Homogenization in Supercritical Carbon Dioxide Enhances the Diffusion of Vitamin E in Ultrahigh-Molecular-Weight Polyethylene

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ABSTRACT: Vitamin E stabilization of radiation-crosslinked ultrahigh-molecular-weight polyethylene (UHMWPE) joint implants was successfully introduced to improve long-term oxidation resistance. Current clinically available vitamin E stabilized UHMWPE implants were prepared by the postirradiation diffusion of vitamin E into 100-kGy-irradiated UHMWPE by a two-step process, which included doping in pure vitamin E at an elevated temperature below the melting point followed by an annealing step at an elevated temperature in inert gas to homogenize the antioxidant throughout components of desired thickness. We hypothesized that the diffusion of vitamin E could be enhanced with supercritical carbon dioxide (SC-CO_2) during homogenization without an increase in the surface vitamin E concentration, which would thus result in faster homogenization. Our hypothesis tested positive; crosslinked UHMWPE doped with vitamin E at 120°C and homogenized in SC-CO_2 at 10–12 MPa had a greater penetration of vitamin E than those homogenized in inert gas. We attributed the faster diffusion of vitamin E in irradiated UHMWPE in SC-CO_2 to the dissolution of vitamin E in the supercritical fluid and a rate of diffusion that was closer to that of the supercritical fluid in the polymer. © 2011 Wiley Periodicals, Inc. J Appl Polym Sci 124: 518–524, 2012

Key words: crosslinking; implant; polyethylene (PE); polymer blends

INTRODUCTION

For over 4 decades, the material of choice for load-bearing components in total joint arthroplasty has been ultrahigh-molecular-weight polyethylene (UHMWPE). Debris generated through the wear of UHMWPE components are known to cause periprosthetic osteolysis; this occurrence usually necessitates revision surgery.[1] Radiation-crosslinked UHMWPE was introduced in the late 1990s as an alternative bearing surface with substantially reduced wear rates.[2–7] The crosslinking of UHMWPE chains is achieved through the recombination of free radicals caused by radiation.[8]

An adverse effect of radiation crosslinking is the increased susceptibility to oxidation. Radiation-induced macroalkyl radicals and their reactions with available oxygen produce peroxy radicals,[9] which in turn, extract hydrogen atoms from adjacent UHMWPE molecules to form hydroperoxides and new macroalkyl radicals.[10] Residual alkyl radicals in the crystalline phase remain active for prolonged periods;[11,12] this allows oxidation and, over time, causes chain scission, which results in surface recrystallization and embrittlement.[13–15] To ensure the long-term oxidative stability of irradiated UHMWPE, these free radicals must be eliminated or otherwise stabilized. A novel method that stabilizes the residual free radicals in radiation-crosslinked UHMWPE is the diffusion of the antioxidant α-tocopherol (vitamin E).[16,17]

Vitamin E is a lipid whose major role *in vivo* is to donate a hydrogen atom to free radicals formed on lipids to hinder peroxidation in cell membranes.[18,19] It consists of a chroman ring, which is responsible for its antioxidant activity, and a phtyl tail, which renders it lipophilic. Its lipophilicity allows it to penetrate through cell membranes and also provides miscibility with polyethylene (PE). Irradiated UHMWPE stabilized by vitamin E has been shown to retain its mechanical properties and fatigue resistance in real-time and accelerated aging conditions.[16,20–22]

For long-term oxidative stability, vitamin E must be present throughout the sample.[23] Previously, a method of vitamin E diffusion in irradiated

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(crosslinked) UHMWPE was developed, which consisted of, first, the doping of irradiated UHMWPE components with pure vitamin E to obtain a high surface concentration. Then, the obtained high surface concentration was distributed throughout the sample by annealing at an elevated temperature; this homogenized the vitamin E concentration profile.[24] Although this method is used in the preparation of clinically available vitamin E stabilized UHMWPEs, the depth of vitamin E penetration depends on the temperature and the duration of the doping and homogenization steps, which grow considerably with increasing part thickness. It would be advantageous to accelerate the rate of vitamin E diffusion in radiation-crosslinked UHMWPE without compromising its wear resistance, oxidative stability, and mechanical strength.

