

Evaluation of disposable medical device packaging materials under ozone sterilization

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Abstract **Introduction:** Ozonization is an alternative sterilization process for heat-sensitive medical devices. However, the side effects of this process on packaging materials should be verified. **Methods:** Four types of commercial disposable packaging for medical devices were evaluated after undergoing ozone sterilization: crepe paper sheet, non-woven fabric sheet (SMS), medical grade paper-plastic pouch and Tyvec[®]-plastic pouch. For each material, the gas penetration through the microbiological barrier was measured. Other packaging properties, such as chemical composition, color, tactile and mechanical resistance, were also evaluated after sterilization, by using characterization techniques, namely microbiological indicators, infrared spectroscopy, tensile test and optical microscopy. **Results:** All commercial disposable packaging showed good ozone penetration. Crepe paper and SMS were chemically and mechanically modified by ozone, while Tyvec[®] only suffered mechanical modification. Paper-plastic pouch was the packaging material which just experienced an acceptable reduction in tensile resistance, showing no variations on chemical or visual properties. **Conclusion:** The results suggest that medical grade paper-plastic pouch is the most appropriate disposable medical device packaging to be sterilized by ozone when compared to other materials.

Keywords Ozone, Packaging, Medical device, Sterilizer, FTIR, Tensile test.

Introduction

By definition, a medical device is any machine, tool, mechanism, apparatus, implant, *in vitro* reagent, contrivance or other similar item intended for use in medical or healthcare procedures that has no metabolic, immunological or pharmacological effects (World..., 2003). Medical devices that enter in contact with sterile tissue or vascular system are classified as critical items and must be sterilized because of high risk of infection (Rutala and Weber, 2016). Sterilization is defined as any method or process where microorganisms present in the material are killed or turned unviable, without changing the initial material properties (Killeen and McCourt, 2012; Rutala and Weber, 2013). The most common sterilization process in medicine uses saturated

steam as sterilant (Govindaraj and Muthuraman, 2015). However, this process is only possible when the material to be sterilized withstands high temperatures and humidity. Moisture-sensitive or heat-sensitive materials should be sterilized at low temperatures (Ackert-Burr, 2010). Gases such as ethylene oxide (EtO), hydrogen peroxide and low temperature steam/formaldehyde mixture (LTSF) are the most common low temperature chemical sterilants employed in hospitals (Rutala and Weber, 2016). Each sterilization method presents both advantages and disadvantages, especially concerning the material compatibility and penetrability in narrow lumens (Govindaraj and Muthuraman, 2015). Other low temperature methods include the use of chemical compounds (glutaraldehyde, alcohol, peracetic acid etc.), chlorine dioxide, gas plasmas or ozone (O₃) (Rutala and Weber, 2013). The relevance of O₃ gas as sterilant has increased in the last two decades, mainly owing to the good compatibility with some polymers of medical use and advances in its generation technology.

Ozone is a strong oxidizing gas, colorless in low concentrations, with a characteristic odor (Bataklijev et al., 2014) and that can be obtained by electrical gas discharge, ultraviolet light, electrolysis or radiochemical processes (Somalwar et al., 2014). The most common method used for generation of O₃ is the electrical gas discharge known as dielectric barrier discharge (DBD) (Kogelschatz, 2003).



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In this method, two metal electrodes are separated by a short gap (generally lower than 1 mm) and at least one of them is covered with a dielectric material. Streamer or microdischarges are created along the electrode gap when oxygen (O₂) or air is injected and a high voltage (ac or pulsed waveform) is applied. The dielectric material forms a barrier, which hinders the development of the arc discharge and the breakdown of the gas flowing into the gap (Peeters et al., 2016). In the case of DBD using O₂ as gas source, electrons dissociate the oxygen molecules into atoms that, through three-body reactions, generate O₃ species (Samaranayake et al., 2000).

