Oxidation and Stabilization of Orthopedic Uhmwpe

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Prosthetic Uhmwpe, after many years of good results, become a clinical problem: rapid and serious deterioration of the material was observed in many failed implants. This degradation is mainly due to sterilisation in air by gamma radiation. In this paper the thermodynamic and the kinetic of the oxidation process and the influence of sterilisation condition on the oxidation process are reported and discussed.

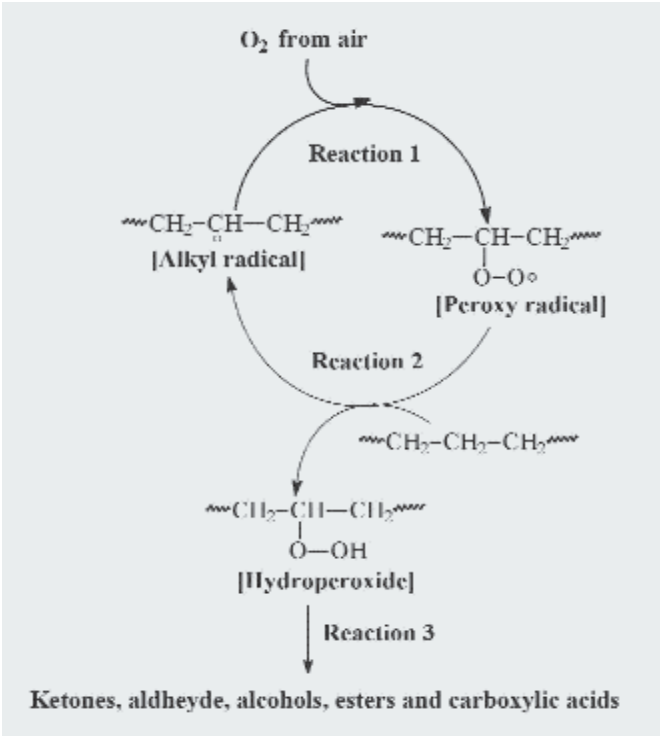
Polyethylene, in particular Ultra High Molecular Weight Polyethylene (Uhmwpe), is a biocompatible polymeric material, used for over forty years in prosthetic implants. The father of prosthetic surgery, Sir John Charnley, has been the first to use polyethylene in orthopaedic surgery in 1962 [1]. After many years of good results, the Uhmwpe become a clinical problem due to implant failures caused by rapid and serious deterioration of the material [2-6]. This degradation is mainly due to sterilisation in air by high energy radiation, gamma radiation in particular. In some new and in many retrieved prostheses the level of oxidative degradation was not uniform and several times a large oxidation degree was detected at one-two mm below the bearing surface [7]. In this paper we report the thermodynamic and the kinetic of the oxidation process and the influence of sterilisation condition (dose, dose rate, temperature of the prosthesis during the sterilisation and concentration of oxygen) on the oxidation process.

Oxidation of short-chain hydrocarbons

The mechanism of oxidation of short-chain hydrocarbons, widely known under the name of Bolland's cycle [8] is reported in Scheme 1. Alkyl radicals react with oxygen giving peroxy radicals (Scheme 1, reaction 1) and this reaction proceeds extremely fast already at room temperature. Then the peroxy radicals can abstract H from hydrocarbons to produce hydroperoxides (Scheme 1, reaction 2) and again alkyl radicals which are able to restart the cycle. This very simple process happens normally in our body, in the food, etc. and generally it can be avoided by adding antioxidant additives [9].

Oxidation of Uhmwpe

During the manufacturing of medical grade Uhmwpe, for producing hip, shoulder and knee prosthetic components, according to Astm F648-98 standard, any stabilizer (i.e. also anti-oxidants) must be avoided [10]. This situation induces an extreme sensitivity of Uhmwpe to the oxidation process.
The oxidation of polyethylene, a long chain hydrocarbon, has been extensively studied [11] and more recently, also oxidation of Uhmwpe has been investigated [12]. The process is mostly similar to oxidation of short chain hydrocarbons, with some exceptions, mainly due to the low mobility of the very long polymeric chains. Unlike the short chain hydrocarbons, radicals can easily be found in the bulk of the polymer, originating from the thermal decomposition of hydroperoxides formed by processing the polymer by compression moulding or ram extrusion. For this reason polyethylenes are less thermally stable than hydrocarbons.
We must bear in mind that it is almost impossible to obtain an oxygen-free polymer during processing because oxygen is always present during the processing and can also diffuse into the polymer from the surrounding atmosphere.
Hydroperoxides, which are the first products of oxidation, are thermally unstable and decompose to ketones, alcohols, carboxylic acids and esters [13]. The main products of thermal decomposition of the secondary hydroperoxides are ketones (Scheme 2). Their formation occur via a molecular process, which does not create new radicals and therefore does not spread oxidation. Furthermore, since the process takes place without chain scissions, it does not induce any variation of the molecular mass but only small changes of the mechanical



