaked in solutions of DL-alpha-tocopherols (molecular weight = 430.71 g/mole) (Acros Organics, Fair Lawn, NJ, USA), β -carotene (molecular weight = 536.87 g/mole) (Sigma Aldrich, St Louis, MO, USA), butylated hydroxytoluene (molecular weight = 220.35 g/mole) (Sigma Aldrich), and the HPAO pentaerythritol tetrakis [methylene-3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate] (molecular weight = 1178 g/mole) (Irganox 1010TM; TCI America, Portland, OR, USA) to form the blends of 0.1 weight percent vitamin E-PE, β -carotene-PE, butylated hydroxytoluene (BHT)-PE, and HPAO-PE, respectively. The rationale for choosing 0.1 weight percentage was the result of the general consensus in industry that this weight percent of vitamin E would be sufficient for oxidative stability in PE, and an identical weight percentage of other antioxidants would make it easy to compare with the vitamin E group. The control used in this study was PE without any antioxidant (control-PE). Ethanol was the choice of solvent for vitamin E and BHT, whereas

Fig. 1 This schematic shows the molecular formula of each antioxidant that was blended with PE.

acetone was used as a solvent for the other two antioxidants because it is a better solvent than ethanol for them. Each antioxidant was added to its respective solvent at 0.08 weight percent (calculated so that the final concentration would be 0.1 weight % in the polymer) and the total volume of solution was 1.2 times that of the volume of polymer so that the solvent filled the voids in between the powder particles and completely submerged the powder. The blends were soaked for an hour and then left for 48 hours to allow the solvents to evaporate at room temperature. They were further hand-mixed for 30 minutes after drying to ensure adequate mixing. The blends were compression-molded at a temperature of 180° C and an applied pressure of 10 MPa followed by slow cooling to room temperature and pressure release to form 2-mm sheets using a hydraulic press (Carver Inc, Wabash, IN, USA). No additional thermal treatment was performed because our experience has been that the plaques or sheets have not deformed appreciably after thermal treatment to warrant an additional thermal treatment step. The sheets were subjected to electron beam irradiation using a 3.0-MeV source (Electron Technologies Corp, South Windsor, CT, USA) at 100 kGy in air at room temperature and atmospheric pressure.

Equilibrium swelling experiments were performed on each group ($n = 6$) using *o*-xylene to determine swell ratios (q_s) and crosslink densities (v_d) [1]. Six 2 mm³ cubes were cut from each sheet using a razor blade and weighed using an analytical balance (resolution: 0.0001 g). Each cube was heated in hot *o*-xylene at 135° C in a custom-built silicone oil bath for a period of 3 hours. The samples

were then retrieved and reweighed once swollen after drying with a paper towel. A gravimetric method was used to calculate q_s and v_d using the following formula:

$$v_d = - \frac{\ln(1 - q_s^{-1}) + q_s^{-1} + \chi_1 q_s^{-2}}{\phi_1 (q_s^{-1/3} - q_s^{-1}/2)}$$

where q_s is the swell ratio calculated using a gravimetric method, the Flory polymer-solvent interaction parameter is $\chi_1 = 0.33 + 0.55/q_s$, and the molar volume of the solvent is $\phi_1 = 136 \text{ cm}^3/\text{mol}$.

Each PE was also subjected to accelerated aging for 2 weeks in oxygen at a temperature of 70° C and at an applied pressure of five atmospheres as performed in ASTM F2003-02 as well as in a previous interlaboratory study [14]. Fourier transform infrared spectroscopy (FTIR) (FTIR6700; ThermoScientific Inc, Fair Lawn, NJ, USA) equipped with a microscope attachment was performed on 50- to 100- μm thick microtomed specimens to measure the oxidation index, which was calculated as the ratio of the area under the curve for the absorbance at 1740 cm^{-1} in the region of 1650 to 1850 cm^{-1} and the area under the 1370 cm^{-1} vibration attributed to the amorphous regions of the polymer chain [18]. The average and standard deviations (SD) of the maximum oxidation index in each subsurface region was recorded ($n = 10\text{--}12$) [21]. This was done following aging only so the oxidation index reflects oxidation during the accelerated aging process as well as any oxidation that occurred during the irradiation and real time aging for 2 days before aging in the oxygen bomb.

Analysis of variance was performed on the crosslink density results from the equilibrium swelling experiments and the maximum oxidation indices obtained from FTIR. Significance was set at $p < 0.05$. Calculations of 95% confidence interval (CI) and effect sizes (ES) were also performed.