We propose the use of a homogenization environment that can dissolve vitamin E and aid in its molecular transport. Thus, we hypothesized that homogenization in supercritical carbon dioxide (SC-CO_2) could enhance the rate of diffusion of vitamin E in radiation-crosslinked UHMWPE. Because UHMWPE is intended for medical use, SC-CO_2 is an attractive processing environment because it is nontoxic and nonflammable. Also, because it is a gas under ambient conditions, its removal from a polymeric product is easy and requires no solvent processes.

SC-CO_2 has been extensively researched in the food industry as a viable substitute for conventional refinement in the extraction of α-tocopherol and monoglycerides and triglycerides, among other molecules from foodstuffs.[25] It has been shown to be a highly effective solvent, controllable by density and pressure[26] and has been successfully used in the extraction of additives from polymers.[26–29] The impregnation of polymers with additives such as dyes with supercritical fluids has also been explored;[28,30] however, it is less common because the solubility of additives in the fluid is commonly low, for example, 3.3 wt % for α-tocopherol at 80°C and 35 MPa.[31] Therefore, we chose to use SC-CO_2 during the homogenization step to enhance the diffusion of the vitamin E already doped into UHMWPE.

EXPERIMENTAL

Compression-molded GUR 1050 UHMWPE stock (Ticona, Bishop, TX) was e-beam irradiated to 100 kGy (Zimmer, Warsaw, IN) and machined into 20 × 20 × 20 mm^3 cubes (Eastern Tools, Medford, MA). The samples were then doped by immersion for 2 h in DL-α-tocopherol at 120°C in a 2-L glass reaction flask under inert gas flow.

To compare SC-CO_2 homogenization to conventional methods, samples were subjected to one of four postdoping homogenization processes ($n = 3$ each): (1) none, (2) 120°C for 24 h under nitrogen flow, (3) nitrogen at 10.3 MPa and 120°C for 24 h, and (4) SC-CO_2 at 10.3 MPa and 120°C for 24 h.

To determine the effect of the doping time on the penetration depth, cubes (20 × 20 × 20 mm^3, $n = 3$ each) machined from 100-kGy-irradiated UHMWPE were doped with vitamin E at 120°C for 2, 4, 8, or 16 h and subsequently homogenized at 120°C in SC-CO_2 at 10.3 MPa for 24 h. To determine the effect of the homogenization time in SC-CO_2, cubes (20 × 20 × 20 mm^3, $n = 3$ each) machined from 100-kGy-irradiated UHMWPE were doped with vitamin E at 120°C for 16 h and subsequently homogenized in 10.3 MPa of SC-CO_2 at 120°C for 24, 48, and 72 h ($n = 3$ each).

High-pressure homogenization was performed in a 1-L cell disruption vessel (HC4635, Parr Instruments, Moline, IL) stored in an air convection oven. Pressure was applied during heating and released after the vessel had cooled to room temperature.

During homogenization in SC-CO_2, CO_2 (purity = 99.97%, Airgas East, Hingham, MA) was pumped into the vessel during heating (Supercritical 24 constant-pressure dual-piston pump, SSI/Lab Alliance, Syracuse, NY) to the static desired pressure.

Quantification of the vitamin E concentration profiles

The vitamin E concentration profiles were determined with Fourier transform infrared spectroscopy (Bio-Rad FTS155/UMA500, Natick, MA). The opposite faces of each 2-cm^3 sample were removed to eliminate smearing during sectioning. The samples were then cut in half, perpendicular to the excised face, and sectioned (150 μm) with a sledge microtome (model 90-91-1177, LKB-Produkter AB, Bromma, Sweden) for analysis.

Infrared spectra were collected from one edge of the sample to the other. Each spectrum recorded consisted of the average of 32 individual infrared scans. The spectra were analyzed to calculate a vitamin E index, which was defined as the area under the α-tocopherol absorbance at 1245–1275 cm^{-1}, normalized to the PE skeletal absorbance at 1850–1985 cm^{-1}. The penetration depth was determined as the depth at which the vitamin E index decreased to 0.02. A surface vitamin E index was calculated as the mean vitamin E index for each set of samples, averaged over the first 0.5 mm of each sample. The plots published are the spline average of each sample set ($n = 3$).