Scheme 1 - Oxidation scheme of hydrocarbons at low temperature

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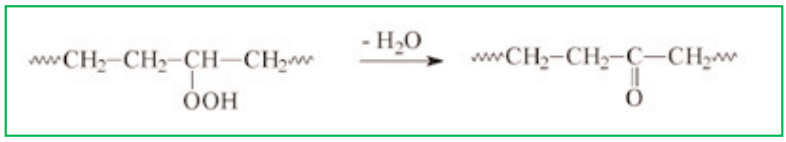
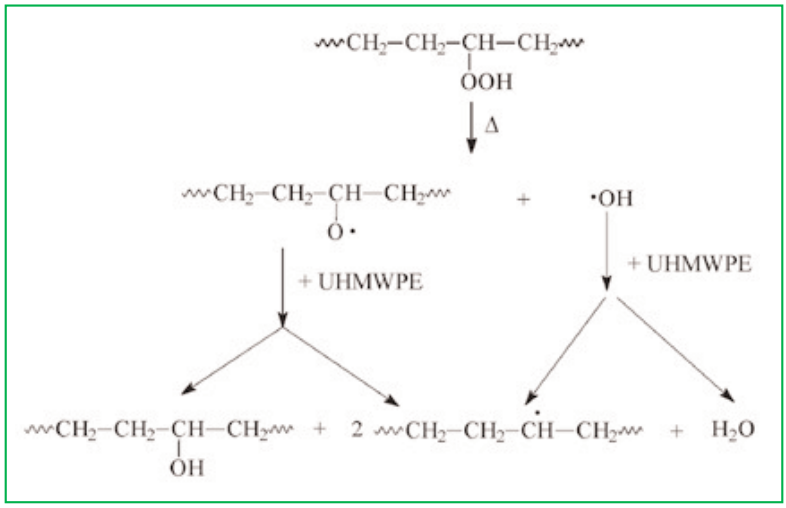


Scheme 2 - Thermal decomposition of hydroperoxides to form ketones



Scheme 3 - Thermal decomposition of hydroperoxides to form alcohols

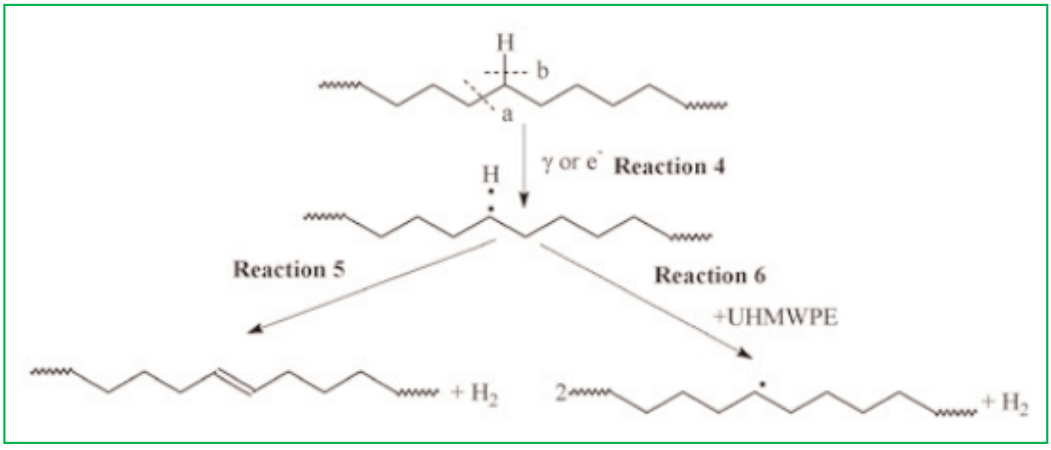
properties of Uhmwpe. Alcohols are formed by decomposition of hydroperoxides [14], through alkoxy and hydroxy radicals, following Scheme 3. In the reactions reported in Scheme 1 and 3 one original radical produces three new alkyl radicals and this contributes to auto-accelerate the oxidation process; this is very dangerous for Uhmwpe properties.
Acids are produced by scission of the polymeric chain, with a mechanisms not really understood yet, which decreases the molecular mass and lead to a progressive deterioration of the mechanical properties of the polymeric material. Acid determination, by using derivatisation techniques and FTIR analyses, makes it possible to quantify the molecular mass (MM) variation of the oxidised material in relation to the original one [7]. Esters formation also occurs through a not completely clear mechanism. One hypothesis considers decomposition of primary peroxides, originated from the termination step of the polymerisation process [15]. Hydroperoxides determination is the key factor to measure the level of oxidation of Uhmwpe specimen [16-17]. Scientific studies and Astm standards usually correlate the amount of ketones to the oxidation degree. It must be pointed out again that ketones, though a product of the oxidative process, do not produce polymeric chain scissions and so they do not induce deep variations in the mechanical properties.
Quantification of ketones is reliable only if the ratio between ketones and carboxylic acids remains constant through the whole oxidative process.