Although O₃ has been discovered in 1840, practical applications were only possible with the development of its first generator by Wener von Siemens in 1857. Subsequently, the first therapeutic application for the purification of blood was reported in 1870 (Grootveld et al., 2004). Due to its high oxidation potential, several studies and applications have been performed using ozone such as water, soil and waste treatment (Ebihara et al., 2012; Mitsugi et al., 2014; Rice, 2012), surface treatment of polymeric materials (Walzak et al., 1995), industrial production with special use in food industry (Varga and Szigeti, 2016), health care, among others. Moreover, O₃ is considered an effective sterilant for various microorganisms. Several studies showed that the use of O₃ promotes the inactivation of a number of pathogenic agents, such as *Escherichia coli* (Hunt and Marinas, 1997), *Enterococcus sp.*, *Clostridium botulinum* (Foegeding, 1985), *Bacillus subtilis*, *Clostridium sporogenes* (Rickloff, 1987), viruses (Srinivasan and Chitra, 2015), and spores. It is important to emphasize that some spores, such as *Geobacillus stearothermophilus* (Sakurai et al., 2003) and *Bacillus atrophaeus* (Mahfoudh et al., 2010), are resistant to several sterilization processes, which suggests their application as bioindicators in sterilization routine monitoring. Despite the microbiocide efficiency, the use of O₃ in health care related sterilization is quite recent and the effects in some materials and packaging properties are still under investigation, which consequently limits its use in many countries (Iwamura et al., 2013; Ohkawa et al., 2004). In the United States and Canada, the first commercial ozone sterilization equipment for reprocessing of health care devices was released only in 2003. In this field of application, one problem concerning the use of O₃ is the compatibility with packaging materials.

Before sterilization, medical devices are cleaned and must be appropriately packaged. Packaging is an important step in the completion of the sterilization because the materials and tools have to remain sterile and safe from external contaminants until their use. Sterilization is required to: (i) prevent contamination after processing; (ii) allow the chemical sterilant action (not applicable to ionizing radiation or dry heat); (iii) eliminate toxic

components, fibers or particles emission; (iv) maintain the color of the packaging; and (v) confer mechanical resistance to punctures, tears and transportation stress (Burlingame et al., 2016).

Packagings are classified into two basic types: reusable and single use. Reusable containers are typically made of stainless steel, anodized aluminum or plastic, and have a box-shape with removable lids, a gasket to secure a tight seal and filters that allow vacuum and sterilant penetration without compromising the microbiological barrier (Seavey, 2009). Alternatives to filters are pressure-sensitive or thermostatic valves that open and close during the sterilization. Single use packagings are typically wraps, bags or pouches. They are made of several materials, which include woven fabrics, nonwoven materials, peel pouches, etc. Among woven fabrics, 100% cotton, synthetic blends and cotton-polyester blends are commonly used. Usually nonwoven materials include plastic polymers, cellulose fibers or special processed papers. Bags or pouches are made mainly of paper. However, often the pouches have been manufactured from laminated paper with polyolefin layers (Seavey, 2008). The choice of packaging depends, among other factors, on the type of sterilant (Billings, 2005) and each packaging must be developed, tested and monitored following a special procedure (Fuente and Bix, 2009). Typical single use packaging in hospitals include crepe paper, nonwoven fabric sheet, medical grade paper-plastic pouch, that are often sterilized either by steam, EtO or LTSF; and Tyvec®-plastic pouch, usually sterilized by hydrogen peroxide, since this process is not compatible with materials that contain cellulose.

To our knowledge, there have been no studies about the compatibility of disposable medical device packaging materials with O₃ gas sterilization, specially investigating the direct correlation between packaging and sterilization cycle. Ozen et al. (2002) concluded that O₃ could modify (depending on the treatment type) the mechanical and chemical characteristics of polymers as polyethylene, polypropylene and polyethylene terephthalate films, commonly applied to food and medical pouches. Eto et al. (2008) demonstrated that Tyvec® bags were submitted to DBD plasma sterilization under different O₂ and N₂ gas concentrations, allowing good microbiological test results, but also produced a negative impact on the mechanical characteristics. In this paper, we evaluate the effects of ozone sterilization in the most common disposable medical device packagings, namely crepe paper, nonwoven fabric sheet, medical grade paper-plastic pouch and Tyvec®-plastic pouch, aiming to establish the ozone sterilization compatibility criteria for common disposable medical device packaging. Therefore, gas penetration, visual appearance after sterilization, qualitative chemical changes in the surface, structural and mechanical modifications were studied.