Large-scale penetration experiments

Rectangular blocks (90 × 45 × 25 mm^3) were machined from 100-kGy e-beam-irradiated medical-

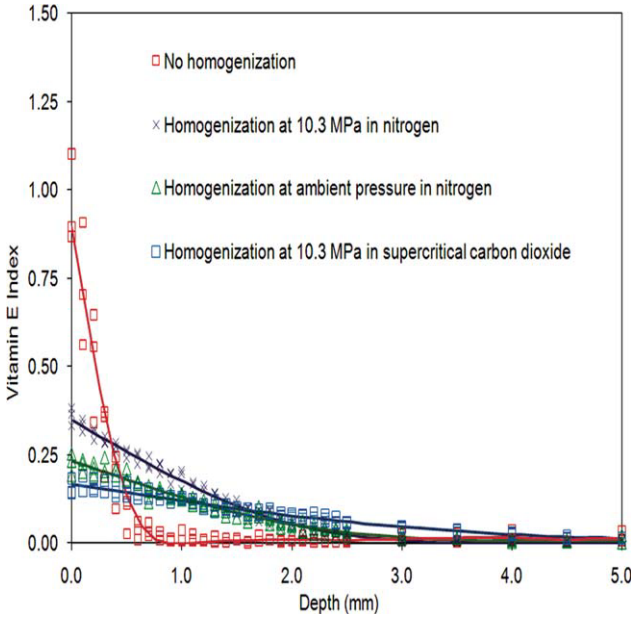

Figure 1 Vitamin E concentration profiles in 100-kGy-irradiated UHMWPE after 2 h of doping followed by 24 h of homogenization at 120°C in nitrogen and SC-CO_2. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

grade GUR1050 UHMWPE. These blocks were doped in pure vitamin E at 120°C for 6 h; then, they were removed from vitamin E and homogenized in SC-CO_2 at 11.7 MPa at 120°C for 16, 24, 72, 90, 100, or 160 h or at 130°C for 16, 48, 72, 90, or 120 h.

Tensile mechanical testing

Sections 3.2 mm thick were machined out of bar stock. These sections were doped with vitamin E at 120°C for 20 min and subsequently homogenized at 120°C for 9 h either in 10.3 MPa in SC-CO_2 or at ambient pressure in nitrogen ($n = 3$ each). Tensile specimens were stamped out of the doped and homogenized 3.2 mm thick sections in accordance with ASTM D 638. The dog-bone-shaped specimens ($n = 5$ each) were tested on an mechanical testing and simulation (MTS) machine (Eden Prairie, MN) at a crosshead speed of 10 mm/min. The axial displacement and force were sampled at a rate of 100 Hz.

The test was also recorded on videotape to visually determine elongation at break (EAB). For this purpose, a gauge length of approximately 7 mm was marked on the specimen per ASTM D 638. The thickness and width of the specimens in the gauge region were measured with calipers before deformation. The separation of the gauge marks just before failure was measured from the recorded videos, and EAB was computed as the ratio of the change in the gauge length at fracture and the initial gauge length.

The engineering stress was computed on the basis of the nominal cross sectional area (before any deformation). The yield strength (YS; MPa) and the ultimate tensile strength (UTS; MPa) were calculated per ASTM D 638.

Transmission electron microscopy (TEM)

The samples used for tensile testing were stained to increase the contrast between the crystalline and amorphous phases when examined in a transmission scanning electron microscope. A small piece of each sample was cut with a scissor, placed in a small glass vial, covered with chlorosulfonic acid, and kept at 60°C for 6 h. The sample was then washed in sulfuric acid and water and subsequently dried. The dry sample was embedded with a room-temperature curing epoxy in a silicone mold and left overnight. This sample block was then trimmed with a razor blade to expose the sample and ultramicrotomed at room temperature. The resulting sections, approximately 70 nm thick, were collected on 300-mesh copper grids and poststained with a 7% aqueous solution of uranyl acetate for 3 h. The sections were then imaged on a Philips 420T TEM instrument (Philips Electronic, Andover, MA) with a 100-kV accelerating voltage.

