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Chemical and Thermal Evaluation of Commercial and Medical Grade PEEK Sterilization by Ethylene Oxide

Michele Savaris[a], Glaucio Almeida Carvalho[a], Asdrubal Falavigna[b], Venina dos Santos[a]*,

Rosmary Nichele Brandalise[a]

[a]Centro de Ciências Exatas e da Tecnologia - CCET, Universidade de Caxias do Sul - UCS, 95070-560, Caxias do Sul, RS, Brasil
[b]Centro de Ciências Biológicas e da Saúde - CCBS, Universidade de Caxias do Sul - UCS, 95070-560, Caxias do Sul, RS, Brasil

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Many polymers have been used as biomaterials due to their physicochemical characteristics and structural versatility. However, usage on the human body requires sterilization in order to prevent microbial contamination and diminish the risk of rejection or inflammation. This study presents the use of thermogravimetric analysis (TGA) as an alternative to monitor the presence of residual ethylene oxide from polymers sterilization processes. This is a simple technique and does not require sample preparation stages which can imply in some ethylene oxide loss. Ethylene oxide has been used to sterilize polymeric biomaterials, but with restrictions in the amount used due to the difficulty in removing the toxic waste after the sterilization procedure. Samples of commercial (PEEKc) and medical (PEEKm) grade poly(ether ether ketone) (PEEK) were manufactured in the form of cylindrical tubes, hygienized and sterilized with ethylene oxide. PEEKs showed no chemical changes, but exhibited thermal changes by TGA, which evidenced weight loss between 100 and 500°C that was attributed to the removal of residual ethylene oxide, so this technique, at a 10°C·min^{-1} heating rate, can be used to monitor the sterilization processes.

Keywords: *PEEK, ethylene oxide, thermal and chemical properties, sterilization*

1. Introduction

Biomaterials are substances of natural or synthetic origin used to replace human body tissues, organs or functions temporarily or permanently[1]. However, biomaterials must comply with basic requirements for use on living beings, such as: biocompatibility, biofunctionality and sterilization, without compromising their chemical structure[2,3]. Sterilization is a crucial procedure in disinfecting biomaterials to be used on living beings, because it would eliminate microorganisms, prevent the spread of diseases and avoid inflammatory reactions triggered by the body defense mechanism. One of the most frequent methods of polymeric biomaterial sterilization is the use of ethylene oxide because of its excellent antimicrobial properties[4-6]. However, the method has the disadvantage of possibly causing harmful side effects, from skin irritation to damage to the gastrointestinal and central nervous system tissues. At a high level of exposure, side effects may lead to neurological and cognitive dysfunctions, polyneuropathic disability, hematological disorders, increased risk of spontaneous abortions and various types of cancerous growth (in the event of chronic exposure)[7].

Other common sterilization techniques include dry heat sterilization, steam sterilization, sterilization by radiation, besides sterilization by peracetic acid and glutaraldehyde. Heat and high humidity are avoided because these conditions cause degradation of a variety of biodegradable polymers[8-10]. After applying the ethylene oxide sterilization method, oxide residual should be checked according to the ANSI/AAMI/ISO 10993-7[11] Standard, so that the samples can be used as biomaterials without causing damage.

The literature has reported that poly (ether ether ketone) (PEEK) shows excellent mechanical and chemical resistance[12,13] as well as physical properties at high temperatures[14], it is inert and biocompatible, including its composites, that show improved mechanical properties[15,16]. In this context, this study aims at performing sterilization of PEEK samples, for both medical and commercial grades using ethylene oxide and monitoring the sterilized parts for residues of ethylene oxide by means of thermogravimetry (TGA).

2. Experimental procedure

Two different types of PEEK were selected for the study of ethylene oxide sterilization. PEEK commercial and medical degree, differentiating the purity of the monomers and their synthesis by the polymerization process. Commercial poly(ether ether ketone (PEEKc) was supplied by Autotravi Plásticos (Caxias do Sul –RS, Brazil) cylindrical parts with as 4 cm diameter and 10 cm length. Medical grade PEEK (PEEKm) is manufactured by Optima of InvibioLtd. (Holland), cylindrical parts with a 6.4 mm diameter and 100 cm length.

