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Isothermal microcalorimetry: an analytical technique for assessing the dynamic chemical stability of UHMWPE

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Abstract

In this work, isothermal microcalorimetry (IMC) was utilized to measure the exothermic heat flow from specimens of ultra-high-molecular-weight polyethylene (UHMWPE), that had been sterilized by various standard methods, under simulated shelf storage (air at 25°C, 30% r.h.) and simulated implantation (phosphate buffered saline, PBS, at 37°C) conditions. Gamma-radiation sterilized UHMWPE yielded initial heat flow rates approximately 7–10 times higher in simulated shelf storage and 2–3 times higher in simulated implantation (even after 1 month in PBS) than specimens which were unsterilized or sterilized using either ethylene oxide gas (ETO) or gas plasma (GP). These results show that gamma sterilization of UHMWPE produces many more unstable bonds in the polymer than is the case when ETO or GP is used, and that the net exothermic physico-chemical change proceeds steadily in a diffusion-limited manner in air or saline. In addition, gamma sterilization in nitrogen rather than in air did not prevent the creation of unstable bonds, but did defer physico-chemical change until the UHMWPE was exposed to oxygen. These results demonstrate the usefulness of IMC as a viable method for studying the stability of polymeric implant materials.

Keywords: Ultra-high-molecular-weight polyethylene (UHMWPE); Isothermal microcalorimetry; Gamma irradiation; Ethylene oxide sterilization; Gas plasma sterilization; Total joint replacement

1. Introduction

Isothermal microcalorimetry (IMC) is a rapid technique for measuring changes in the susceptibility of a material to physico-chemical change and the aggregate rate of such changes. Changes in heat content accompany all chemical and physical changes, including material degradation. For a given degradation process, the rate of heat produced or absorbed is directly proportional to the reaction rate. Short-term IMC data have been used successfully to predict long-term stability of solid pharmaceuticals [1–3], with the validity of this approach having been verified by comparing results from conventional long-term degradation studies with those from IMC [3]. To our knowledge, other than in our recent work [4,5], IMC has not been used to study the stability of implant materials.

In IMC evaluation of the stability of a material, a specimen of the material is placed in a test well of the microcalorimeter, under conditions of simulated use, and the net heat flow rate between the well and its surroundings at constant temperature is measured. Since the microcalorimeter can measure a few microwatts of heat flow precisely and accurately, it is uniquely suited for monitoring the progress of processes with very low reactivities, such as the room-temperature oxidation of a few grams of ultra-high-molecular-weight polyethylene (UHMWPE).

Willson et al. [6] described a powerful and straightforward method for interpreting IMC data. It is based on continuous measurement of heat flow at the temperature of interest for an extended period of time, typically 50–100 h. The method involves obtaining an empirical equation that best fits the experimentally obtained heat flow rate data. That equation is then integrated from

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time 0 to ∞ to obtain the total theoretical heat content (H_t) for the test specimen-medium system. The fitted equation is then re-integrated from 0 to some specified time to give the heat produced (H_p) over that time. The percent reaction occurring over the specified time at the temperature of interest is calculated as follows:

$$\text{Percent rxn.} = \frac{H_p}{H_t} \times 100. \quad (1)$$

This one-temperature direct approach avoids a basic problem inherent in conventional rate process studies [3]; namely, the reaction rate is determined at several temperatures to yield an activation energy and rate constant. A major drawback of that approach is that it is valid only if the reaction mechanism does not change with temperature.

Different sterilization methods are known to affect the chemical stability (e.g., susceptibility to oxidation) of UHMWPE to varying degrees. This translates into changes in the material's in vitro mechanical properties [7–9] and, more importantly, in the in vivo wear performance of UHMWPE articular components [10,11]. In the present work, IMC was used to compare the shelf storage stability of UHMWPE in moist air (30% r.h.) at 25°C after sterilization by gamma irradiation in air (γ-air) and in N_2 (γ-N_2), ethylene oxide gas (ETO), and gas plasma (GP). Orthopaedic implant industry standard commercial sterilization methods were used in all cases. In addition, the stability of UHMWPE subjected to the same sterilization methods was assessed under simulated implantation conditions (PBS, 7.4 pH, at 37°C).