Statistical analysis

Statistical comparisons were based on a Student's test with two-tailed distributions with unequal variance. A p value of less than 0.05 was denoted to be significant.

RESULTS

The homogenization of vitamin E in 100-kGy-irradiated UHMWPE was improved with SC-CO_2 compared to the ambient and high-pressure inert environments (Fig. 1 and Table I; $p = 0.003$ and 0.008, respectively). Postdiffusion homogenization decreased vitamin E concentration at the surface in all samples (Fig. 1). There was no significant effect of pressure on the depth of penetration of vitamin E in crosslinked UHMWPE when the homogenization pressure was increased from ambient to 10.3 MPa in N_2 ($p = 0.35$).

TABLE I
Average Vitamin E Surface Concentration and Penetration Depth for 100-kGy Irradiated, Vitamin E Doped UHMWPE (120°C for 2 h) after Homogenization in Nitrogen and SC-CO_2 at 120°C for 24 h

	Surface Vitamin E Index (SVI)	Penetration depth (mm)
No homogenization	0.18 ± 0.04	0.87 ± 0.21
N_2, ambient pressure	0.16 ± 0.00	2.67 ± 0.27
N_2, 10.3 MPa	0.22 ± 0.02	2.40 ± 0.17
SC-CO_2, 10.3 MPa	0.13 ± 0.01	4.17 ± 0.29