The cylindrical PEEKc were machined to manufacture the specimens by mechanical processing in a Dyna DM 4500 vertical Machining Centre (USA) resulting in nine smaller

* e-mail: vsantos2@ucs.br

tubes of 2 mm internal diameter, 3 mm external diameter and 20 mm length.

For cylindrical PEEKm were machined, from a 6.4 mm diameter solid cylinder tubes of the same diameters and lengths as those of PEEKc were obtained.Formachining, Blasocut BC20 oil was used. The cylindrical parts were submitted to compressed air jets to remove any residues remaining from the machining process.

Hygienization of PEEKc and PEEKm samples was carried out by a first rinse with double filtered water, followed by drying on sterilized compressed air and then sonication with the aid of enzymatic compounds for better release of possible residues. The advanced proteolytic action enzymatic detergent employed in this stage is Endozime® AW Plus, based on amylase, lipase, protease and carbohydrase, developed for full removal of all organic materials andhaving corrosion inhibition properties. Its composition includes isopropyl alcohol, and the cited group of enzymes amylase, protease, lipase, carbohydrase, ethoxylated nonylphenol nonionic detergent, dye, fragrance and water. Standard sterilization techniques for using ethylene oxide procedures were in agreement with the instructions of Interministerial Ordinance Nº. 482 of 16 April 1999[17].

Polymers were characterized by differential scanning calorimetry (DSC) on a DSC Shimadzu DSC-50 (Japan), at heating and cooling rates of 10°C·min^{-1} and N_2flow circulation of 50 mL·min^{-1} in an oven at temperatures from 23 to 420°C. The crystallinity index (Xc) was calculated based on the fusion enthalpy of PEEK readings of DSC (ΔH_m) and fusion enthalpy of theoretically 100% crystalline polymer (ΔH°_m = 130 J·g^{-1})[18] using the equation:

$$X_c(\%) = \frac{\Delta H_m}{\Delta H^\circ_m} \times 100$$

Thermal degradation of the polymers was measured by thermogravimetric analysis (TGA) run on a Shimadzu TGA-50 (Japan) instrument N_2 inert atmosphere (flow of 50 mL·min^{-1}) at temperatures from 23 to 900°C.

In this study this technique was chosen in order to monitor residual ethylene oxide residues in samples submitted to hygienization and sterilization at temperatures ranging from 100 to 500°C, and to assess the residual ethylene oxide degradation of the samples (at 450 - 550°C) and at temperatures prior to the event of PEEK degradation (560°C). The uncertainty of the thermal gravimetric technique was 0.01 mg, obtained by analysis of measurement uncertainty, for this purpose it being considered: scale accuracy, standard weight and calcium oxalate analytical grade standard deviation.

Different heating rates were proposed for the TGA analysis: 5, 10 and 20°C·min^{-1}, to evaluate the residual ethylene oxide degradation after simulation of different processes and conclusion of the sterilization. Chemical analysis was performed by Fourier Transform Infrared Spectroscopy (FTIR) (USA), on a Thermo Nicolet, model iS10 device, band range from 4000 to 600 cm^{-1}, using 32 scans at 4 cm^{-1} resolution, utilizing the technique of Attenuated Total Reflectance (ATR) with diamond crystal at one reflection for PEEK and NaCl oil cell.

3. Results and discussion

For sterilization, PEEKc and PEEKm samples were submitted to three different process stages: machining, hygienization and sonication.

Figure 1 illustrates the %weight loss obtained by TGA for the different process stages of the study.

During machining, there was a percentage of weight loss between the temperatures of 100 and 500°C attributed to the oil used in cutting associated with sample humidity. This amount of oil shows significant loss after hygienization. Oil removal from the PEEKc sample can be confirmed by the TGA of oil, Figure 2, and FTIR, as shown in Figure 3.

Analysis of the cutting oil thermogravimetric curve as illustrated in Figure 2 points out that the highest degradation range which corresponds to 99.7% weight loss could be found between 314°C and 352°C. When the influence of cutting oil degradation is evaluated on the PEEKc and PEEKm TGA curves, practically no significant loss changes at this temperature range could be found, which indicates that no significant amounts of cutting oil were lost, even after the machining process stage.