2. Materials and methods

Two different lots of reference grade UHMWPE, supplied in extruded rod (76.2 mm diameter) stock form, were used in this study (Table 1). Cylindrical slices were cut from the rods, which were then machined to a final thickness of 2.00 ± 0.03 mm. Cylindrical pellets (nominally, 2-mm thick by 6-mm diameter) were punched from each slice with a mechanical die cutter (Fig. 1). The pellets were washed in two changes of de-ionized water and dried for approximately 48 h.

The pellets were subdivided into six different groups: 4 to be commercially sterilized and 2 unsterilized controls. Pellets to be gamma sterilized in nitrogen (γ-N_2) were flushed with nitrogen gas, sealed in double oxygen-barrier pouches, and sterilized with a 2.5–3.2 Mrad dose of gamma radiation. Pellets sterilized by gamma in air (γ-air) were sealed in double air-permeable pouches and subjected to the same radiation dose. Pellets sterilized by ethylene oxide (ETO) and gas plasma (GP) were also double sealed in air-permeable packaging. Negative controls consisted of untreated UHMWPE pellets stored until testing in either a double oxygen-barrier pouch (control 1), or in air-permeable packaging (control 2). Following sterilization, the pellets were kept in their packaging, away from fluorescent lighting, and under room conditions (temperature and relative humidity) until the IMC measurements were made. The isothermal microcalorimeter used in these studies (Model 4400, Calorimetry Sciences Corp., Provo, UT) has three test wells and one reference well (Fig. 2). To filter out fluctuations in heat flow that affect all wells, heat flow to or from each of the test wells is measured relative to the reference well. However, the heat flow rate for each of the test wells relative to the reference well is slightly different since each test well has a slightly different physical (and therefore thermal) relationship to the reference well. Thus, prior to the start of measurement of heat flow in a given test material-medium system, the baseline for each test well must be determined by measuring the heat flow from all the test wells when they and the reference well contain ampoules with an identical amount of a reference specimen (in the

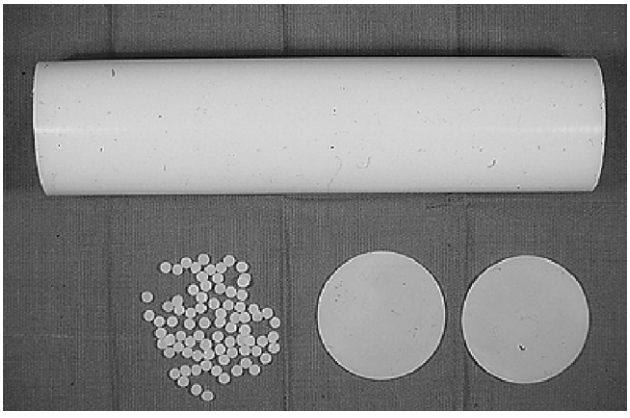

Fig. 1. Reference-grade UHMWPE specimen preparation—rod stock, cylindrical slices, and 2 mm thick by 6 mm diameter punched pellets.

Table 1
Summary of the UHMWPE materials and respective sterilization methods that were used in these studies

UHMWPE source	Type	Bar stock	Lot number	Sterilization			
				γ-N2	γ-air	ETO	GP
The Hospital for Special Surgery, New York, NY	Reference grade rod stock	4510 GUR	9321500	3/28/97	3/28/97	3/27/97	3/26/97
		4150 GUR	9481353	6/12/97	6/12/97	6/12/97	6/5/97