Methods

A homemade ozone sterilizer system with a pre-validated cycle was applied in this study. Herein, sterilant penetration was evaluated by using biological indicators. Chemical modifications were verified by Fourier-Transform Infrared Spectroscopy (FTIR), structural barrier changes by microscopy, and mechanical resistance by tensile test.

Ozone sterilizer

The ozone gas sterilization procedure for medical devices was designed in agreement with ANSI/AAMI/ISO 14937:2009 standard. Microbiological performance qualification study was performed in accordance to Annex D of this standard. The cycle design was based on the work

of Sakurai et al. (2003). The variables that affect the sterilization process are concentration, temperature, exposure time, relative humidity (when it is present in the cycle) and resistance of biological indicator. In the present work, the ozone concentration was fixed in 15000 ± 1500 ppm with dry air (relative humidity lower than 25%), the temperature was maintained at 37 ± 2 °C, according to Ohkawa et al. (2004), and the biological indicator used was the *Geobacillus stearothermophilus* ATCC 7953 with population of 10^6 . Exposure time was determined in accordance with the standard method (240 min per pulse) and represents the overkill method.

Figure 1 shows the schematic diagram of the ozone sterilizer system. Figures 2A and 2B show the cycle profile and the concentration level for the same profile, respectively. The cycle was divided in seven steps: first

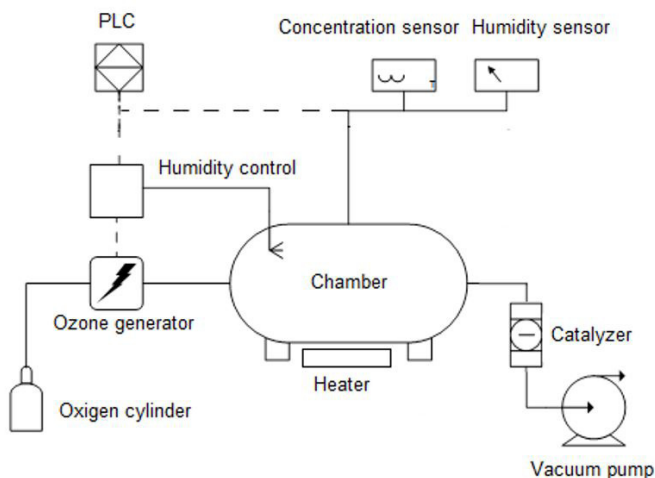


Figure 1. Schematic diagram of the homemade ozone sterilizer.

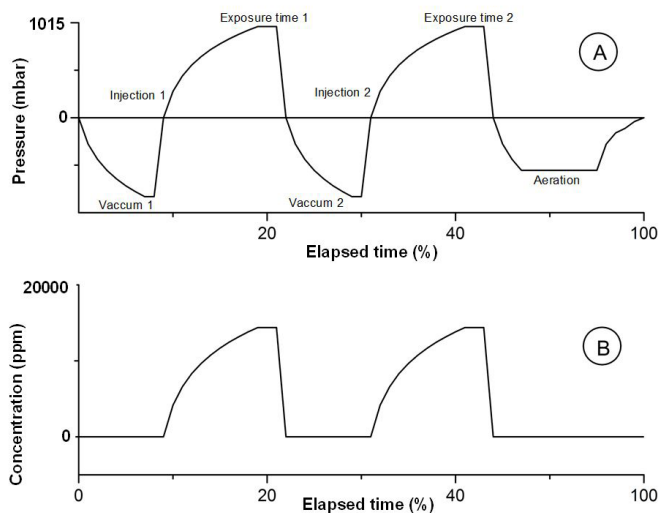


Figure 2. Standard sterilization time-pressure and concentration curves during the ozone cycle. (A) Pressure versus elapsed time cycle; (B) Concentration during cycle period.

vacuum, first O₃ injection, first exposure, second vacuum, second O₃ injection, second exposure, and aeration.