By analyzing the mineral oil absorption bands of Figure 3 (B), one can see bands at 2954.5, 2922.7 and 2852.8 cm^{-1} from CH_2 and CH_3 groups stretching, also bands at 1376.9 and 1463.2 cm^{-1} related to angular deformations of the same groups and at 721.7 cm^{-1} for rock of grouping $(CH_2)_4$ chain indicating an essentially aliphatic mineral oil. In seeking traces of these bands in PEEKc and PEEKm spectra, according to Figure 3 (A) these were not seen. The choice of checking the success of the chosen approach usingthe ATR technique is due to the fact that superficial contamination is evident since penetration of the IR beam into the sample is approximately 5 µm, so this technique is sufficiently adequate for contamination observations[19-21].

The lowest weight loss of all processes was found for the hygienization stage performed by cleaning samples with enzymatic detergents. Hygienization obtained by cleaning could be observed by color alteration detected through optical microscopy (OM) during the PEEKc samples hygienization process, with gradual removal of dirt (Figure 4) with initial 50x magnification.

Table 1 shows the weight loss (in mg) by TGA after samples machining, hygienization and sterilization process stages.

For the sterilized samples, weight loss percentage was found through all the process stages, as being 1.3% for PEEKc and 1.2% for PEEKm at a temperature range between 100 and 500°C. These temperatures are lower than the PEEK degradation temperatures (± 560°C)[22], however they are within the temperature range of ethylene oxide degradation (450 - 550°C), to which the loss is attributed. It should be emphasized that care must be taken in removing humidity at the hygienization and sterilization stages prior to carrying TGA analysis. From Table 1 it is clear that the analysis results for weight loss are higher for PEEKc than for PEEKm, since the processes for obtaining commercial and medical grade polymers are different.

The maximum amount of residual ethylene oxide among the polymer chains must obey the National Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária*) (ANVISA) regulation that establishes for small implants (10 g), similar

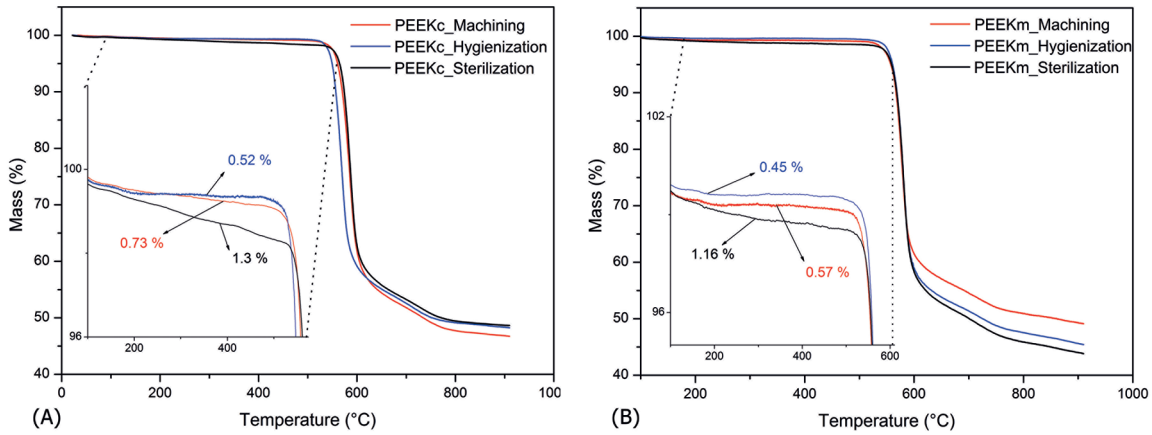

Figure 1: TGA curves after machining, hygienization and sterilization process stages: (A) PEEKc and (B) PEEKm.

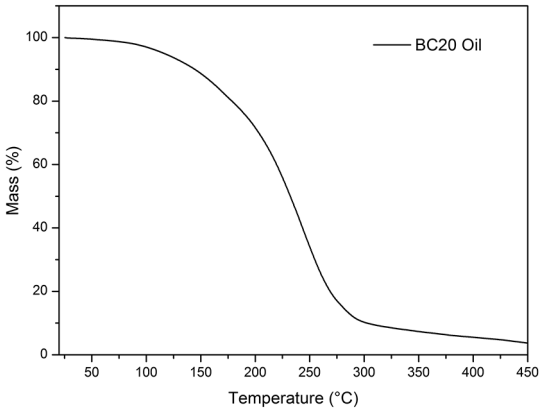

Figure 2: TGA curve of BC20 machining oil.

to the mass of the samples of this study, a maximum limit of 250 ppm (0.0025 mg). Ethylene oxide remaining above this limit is not considered safe for living beings[17]. In this study, it was observed that the remaining oxide in the sterilized, non-aerated hyperventilated samples was higher than that allowed by ANVISA and that the sensitivity of the proposed technique, TGA, was suitable for the monitoring of the sterilization process stages.