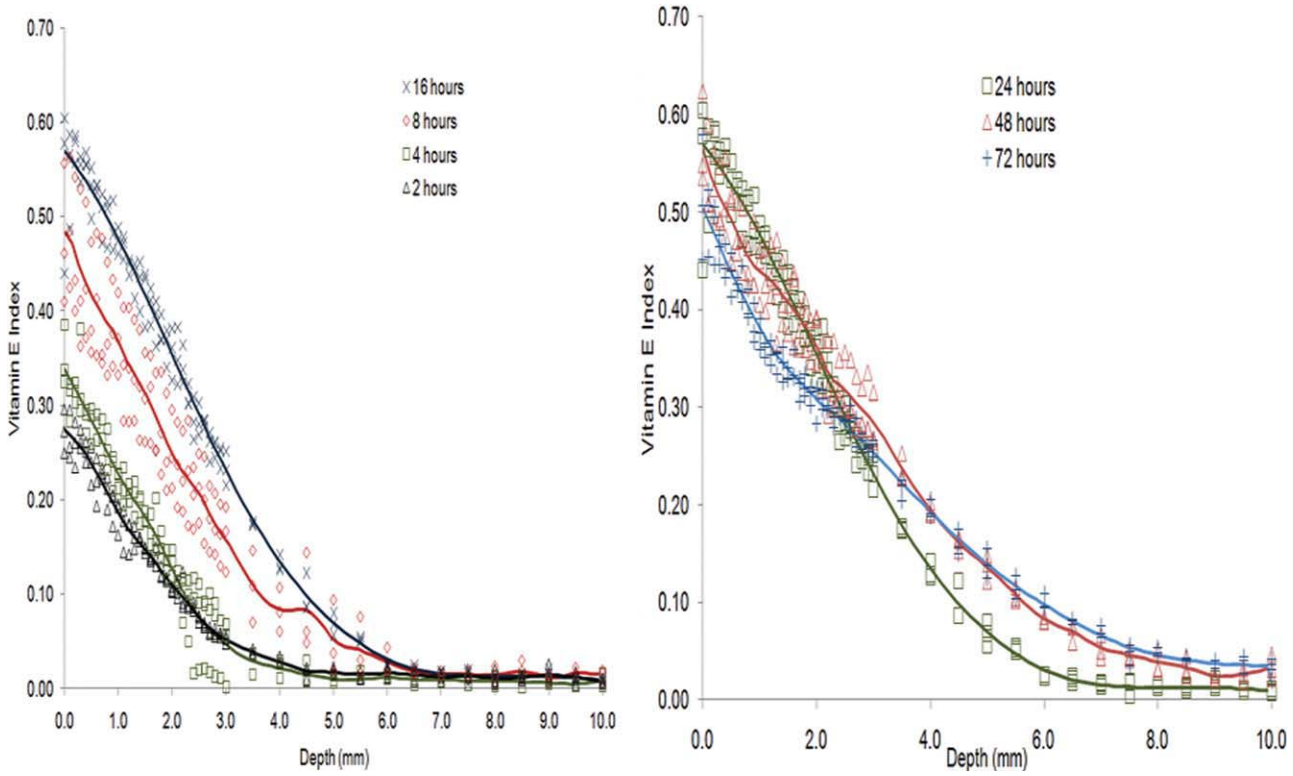

Figure 2 (a) Diffusion of vitamin E into 100-kGy-irradiated UHMWPE as a function of the doping time at 120°C after subsequent homogenization in SC-CO_2 for 24 h at 10.3 MPa and 120°C. (b) Diffusion of vitamin E into 100-kGy-irradiated UHMWPE as a function of the homogenization duration in SC-CO_2 at 10.3 MPa and 120°C after 16 h of doping at 120°C. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

In contrast, the penetration depth at 120°C and 10.3 MPa in SC-CO_2 was almost twice that achieved with N_2 at the same temperature and pressure ($p = 0.008$). The diffusion coefficient calculated for vitamin E in crosslinked UHMWPE, as described previously,[17] was 60% higher for homogenization in SC-CO_2 (3.0×10^{-11} m^2/s) than in inert gas (1.8×10^{-11} m^2/s).

Increasing the duration of doping at 120°C followed by 24 h of homogenization in SC-CO_2 at 120°C and 10.3 MPa increased the surface vitamin E index and the depth of penetration into 100-kGy-irradiated UHMWPE [Fig. 2(a); $p < 0.05$ for 8 and 16 h of doping compared to 2 h of doping]. The duration of homogenization had little impact on the surface vitamin E concentration and increased the depth of penetration significantly [$p < 0.05$; Fig. 2(b), Table II]. While increasing doping increased the penetration depth quickly initially for the samples presented in Figure 2(a,b) (up to 8 h at 0.66 mm/h), the rate slowed down at longer durations (0.01 mm/h at 8–16 h). In contrast, over the 72-h period of homogenization, the rate was steady at 0.087 mm/h during homogenization [Fig. 2(b)].

The penetration depth achieved by doping large blocks for 6 h at 120°C in inert gas followed by inert gas homogenization at 130°C was comparable to that achieved by SC-CO_2 homogenization at 120°C (Fig. 3). Alternatively, homogenization in SC-CO_2 at 130°C decreased the time to achieve a desired penetration by 26 h for a clinically relevant implant thickness of 15 mm by 34 h for a thickness of 20 mm and by 40 h for a thickness of 23 mm (Fig. 3).

No difference was seen in the mechanical properties (UTS, YS, and EAB) of the 100-kGy-irradiated UHMWPE doped at 120°C in vitamin E and subsequently annealed at 120°C in SC-CO_2 compared with those homogenized in argon gas (Fig. 4). In addition, the morphology of the samples annealed in SC-CO_2 appeared to be similar to those annealed in argon gas (Fig. 5).

DISCUSSION

Clinically available vitamin E stabilized implants were prepared by doping of 100-kGy-irradiated UHMWPE in pure vitamin E followed by homogenization to redistribute the vitamin E in the rich

TABLE II
Diffusion Coefficients (*D* Values) for Homogenization in Nitrogen and SC-CO_2