Uhmwpe radicals produced by high energy irradiation

Uhmwpe can be treated with high energy radiation for sterilisation. The interaction between radiation and Uhmwpe leads, through a complex energy transfer, to the scission of C-C and C-H bonds [18]. The scission of a C-C bond in normal condition does not produce macroradicals because recombination is very likely. Scission b (C-H bond) instead gives vinylene double bonds, H radicals and secondary alkyl macroradicals, in both the crystalline and the amorphous phase of the polymer (Scheme 4). The alkyl macroradicals, react promptly with the residual oxygen in the material, triggering the oxidation process reported in Scheme 1.
Whereas the distribution profile of the radicals in the bulk cannot be determined, the distribution of the products of interaction radiation-Uhmwpe can (Scheme 4 reaction 5, trans-vinylene double bonds). In other words, the degree and distribution of radicals produced in the bulk can be estimated by measuring the distribution of the trans-vinylene double bonds, using infrared spectroscopy (FTIR). As reported in Figure 1 the distribution of trans-vinylene is uniform, therefore it can be assumed that also the radical distribution is uniform.

Uhmwpe oxidation induced by high energy irradiation

One of the reasons for the revision of orthopedic implant is the failure of the polyethylene components, particularly for delamination, which is due to the oxidation of Uhmwpe [13].
The oxidation of Uhmwpe prosthetic components sterilized with gamma ray is not uniform, but it varies from sample to sample [20]. In order to understand why this occurs, the oxidation process during sterilization will be thoughtfully described here. Since during irradiation a number of radicals are formed at a very high rate, oxidation proceeds much faster than in unirradiated Uhmwpe.
The rate of hydroperoxides formation, that is correlated to the oxidation degree of a prosthetic component, according to Scheme 1 reaction 1 and 2, depends on the actual concentration of alkyl radicals and on the amount of available oxygen:



Scheme 4 - Macroradicals formation during high energy irradiation

rate of oxidation =

$K_{oss}[O_2][R^\bullet]$ at temperature constant

The actual concentration of alkyl radicals is a function of the dispensed dose rate and of the temperature of the material, namely that of the sterilisation room. It has to be noted that further radicals can result from thermal decomposition of hydroperoxides. At the beginning of the sterilization process the concentration of oxygen is generally constant throughout the sample, but, when oxygen is consumed by the oxidation reactions, other oxygen, if available, diffuses from the surroundings into the sample.

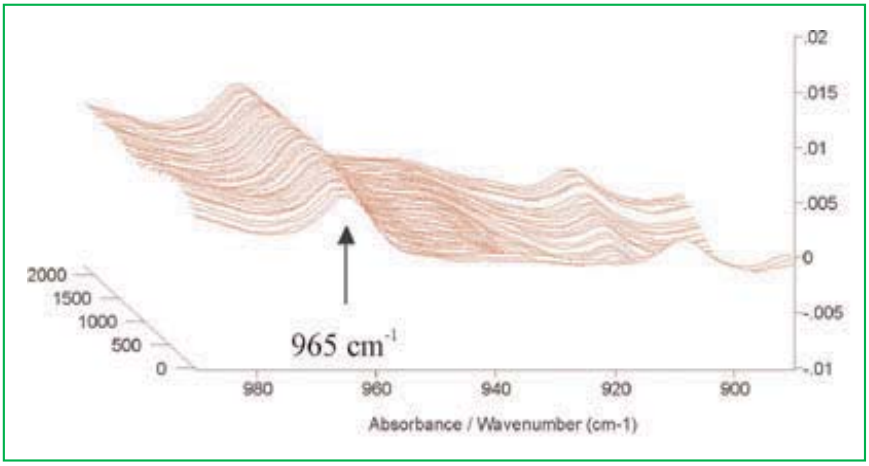


Figure 1 - Trans-vinylene double bonds distribution in a Uhmwpe component

Experimental condition (in the prosthetic component) of the sterilization process