The main components of the system are the cylindrical stainless steel chamber with 60 L (total volume), ozone generator and vacuum pump. The chamber has a heater surrounding the entire structure that maintains a uniform temperature across its surface. The ozone DBD generator from Plasma Technics Inc. (PTI), Plasma Block® (model PBA-20g-E1-UNIV-1Ø-245w-D31), is filled with O₂ gas (purity of 99.5 %) and injects O₃ gas in the chamber. Between the chamber and the vacuum pump, a catalyst converts ozone in oxygen during the vacuum process. Moreover, sensors connected to the chamber measure the process variables and a humidifier controls the humidity in the chamber according to the cycle program. A Programmable Logic Controller (PLC) controls the whole system. Directional valves and other minor components (suppressed in schematic diagram) are responsible to control all the flow during the cycle.

When the cycle starts, initial vacuum removes the air from the chamber, providing a good condition for ozone penetration in the material to be sterilized. Before the vacuum phase, ozone is generated in a dielectric barrier discharge generator (DBD), by using the oxygen supplied to the chamber. When the ozone concentration reaches the preset value, the exposure time phase is started. This phase is repeated twice. At the end of the second exposure time, vacuum-air pulses promote the aeration,

and the catalyst destroys the non-reacted ozone. During the whole cycle, the chamber temperature was monitored and controlled by PLC, as well as the concentration and humidity during the ozone exposure time. If any variable does not reach the preset value or if it oscillates out of a tolerance level, an alarm is displayed in the human interface machine and the cycle is cancelled. For more details concerning the ozone sterilization system, see the reference (Luqueta et al., 2016).

Material preparation and sterilant penetration

Four materials were prepared for sterilization: two types of bags and two different sheets. All samples are commercial products, designed according to ISO 11607-1 (International..., 2006). Figure 3 shows the samples. Sample A consists of a paper-plastic bag with one side made by medical grade paper, and the other side made by a thin plastic film (PET/PE). Paper and plastic are bonded in the corner by heating, and by sealing the pouch. Sample B consists of another type of bag, whereas the paper is replaced with a synthetic material called Tyvec® (from Dupont Co.). Tyvec®-plastic pouch is the preferable disposable medical device packaging in H₂O₂ sterilization processes. Sample C is a Spunbond+Meltblown+Spunbond nonwoven fabric (SMS) (55gsm) sheet and the sample D consist of a crepe paper (60gsm) sheet.



Figure 3. Pictures of the packaging studied. (A) = paper-plastic; (B) = Tyvec-plastic; (C) = SMS; and (D) = crepe paper. Inside each packaging, there is a self-contained ampoule with a biological indicator.

A self-contained biological indicator (BI) was placed inside the packaging and, subsequently, this was sealed. In the sheets, the BI was placed in the center and was folded in two directions, and then sealed with self-adhesive latex free tape. The samples were sterilized and, after sterilization, the indicator was extracted and incubated at 57 °C during 48 h. A non-sterilized BI was incubated as positive reference.

Tests after ozone sterilization

After sterilization process, all samples were compared with the non-sterilized reference and qualitative differences in color, appearance and tactile of each material were observed.

In order to investigate the chemical bonds of the non-treated and treated samples, infrared measurements were performed on an attenuated total reflection (ATR) FTIR Perkin Elmer 400 spectrometer at a resolution of 2 cm⁻¹. Each ATR spectrum was recorded with the blank ATR cell as the background.