	D (mm^2/s) $\times 10^{-5}$
N_2, ambient pressure	1.8
SC-CO_2, 10.3 MPa	3.0

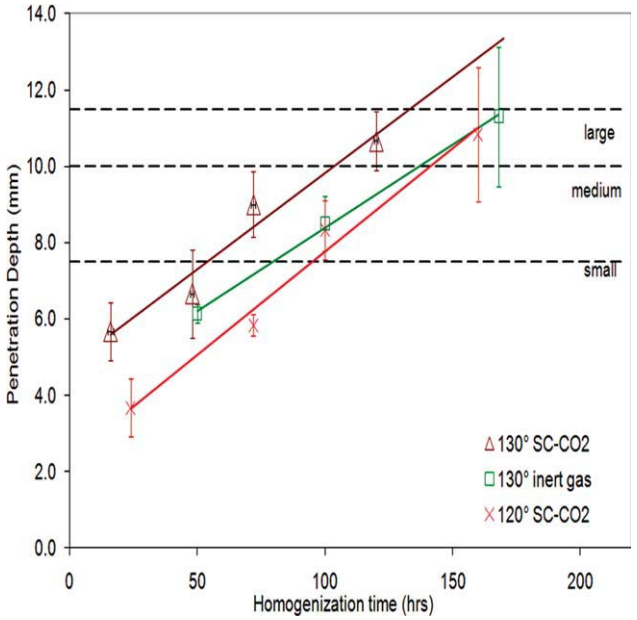

Figure 3 Penetration depth of vitamin E into 100-kGy-irradiated UHMWPE doped with vitamin E for 6 h and subsequently homogenized in argon and SC-CO_2 for various durations at 11.7 MPa. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

surface layer throughout the rest of the implants. Despite an increase in the diffusion coefficient at the processing temperatures (120–130°C), obtaining vitamin E penetration through thick components, for example, a 23-mm-thick tibial bearing preform, would take on the order of a week to complete. The goal of this study was to enhance the diffusion of vitamin E in radiation-crosslinked UHMWPE by homogenization in SC-CO_2 to thus decrease the time to achieve vitamin E stabilization of total joint implants.

Because the solubility of vitamin E is low in SC-CO_2, we achieved a high surface concentration of vitamin E that could subsequently be redistributed by first doping the irradiated UHMWPE in pure vitamin E in inert gas. Although continued doping could also increase the penetration depth, the surface concentration also increased; this increased the concentration gradient and hindered a more homogeneous distribution of antioxidant. We showed previously that a vitamin E stabilized UHMWPE with a high vitamin E concentration on the surface eventually eluted most of this vitamin E when it was in contact with an aqueous environment over 36 months.[32] The vitamin E concentration at the end of the 36 months was uniform at a vitamin E index of 0.1 ($\sim$ 0.7 wt %). We attributed this behavior to the release of the vitamin E from the polymer network due to the solubility difference of vitamin E in UHMWPE at 120°C, where it was prepared and 40°C where it was stored. Thus, we concluded that 0.7 wt % was the saturation concentration of vitamin E under these conditions and that the preparation of the UHMWPE with a homogenized vitamin E concentration profile around this level before implantation was desirable to prevent elution.

We based our hypothesis in this study on the assumption that vitamin E dissolved in SC-CO_2 would diffuse at the rate of the supercritical fluid (10^{-7} to 10^{-8} m^2/s),[33] which was faster than that of vitamin E by itself (10^{-10} to 10^{-11} m^2/s).[17] A preliminary study with a short-term doping cycle (2 h) followed by homogenization in inert gas or SC-CO_2 for 24 h, where the penetration of vitamin E was increased by 1.5 mm by the homogenization in SC-CO_2, proved our hypothesis (Fig. 1 and Table I). The sorption of SC-CO_2 into the PE may result in its swelling,[34] which may cause an increase in the free volume of the polymer to allow chain mobility and improved solute diffusivity.[35,36] In general, the solubility of small molecules increases with increasing density of SC-CO_2,[35] which rises substantially until about a pressure of 40 MPa. However, the polymer–solvent interaction, causing swelling of the polymer, decreases with increasing pressure after a threshold is overcome;[34,36] this is due, presumably, to the compression of the polymer chains. Increased pressure in inert gas decreased diffusion into crosslinked UHMWPE slightly, presumably because of the compression of polymer chains (Fig. 1, Table I). While our experiments were done at 10–12 MPa, the further increase in the density of SC-CO_2 (up to 40