Temperature

Unsterilised ready-to-use prostheses are presumably stored at room temperature for variable time before to be sent to the sterilisation plant. The temperature of the sterilisation cell depends on the external temperature (sterilisation occurred in winter or summer results in a different initial cell temperature) and of course on the intrinsic characteristic of the plant itself. In addition, gamma rays yield energy into the sample, increasing its temperature and the temperature of the cell.
Reasonably, the cell temperature is in the range between 25 and 45 °C. According to regulations, orthopaedic prostheses should be sterilised at least with 25 kGy (namely 25 kJ/kg). However this value is often exceeded and in average, samples receive about 30 kGy. It means that, in adiabatic conditions, the temperature increase of the sample is of ca. 20 °C, being the specific heat of Uhmwpe about 1.5 J/K g, but local overheating cannot be excluded. However, this energy is partially transferred to the surrounding.
Uhmwpe, as polymers usually do, shows a low linear heat transfer coefficient (K_{Uhmwpe} = 0.33 W/mK). As a consequence, the specimen temperature will be really inhomogeneous, being similar to that of the irradiation cell on the surface and to the adiabatic limit in the deep bulk. Thus, it can be considered that the temperature inside the sample during gamma sterilisation varies from 45 to 65 °C. After sterilisation, prostheses are kept at room temperature for very variable times and temperature re-equilibrates. Eventually, during in vivo use (in body implants) the temperature raises to 37 °C.

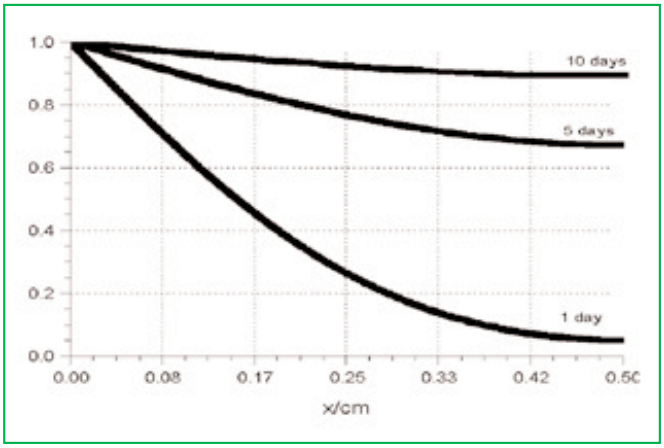


Figure 2 - Oxygen diffusion in Uhmwpe

Oxygen concentration into Uhmwpe prosthetic components

Fick's Law governs the oxygen diffusion into the Uhmwpe prosthetic component as reported in Figure 2. Oxygen dissolves and diffuses in the amorphous phase of polymers. It has been reported that oxygen solubility in a high density polyethylene, whose crystallinity degree is similar to that of Uhmwpe, is 1 mmol/kg at 25 °C.
From these data and taking in account that cups and tibial plateau thicknesses are between 12 and 15 mm, the hypothesis that ready-to-use prostheses are oxygen saturated is supported by realistic considerations: in effect it is likely that span time between sterilisation and implant be beyond 10 days. Oxidation only occurs in the amorphous domain, where oxygen is available. The concentration of $R^\bullet$ formed in gamma irradiation according to Birkinshaw (20) is about 2 mmols/kg every 10 kGy. $R^\bullet$ concentration raises continuously at a rate depending on the dispensed dose rate; however the maximum concentration will be around 6 mmols/kg, then much higher than the oxygen saturation concentration (1 mmol/kg). Thus, the reaction between alkyl radicals and oxygen will be oxygen diffusion controlled.

Alkyl macroradicals ($R^\bullet$).

Alkyl macroradicals $R^\bullet$ originate either by direct interaction of the polymer with gamma rays or e-beam or by hydrogen abstraction to Uhmwpe from reactive radicals as $ROO^\bullet$, $RO^\bullet$, $OH^\bullet$ and $H^\bullet$ (Scheme 1, 2 and 3). The amount of $R^\bullet$ is proportional to the absorbed dose and their actual concentration depends on dose rate and on the actual temperature of the sample. In conclusion, the rate of oxidation of bulk Uhmwpe induced by high energy radiation, depends on:

- characteristics of the sterilisation plants;
- temperature of the sterilisation cell;
- absorbed dose, which controls the generation of primary alkyl radicals;
- dose rate, which governs the residence time in the sterilisation cell and the rate of radical generation;

- sample thickness, which governs oxygen availability into the sample.