Results

All of the antioxidants used in this study reduced crosslinking when blended with PE before irradiation compared with control-PE ($p < 0.001$ except for HPAO for which $p = 0.005$, analysis of variance; Fig. 2) with vitamin E being the most potent at reducing crosslink density and HPAO being the least potent. The crosslink density of control-PE was 0.203 (95% CI, 0.170 – 0.235) mol/dm^3 . The results for crosslink density for the antioxidant blends in

Fig. 2 This histogram compares the crosslink density (mol/dm^3) for control-HXLPE and HXLPE blended with the different antioxidants (mean $\pm$ SD) ($p < 0.001$ for all pairs except for the pairs indicated).

Fig. 3 This histogram compares the maximum oxidation index for control-HXLPE and HXLPE blended with the different antioxidants (mean $\pm$ SD) ($p < 0.001$ except for the pairs indicated).

decreasing order of crosslink reduction were 0.130 (ES = 1.79 ; 95% CI, 0.124 – 0.136) mol/dm^3 , 0.131 (ES = 1.77 ; 95% CI, 0.123 – 0.139) mol/dm^3 , 0.139 (ES = 1.57 ; 95% CI, 0.132 – 0.146) mol/dm^3 , and 0.167 (ES = 0.87 ; 95% CI, 0.162 – 0.173) mol/dm^3 for vitamin E, β -carotene, BHT, and HPAO, respectively. Vitamin E, β -carotene, and BHT reduced crosslinking compared with HPAO ($p = 0.003$, $p = 0.004$, and $p = 0.020$, respectively) but there was no difference among the former three antioxidants.

The FTIR results for maximum oxidation index showed that the antioxidant additives all improved oxidation resistance compared with accelerated-aged irradiated, unstabilized control-PE ($p < 0.001$), which had an oxidation index of 0.50 (95% CI, 0.49 – 0.51) (Fig. 3). BHT-PE had an oxidation index of 0.21 (ES = 13.14 ; 95% CI, 0.19 – 0.22) followed by HPAO-PE, vitamin E-PE, and β -carotene-PE, which had oxidation indices of 0.28 (ES = 9.68 ; 95% CI, 0.28 – 0.29), 0.29 (ES = 9.59 ; 95% CI, 0.27 – 0.30), and 0.35 (ES = 6.68 ; 95% CI, 0.34 – 0.37), respectively.

BHT-PE had the lowest ratio of oxidation index to crosslink density of the materials tested (1.49 , ES = 1.94 ; 95% CI, 1.32 – 1.66) followed by HPAO-PE (1.70 , ES = 1.52 ; 95% CI, 1.61 – 1.80), vitamin E-PE (2.21 , ES = 0.52 ; 95% CI, 2.05 – 2.38), and β -carotene-PE (2.69 , ES = 0.43 ; 95% CI, 2.46 – 2.93) compared with control-PE (2.47 , 95% CI, 2.07 – 2.88) with β -carotene ($p = 0.208$) and vitamin E ($p = 0.129$) not being different from the control.

Discussion

Oxidative degradation resulting from the presence of free radicals attributable to radiation sterilization has historically been a clinical problem because of mechanical damage and delamination wear [26]. Postradiation thermal treatments such as remelting and annealing to quench free radicals conducted with the first generation of HXLPEs decreased resistance to fatigue crack propagation in HXLPE [2, 17, 22]. To avoid such thermal treatments, antioxidants must be incorporated into PE to combat free radicals. It is therefore important to study the efficacy of an antioxidant in quenching free radicals to provide long-term oxidative stability to HXLPE. In this study, we investigated the effect of incorporating various antioxidants on the oxidative stability and crosslink density in HXLPE. Such a comparative evaluation of various antioxidants in HXLPE under controlled irradiation and aging conditions has not been performed. We quantified both the undesirable reduction of crosslinking by the presence of antioxidants in PE before radiation as well as the oxidation resistance imparted to HXLPE by an accelerated aging method. Among the antioxidants studied, BHT was found to impart the highest oxidation resistance and also the lowest ratio of

oxidation index to crosslink density compared with vitamin E, HPAO, and β -carotene.