The crystallinity index of PEEK (Xc) calculated by DSC, is shown in Table 2.

The crystallinity index showed that samples crystallinity values after machining are similar, where PEEKm = 24.2% and PEEKc = 23.5%; both samples being semicrystalline, even though at low levels. After the various process stages effected for PEEKm sterilization it showed no changes (Xc = 24.2% after machining; Xc = 22.7% after hygienization and Xc = 23.8% after sterilization). This behavior was attributed to the purity of the starting monomers and the process for obtaining the products, which do not contain impurities influencing crystallization. For PEEKc, one can observe increased crystallinity after the proposed process stages (Xc = 23.5% to 42.4%). This increase can be attributed the impurities resulting from the polymerization process as well as any additives used, influencing in the crystallization[23].

For amorphous PEEK crystallization occurs at temperatures approaching Tg (~ 143ºC) but still far below the main crystalline melt transition at 335°C. For industrial applications, which can expose PEEK to continuous temperatures of up to 250°C, operating near or above Tg can induce in-service crystallization[14].

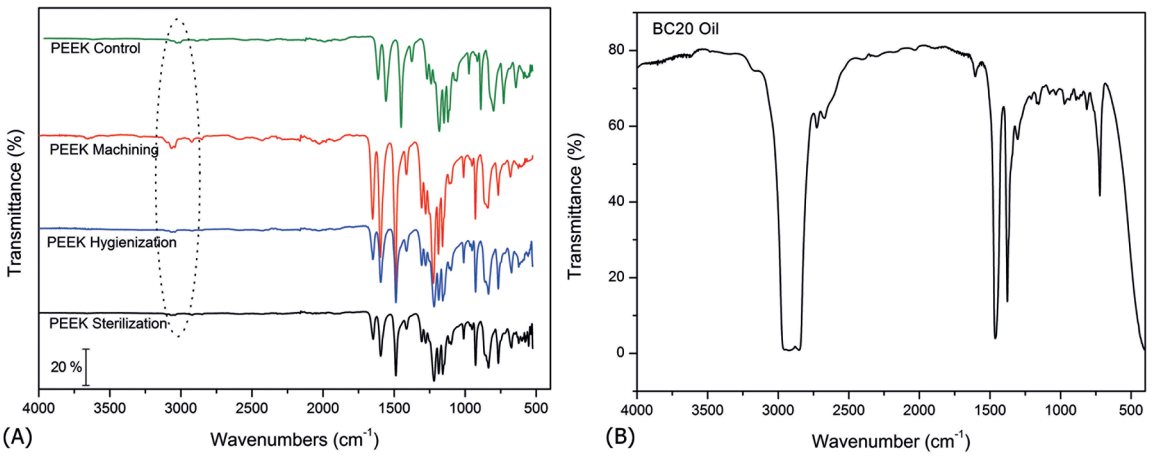

Figure 3: FTIR of PEEKc samples (A) before and after machining, hygienization and sterilization process stages and (B) BC20 machining oil by ATR.