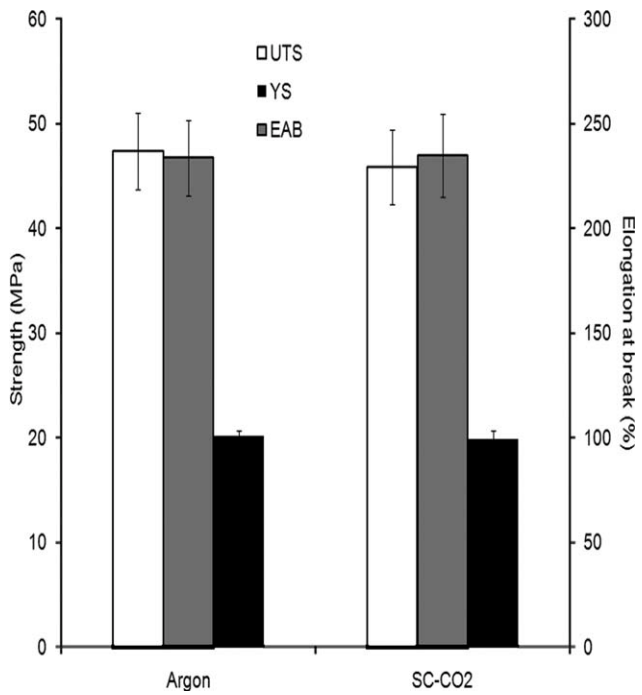

Figure 4 Comparison of the mechanical properties of vitamin E doped UHMWPE subsequently homogenized in SC-CO_2 and argon.

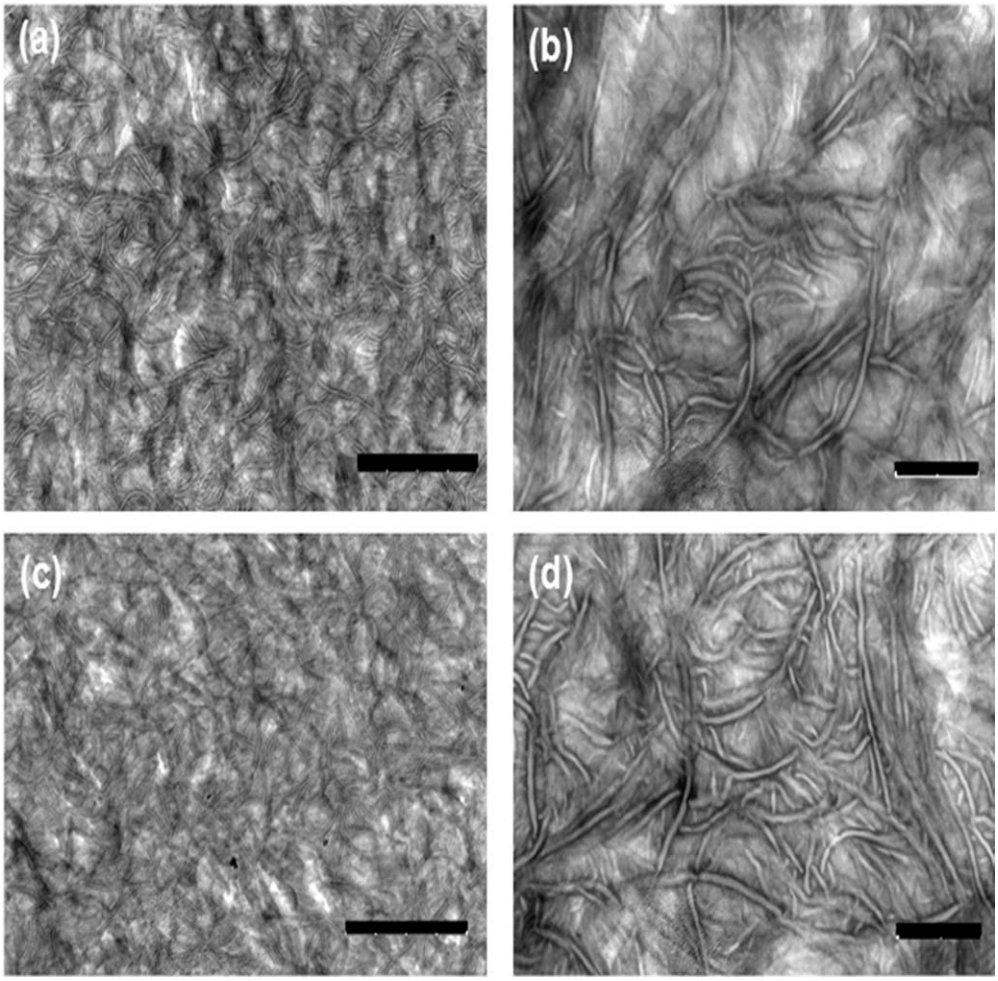

Figure 5 TEM images of vitamin E doped UHMWPE homogenized in (a,b) argon and (c,d) SC-CO_2. The scale bar represents (a,c) 1 μm and (b,d) 200 nm.