In the packaging where no visual and relevant chemical modifications were observed, microscopy and tensile tests were executed. In microscopy, the non-treated and treated samples were analyzed by optical microscopy using a Carl Zeiss microscope model A1. The AxioVision software was used to treat digital images and to compare fiber integrity and barrier conditions before and after sterilization process. The tensile test was conducted according to the ASTM D882-02 standard (American..., 2002). This test aims to determine tensile properties of plastics in film form similar to that of the bag side. The procedure result is the *Breaking Factor* expressed in N/mm that must be calculated by dividing the maximum load by the original minimum width of the sample. To compare results, both plastic film and paper were tested by using the same method. The equipment used for this test was a computer controlled universal testing machine from *Time*, model WDW-100E, with a load cell Celtron, model STC-500kg. By following the standard procedure, five samples of each sample were cut into rectangles of 160x20mm, fixed by clamps in the equipment and tested with a displacement of 15mm/min.

Results

Microbiological challenge

After incubation time, the self-contained BI was examined to verify if the media has suffered color modification. The original media color is purple. If the media color turns from purple to yellow it means that the microorganisms are viable (positive) and if color does not change, they are not viable (negative). All samples

presented negative results in comparison with references that demonstrated positive results.

Fourier-Transform Infrared Spectroscopy

Figure 4A presents the FTIR spectrum for the paper side of paper-plastic pouch for sterilized and non-sterilized samples. The highlighted peaks in the spectrum indicate aliphatic hydrocarbons and carboxylic acids. The curves overlap, due to the same results for sterilized and non-sterilized samples. Figure 4B shows the FTIR spectrum in both sterilized and non-sterilized Tyvec® samples (curves overlap). It was also observed in this spectrum the presence of carboxylic acids and aliphatic hydrocarbons. No color change was visible after sterilization, but, differently than medical grade paper, the tactile verification revealed that the Tyvec®'s mechanical resistance was affected by ozone, generating a fragile and crumbly surface, which could compromise the microbiological barrier after sterilization during manipulation and transportation stress.

The FTIR spectra of non-sterilized and sterilized SMS sheets are presented in Figures 5A and 5B, respectively. Results show the presence of tertiary amide and aliphatic hydrocarbon groups in non-sterilized material. Tertiary amide was removed after sterilization, while carboxylic acid was added. After sterilization, the color changed from blue to light blue and, when touched, the material was slightly crumbly, exactly as Tyvec® was.

Figures 6A and 6B present the FTIR spectra of the non-sterilized and sterilized crepe paper, respectively. Results indicate that the reference material has carboxylic acids, aromatic and aliphatic hydrocarbons in the structure and that sterilization caused the removal of the aromatic hydrocarbons. By concerning the visual aspect, crepe paper changed the color, from green to soft green, with ozone sterilization. There were no tactile changes.

Tensile and optical tests

If one considers that medical device packaging should be mechanically resistant to punctures, tears and transportation stress, SMS and Tyvec® could not proceed to the next step of the analysis. In the same way, crepe paper had its color changed, demonstrating it is incompatible to ozone. Only the paper-plastic pouch was approved in all previous tests and thus it was analyzed mechanically. Table 1 demonstrates the results of tensile test in paper and plastic portion. The number of samples was limited to five specimens, following procedure described in section 8 of the ASTM D882-02 standard (American..., 2002).

The results in plastic portion show that the mean rupture force reduces from 44.6 N/mm to 41.2 N/mm and the mean displacement decreases from 16.0 mm to

12.7 mm. The decrease in standard deviation suggests that the plastic has become more rigid after sterilization. Accordingly, the mechanical resistance of the plastic decreases in 7.6% and the displacement in 20.8%. In the paper side, as the results show the mean rupture force is reduced from 76.1 N/mm to 64.4 N/mm and mean displacement decreases from 2.4 mm to 2.2 mm. Therefore, the resistance of the paper experiments a reduction of 15.4% and a displacement of 10.6%. It is

important to note that there was no statistical treatment for the differences pointed out, and the number of samples was restricted to the minimum defined by the standard, which may restrict the results to the studied event.