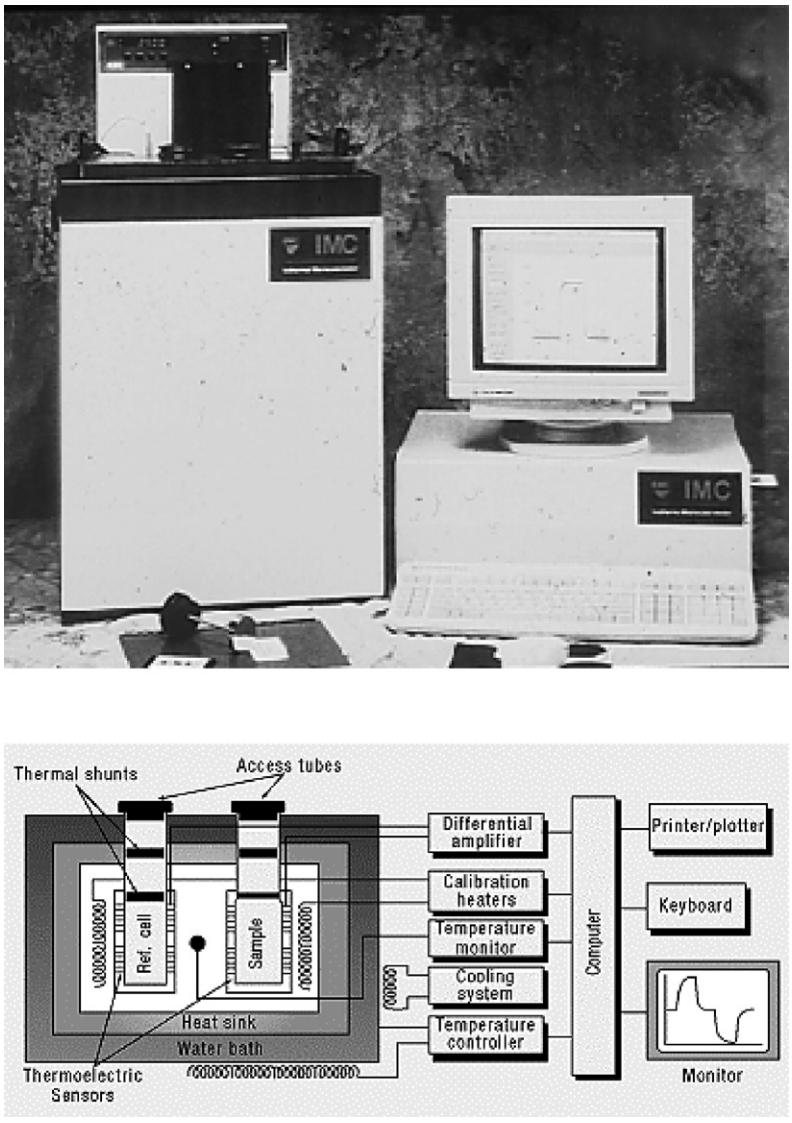

Fig. 2. Calorimetery Sciences Corporation Model 4400 isothermal microcalorimeter.

present study, 5 g of glass beads) (Fig. 3). These baseline results will then be used to correct the heat flow recorded from test wells when they contain ampoules with the test material.

For each IMC measurement, 5 g of pellets (total surface area = 10 300 mm^2) were loaded into a clean and sterile 20 ml glass test ampoule, with the ampoule being filled with either dry air or 10 ml of PBS for the simulated shelf storage and implantation runs, respectively. In all experiments, a sealed ampoule containing 5 g of clean glass beads (reference material), either without or 10 ml of PBS, was placed in the reference well for the simulated shelf storage and implantation experiments, respectively.

The simulated shelf storage and implantation IMC experiments were performed at 25°C and 37°C, respectively. This necessitated the use of an auxiliary-cooling bath to dampen noise generated by the calorimeter's

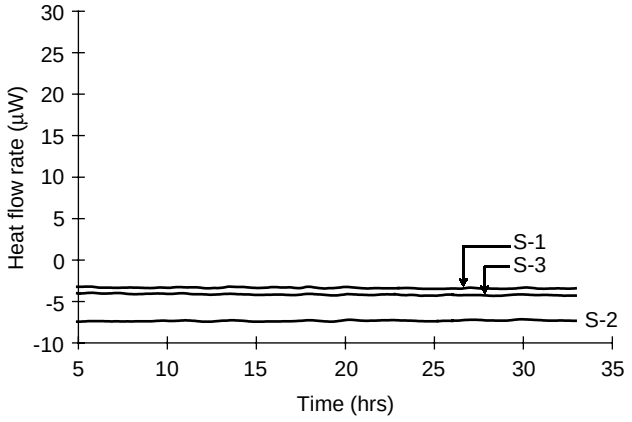

Fig. 3. Baseline heat flow recordings measured for each IMC test well for simulated shelf-storage experiments (5 g clean glass beads sealed in air).

heater turning on and off when the temperature was close to ambient. This bath was filled with a 50/50 mixture of ethylene glycol and deionized water, and set to 21°C and 30°C for the simulated shelf storage and implantation experiments, respectively.