MPa)[26,37] could have potentially further enhanced its diffusive properties. The total amount of vitamin E introduced into the implants could be increased by an increase in doping time [Fig. 2(a)]. As previously shown,[17] the surface concentration was increased over time, approximately up to 24 h of doping, until a saturation concentration was reached at the surface at the doping temperature used. While an increase in doping time also increased the penetration, the majority of the penetration was obtained during homogenization [Fig. 2(b)]. For larger implants, though, the doping time and the associated vitamin E content had to be increased to achieve a desired vitamin E concentration throughout the implant component.

In many cases, the processing of implant components is performed on blocks of UHMWPE that are oversized versions (preforms) of the final implant components. In this manner, processing steps involving heating, cooling, irradiation, and doping do not affect the final dimensions and tolerances of the implant, which are achieved by a final machining step. To demonstrate the effect of SC-CO_2 homogenization on realistically sized implant components, doping was performed for 6 h in large implant preforms with 15 mm (small), 20 mm (medium), and 23 mm (large) thicknesses. Homogenization in inert gas at 130°C was used as a control because this was the highest temperature at which homogenization could be achieved with our method without a significant decrease in the crystallinity of the crosslinked UHMWPE.[17] The benefit of homogenization in SC-CO_2 over inert gas was two-fold (Fig. 3); at the same homogenization temperature, shorter homogenization duration could be used and alternatively, similar penetration depth could be achieved at 120°C in SC-CO_2 compared to 130°C in inert gas, presumably preserving more of the vitamin E from thermal degradation.[38] At the same homogenization temperature, it appeared that the shortening of processing times of 24–32% could be achieved.

Although the goal of this study was to use SC-CO_2 to dissolve and transport vitamin E in UHMWPE, it has been shown that the use of SC-CO_2 in the processing of glassy polymers may

induce drawing and crystallization in the amorphous region, affecting the mechanical strength and gas permeability.[26] A decrease in the mechanical strength is undesirable in UHMWPE that is to be used as a bearing surface in load-bearing human joints. Therefore, we also ascertained the tensile mechanical properties and semicrystalline morphology of vitamin E doped, radiation-crosslinked UHMWPE homogenized in SC-CO_2. We were not able to detect any changes in the tensile mechanical properties (Fig. 4) or morphology (Fig. 5), but further study is warranted to ascertain if SC-CO_2 exposure for a prolonged period of time would initiate pores or decrease the crosslink density. Any decrease in the crosslink density is not desirable, as this will increase the wear of UHMWPE and also increase in periprosthetic bone loss in total joint implant patients, and any changes in these properties could change implant performance significantly.

Homogenization in supercritical fluids may also provide the possibility of terminal sterilization by this method and an alternative to γ sterilization. A recent study showed that exposure to SC-CO_2 for 25 min at 105°C and 30 MPa completely deactivated approximately 6 decades of bacterial spores on commercially available biological indicator spore strips containing *Geobacillus stearothermophilus* and *Bacillus atrophaeus*.[39]

CONCLUSIONS

In this study, SC-CO_2 was shown to be a more efficient diffusion medium for vitamin E in radiation-crosslinked UHMWPE at 10–12 MPa. We attributed this behavior to the dissolution of vitamin E in SC-CO_2 and its diffusion at a rate closer to the diffusion rate of SC-CO_2 in crosslinked UHMWPE. We also demonstrated that because of faster diffusion, this method could result in significant time savings in the manufacture of orthopedic implants. Preliminary data suggested that supercritical fluid homogenization did not detrimentally affect the morphology or the mechanical properties of the polymer as related to its use as a total joint implant bearing surface.

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