Typical condition to which sterilised prosthetic components have been subjected are:

- initial temperature of sterilisation cell between 15-50 °C;
- absorbed dose between 28 and 40 KGy;
- dose rate between 1 and 10 kGy/h corresponding to 3-40 hours of irradiation;
- temperature increase of the sample bulk of more than 20 °C.

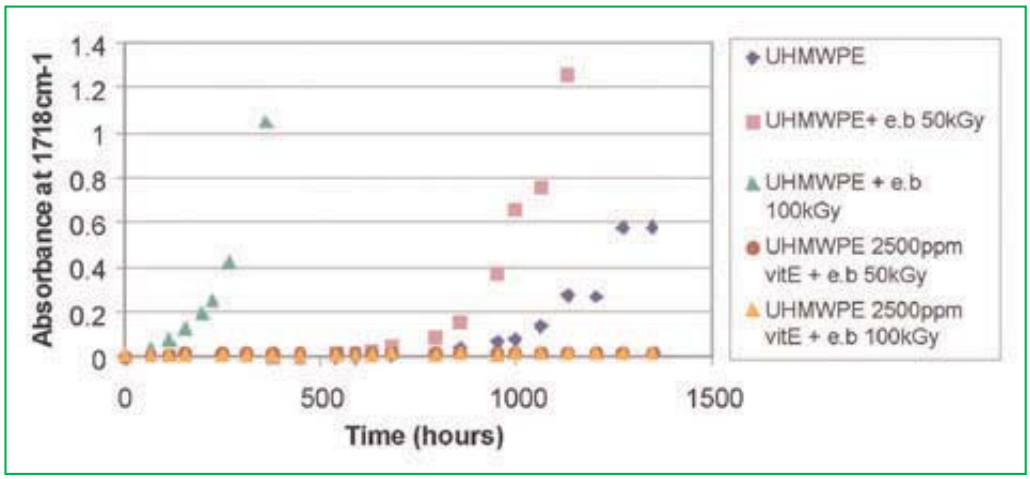


Figure 3 - Ketones evolution at 90 °C

In conclusion, a dynamic gradient of both [O_2] and temperature will be created along the thickness of the irradiated sample, whereas the dose rate can be considered as constant during irradiation. The O-O bond in ROOH is thermally unstable (bond energy 40 Kcal/mol), therefore it easily decomposes producing very reactive $OH^{\bullet}$ and $RO^{\bullet}$ radicals (Scheme 3). Thus, a competition between ROOH formation and consumption occurs in the oxidative processes.

The oxidative process initiated during sterilisation can continue through storage and in vivo time. The rate and the extent of the process will depend on the storage temperature in the shelf and on the human body temperature, together with the amount of available oxygen in vivo.

Stabilization of Uhmwpe

Stabilisation strategies of polymers against oxidation are all based on reduction either of oxygen concentration or radical concentration/reactivity. For that reason, in contrast to the past, sterilisation is nowadays carried out in a inert atmosphere which make oxygen starving into the item to be processed. On the other hand, a wide selection of additives able to control the radical reactivity are available on the market. Despite addition of preservatives is not yet permitted in medical purpose items, this approach should be now considered and investigated in order to improve the properties of the polymer components. Provided that the most dangerous species in growing up the oxidation process are the ROOH, stabilising additive generally act on the basis of two different mechanisms:

- by decomposing ROOH *via* ionic intermediates,reducing so far the radical concentration;
- by reacting with alkyl and peroxy radicals producing less reactive species.

Whilst the first approach is not suitable for medical items in contact with the human body because it most often involves toxic substances and intermediates, the second is just that adopted by the human body antioxidants, for instance the vitamin E. In addition, food stabilised with tert-butyl hydroxy toluene (BHT) or similar additives, which also acts on the basis of this stabilisation mechanism and has been approved by the competent authority, are on the marked since long. Vitamin E seems to be a likely candidate for use in orthopaedic Uhmwpe because it is obviously biocompatible and it is approved as antioxidant for food packaging. Thermoxidation of original Uhmwpe e-beam irradiated at100 kGy, of Uhmwpe stabilised with vitamin E (1,000 ppm) and of stabilised (Vitamin E, 1,000 ppm) e-beam irradiated at 50 and 100 kGy are reported in Figure 3. Ketones evolution in the three cases clearly shows that the original sample is less stable toward oxidation that the two vitamin E stabilised samples.

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