For all IMC runs, scrupulous techniques were employed to eliminate uncontrolled sources of heat (e.g., oxidizable surface deposits on ampoules). Thus, Teflon-coated silicone disks and aluminum crimp caps (Alltech Associates Inc.) were cleaned with isopropyl alcohol, allowed to dry for a minimum of 2 h, and then used to seal the ampoules. Also, all ampoules containing UHMWPE pellets were handled with surgical gloves. Furthermore, various precautions were taken to minimize 'thermal noise' prior to and during the IMC measurements. For example, each test ampoule was brought to temperature in an external chamber, and then in a raised position just above the bottom of the respective test well. Once stabilized, ampoules were gently lowered to rest on the bottom of the wells, and thermal shunts were dropped into place. Once in position, another 2–4 h was required for the thermal gradients to dissipate.

3. Results and discussion

It is seen that, in both sets of experiments, the γ-air and γ-N_2 sterilized UHMWPE pellets were more reactive than the ETO- and the GP-sterilized ones. However, the differences were more pronounced in the simulated shelf storage runs (Figs. 4 and 5).

Based on other UHMWPE studies [7,12,13], the exothermic activity measured here can be postulated to be mainly oxidation of various susceptible chemical bonds, either inherently present or caused by sterilization. The heat flow rate at constant temperature at a given time after specimen preparation depends on availability of reacting species, namely, O_2 and oxidizable bonds. Changes in heat flow rate reflect changes in availability of these species. In these studies, a fixed amount of O_2 was initially available. Factors that could affect rate are O_2 depletion, the number of oxidizable bonds available, and the time required for inward diffusion of O_2 to reach these bonds.

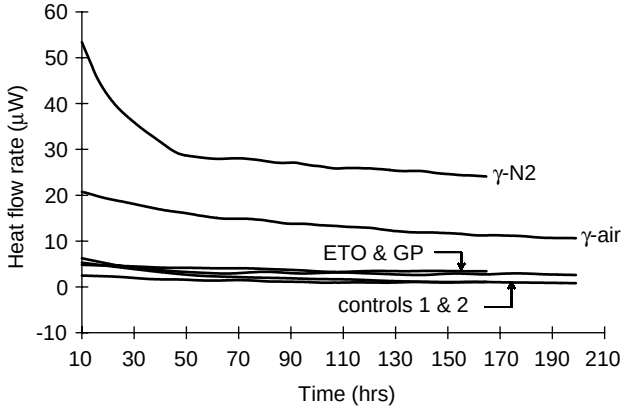

Fig. 4. Heat flow recordings from simulated shelf-storage experiments of differently sterilized reference grade UHMWPE.

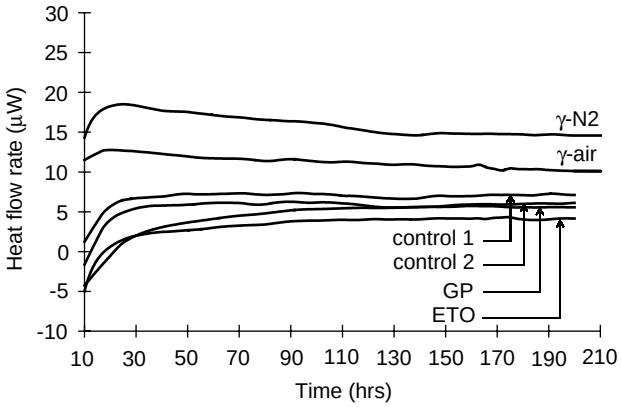

Fig. 5. Heat flow recordings obtained from simulated implantation experiments using sterilized reference grade UHMWPE specimens.

3.1. Simulated shelf-storage experiments

Results for GP and ETO sterilized UHMWPE showed no significant increase in heat flow rate compared to unsterilized controls. Also, the lack of change in rate with time indicates no measurable change in availability of reacting species. In contrast, the initial rate of reaction for γ-air sterilization indicates a 10-fold higher heat flow rate present at the same point in time after sterilization. The initial heat flow rate for γ-N_2 was even higher than for γ-air but dropped rapidly to a similar rate. It is not likely that the initial higher rate for γ-N_2 means more oxidizable bonds were created than by γ-air. Rather, it reflects the fact that the bonds did not begin to oxidize until specimens were exposed to air. Fig. 6 shows typical heat flow recordings for the gamma-sterilized pellets, shifted to account for the time at which initial exposure to oxygen occurred. Correcting the heat flow curves in this way caused them to coincide substantially.