This study was limited by the fact that we only looked at a single concentration of 0.1% by weight of different antioxidants. However, this weight percentage was chosen for the study because it is currently the standard used for vitamin E in PE, facilitating comparison of our results with other studies. It should be noted that given that the different additives used in this study have different molecular weights, the number of moles of additive in each blend would have differed. This would have consequences for the degree of dispersion of the various antioxidants during processing as would differences in solubility of each antioxidant in the solvent as well as the polymer. BHT was expected to disperse more uniformly because smaller molecules such as BHT have the potential to diffuse more easily in the polymer melt compared with HPAO, which is five times its molecular weight. Another limitation is that BHT, having a lower molecular weight than vitamin E, the other liquid antioxidant at 37° C has the potential for migration out of the PE [27]. Elution of BHT into the periprosthetic environment would diminish its protective role as an antioxidant and the toxicity of all these antioxidants and their degradation products must be considered, which has not been investigated in this study.

A major result of this study was that when antioxidants were added at a 0.1 weight percentage of HXLPE and irradiated to a dose of 100 kGy, the antioxidants had different degrees of potency from the standpoint of reducing crosslinking. HPAO was the most favorable antioxidant with regard to its effect on crosslinking because it caused the least crosslinking reduction. This is likely the result of HPAO having the highest molecular weight in this series of antioxidants. Thus, for the same weight percent antioxidant present in HXLPE, it had the lowest molar fraction (= ratio of weight fraction to molecular weight) followed by β -carotene, vitamin E, and BHT. Although BHT had the lowest molecular weight compared with the other antioxidants, its crosslink density reduction was not different from that of vitamin E and β -carotene, suggesting that all three were potent in terms of crosslink reduction. Crosslinking is generally affected by the concentration of vinyl double bonds in PE, the radiation dose, and the concentration and efficiency of the antioxidant. Blocking of oxidation by the antioxidant would result in a small amount of macroradicals present, resulting in a lower crosslink density in HXLPE. From the standpoint of HXLPE with an antioxidant present before irradiation, HPAO ranks as the best of the antioxidants investigated here with respect to degree of crosslinking required for high wear resistance [18]. It should be noted that the equilibrium swelling results in this study for unstabilized HXLPE were comparable to those reported previously [18, 20].

BHT induced the highest oxidation resistance (lowest oxidation index) compared with the other additives. The efficiency of antioxidants in inducing oxidation resistance, particularly hindered phenols, has complex underpinnings, being attributed not merely to the antioxidant present in the PE during irradiation, but also to the transformation products of the antioxidant after it has reacted to the peroxy radical [4, 5]. β -carotene ranked last in both oxidation index as well as ratio of oxidation index to crosslink density compared with the other additives, including HPAO, which had a much higher molecular weight; thus, diffusion limitations associated with molecular weight cannot be an argument for its relative lack of potency. Unlike the other additives, which were all phenolic compounds, β -carotene is a highly unsaturated carotenoid, shown to have both pro- and antioxidant properties in vitro [25] and to act as an antioxidant at low oxygen partial pressures such as the conditions in which the stabilized HXLPE was irradiated. At high oxygen tensions, it has been shown to be a pro-oxidant [25], similar to the conditions in which the accelerated aging experiments were performed, which could possibly account for β -carotene's ability to strongly reduce crosslinking while being ineffective at preventing oxidation.

Although the value of the oxidation index is critical in ranking antioxidants purely from the standpoint of oxidation resistance, the ratio of oxidation index to crosslink density helps in ranking the antioxidants taking into account both crosslink density, which must be maximized, and oxidation index, which must be minimized. In this case, BHT ranks highest followed by HPAO, vitamin E, and then β -carotene taking into account both crosslink reduction and oxidation resistance.

To our knowledge, there have been no direct comparisons made between a variety of antioxidants added to HXLPE at the same weight fraction and processed and aged in the same batch, thereby enabling a direct comparison of their ranking with respect to crosslink reduction and ability to provide oxidative stability to HXLPE. β -carotene, a naturally occurring antioxidant commonly used in the food industry, was investigated as part of this study because it has been isolated from the synovial fluid of patients with PE wear debris [9]. β -carotene, however, ranked the last among this group. BHT is a synthetic antioxidant commonly used in the polymer industry to prevent long-term oxidative degradation and has been approved by the FDA for use in cosmetics and foodstuffs whose use in polymers and likely biocompatibility make it an attractive potential stabilizer for UHMWPE, although its high mobility can potentially lead to migration out of the implant [27]. BHT was shown to rank the highest with respect to having the best (lowest) ratio of crosslink reduction and oxidation resistance in 100 kGy HXLPE

compared with vitamin E, HPAO, and β -carotene. Further studies must be conducted with respect to its biocompatibility, wear and mechanical properties as well as other factors such as its potential migration out of the implant as a result of its high mobility before it can be considered for implant applications.

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