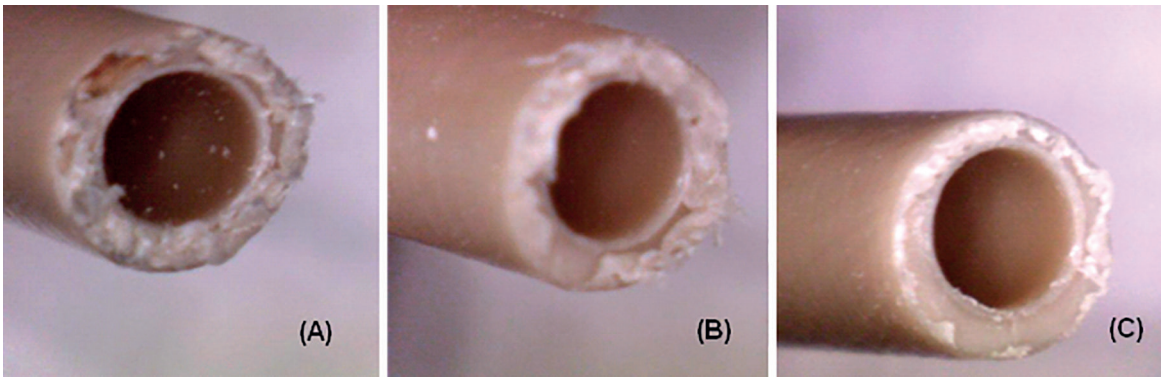

Figure 4: OM Micrograph of PEEKc samples after (A) machining, (B) hygienization and (C) sterilization process stages with original magnification of 50x.

Table 1: Weight loss in mg for PEEKc and PEEKm after machining, hygienization and sterilization process stages by TGA at 10°C·min^{-1} heating rate.

Samples/ process stages	PEEKc				PEEKm			
	Initial mass (mg)	100°C (mg)	500°C (mg)	Weight loss(mg) between 100 and 500°C	Initial mass (mg)	100°C (mg)	500°C (mg)	Weight loss(mg) between 100 and 500°C
Machining	10.485	10.468	10.392	0.08	9.189	9.162	9.107	0.05
Cleaning	12.524	12.494	12.429	0.06	9.892	9.882	9.838	0.04
Sterilization*	14.492	14.443	14.255	0.19	11.853	11.824	11.687	0.14

*without aeration and hyperventilation.

Table 2: Crystallinity index (Xc) for PEEKc and PEEKm calculated by DSC after machining, hygienization and sterilization process stages.

Sample	Process stages	Xc (%)
PEEKc	Machining	23.5
	Cleaning	35.8
	Sterilization	42.5
PEEKm	Machining	24.2
	Cleaning	22.7
	Sterilization	23.8

Ethylene oxide gas diffuses through the samples amorphous segments. For polymer materials, diffusion is generally higher throughthe amorphous than throughthe crystalline phase[23]. The amount of weight loss indicated by the TGA technique is that of the oxide residual since after biomaterials sterilization there is a period of aeration at a given temperature and time to ensure the removal of values compatible with the ANVISA regulations.

Considering the different process simulations carried outon PEEKc and PEEKm samples (Table 3) heating rate values observed at 10°C·min^{-1} (by TGA) are lower when compared with other rates, but the results are similar to those displayed in Table 1.

Also highlighted are the results of Table 3 which show that the proposed drying, aeration and hyperventilation steps are efficient for the removal of residual ethylene oxide since weight loss Figures in mg (steps 5 and 6) are lower than those of the samples which were not submitted to these treatments. Hyperventilation and aeration times longer than those proposed in this study are however recommended since the values obtained so far are higher than those accepted by ANVISA, of up to 0.0025 mg for 10 g.TGA heating rate of 10°C·min^{-1} was the one of higher coherence relative to the processes proposed in this study as well as the evidenced weight losses.

4. Conclusion

The chosen machining methodology enabled making PEEK cylindrical tubs of the required dimensions for the purpose of this study. Medical and commercial PEEK grades showed similar behaviors regarding sterilization processes due to similar crystallinity. Using thermogravimetry at a heating rate of 10°C·min^{-1} it was possible to evaluate the residual ethylene oxide in the sterilized samples, these values being higher than those allowed by the Interministerial Ordinance Nº. 482 of 16 April 1999, in accordance with the thermogravimetric analyses carried out in this study.

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Table 3: Weight loss in mg, for PEEKc and PEEKm by TGA after machining, hygienization and sterilization process stages at different TGA heating rates.

Tests / TGA heating rates (between 100 and 500°C)	5°C·min^{-1} Weight loss(mg)	10°C·min^{-1} Weight loss(mg)	20°C·min^{-1} Weight loss(mg)
Without sterilization - before	0.06	0.04	0.07
Cleaning (ultrasound, sonification)	0.04	0.04	0.07
Cleaning + drying (80ºC/60 min)	0.07	0.05	0.08
Cleaning + drying (80ºC/60 min) + sterilization	0.05	0.04	0.06
Cleaning + drying (80ºC/60 min) + sterilization + aeration + hyperventilation	0.04	0.03	0.07
Cleaning + drying (80ºC/60 min) + sterilization + aeration + hyperventilation + aeration 24 hours	0.06	0.03	0.07

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