The decrease in heat flow rate for gamma-sterilization indicates a change in availability of reacting species and invites treatment of data by the Willson method [6]. The γ-air and γ-N_2 results were best fitted by an equation of the form

$$Q = Q_0 \exp\left(\frac{Q_1}{t + Q_2}\right), \tag{2}$$

where Q is the heat flow, t is the time, and Q_0, Q_1, and Q_2 are test material-medium system constants.

The predicted extent of the measured exothermic processes taking place in 1 year under simulated shelf

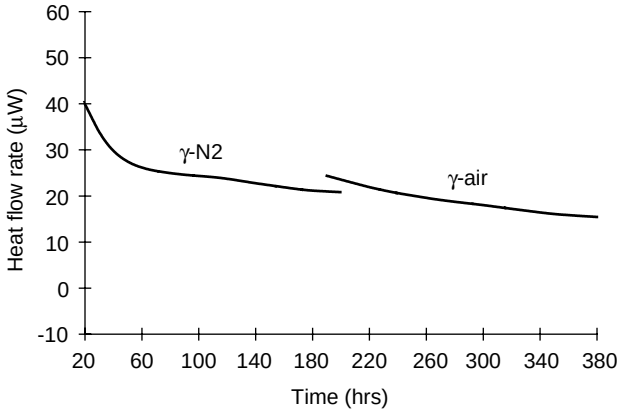

Fig. 6. Heat flow rate recordings for gamma-sterilized pellets from simulated storage experiments corrected for time to account for initial exposure to oxygen.

Table 2
Sample calculations for predicted extent of the reaction taking place in 1 year under simulated storage conditions using the Willson method.

Sterilization condition	H_p(μJ)	H_t (μJ)	Extent of reaction (%/yr)
Gamma sterilized in air (γ-air)	0.057	4.50	1.27
Gamma sterilized in nitrogen (γ-N_2)	0.069	6.02	1.15

storage conditions was $1.27 \pm 0.17\%$ for γ-air and $1.15 \pm 0.21\%$ for γ-N_2 (see calculations in Table 2). The extremely slow rate makes it unlikely that there was enough oxygen depletion in 200 h to cause the decrease. A more likely cause was an increasing time for O_2 to diffuse further into UHMWPE and reach unoxidized bonds.

3.2. Simulated implantation experiments

Even after 1 month, the exothermic heat flow rate exhibited by the gamma-sterilized UHMWPE was still greater than the rate for the unsterilized controls, and the ETO and GP sterilized pellets (Fig. 5).

The Willson method [6] was applied to the first 200 h of continuous heat flow rate data obtained for each of the two IMC simulated implantation experiments performed. The data were best fitted by Eq. (2). The predicted extent of the measured exothermic processes taking place in 1 year under these conditions was $1.16 \pm 0.22\%$ for γ-air and $1.11 \pm 0.22\%$ for γ-N_2. While the magnitudes of the observed heat flow rates for the two test conditions were different, analysis of the data using the Willson method [6] suggests that the reaction (e.g., oxidation) rate per year were approximately the same.

4. Conclusions

This initial study indicates that IMC is a very sensitive technique for evaluating and predicting changes in the stability of implant polymeric materials. Simulated shelf storage results imply that gamma-sterilization of UHMWPE causes the material to produce roughly 10 times as many oxidizable bonds compared to the case when ETO or GP sterilization is used. Furthermore, these results indicate that oxidation of the polymer proceeds steadily in a diffusion-limited manner in the presence of oxygen. Gamma sterilization of UHMWPE in nitrogen does not prevent the creation of oxidizable bonds, but does deter their oxidation until the material is exposed to oxygen. Gamma-sterilization effects (i.e., % reaction occurring in 1 year) on UHMWPE were virtually the same for simulated shelf-storage and simulated implantation conditions.

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