In the plastic-paper pouch, the microbiological barrier, whose integrity must be preserved after sterilization, occurs in the paper portion. Figure 7A presents the optical micrograph of the paper surface before sterilization and Figure 7B after sterilization. No changes were observed.

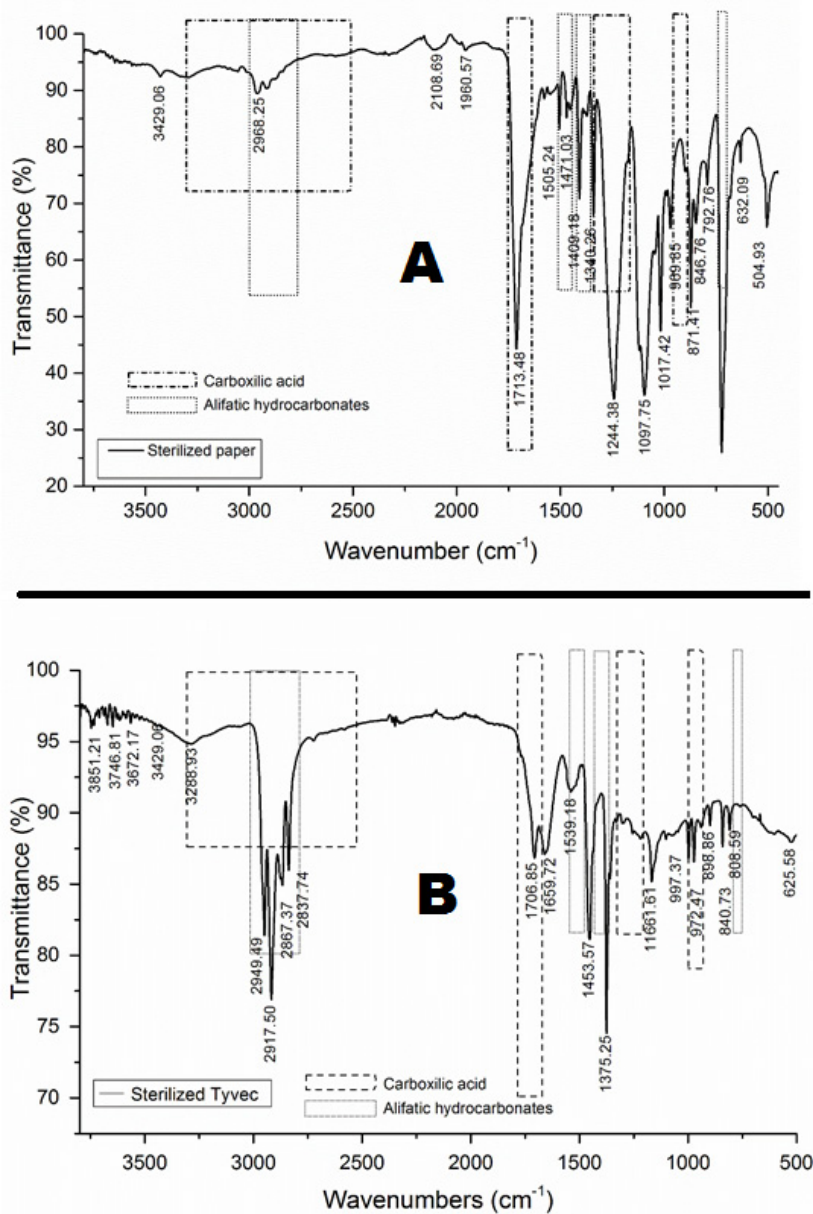


Figure 4. (A) = The FTIR spectra of the paper-plastic pouch (paper side) in the sterilized material with peaks values; and (B) = The FTIR spectra of the Tyvec-plastic pouch (Tyvec side) in the sterilized material with peaks values. Both materials present carboxylic acid and aliphatic hydrocarbonates in sterilized and non-sterilized samples. No changes were observed in non-sterilized materials and the curves are overlapped.

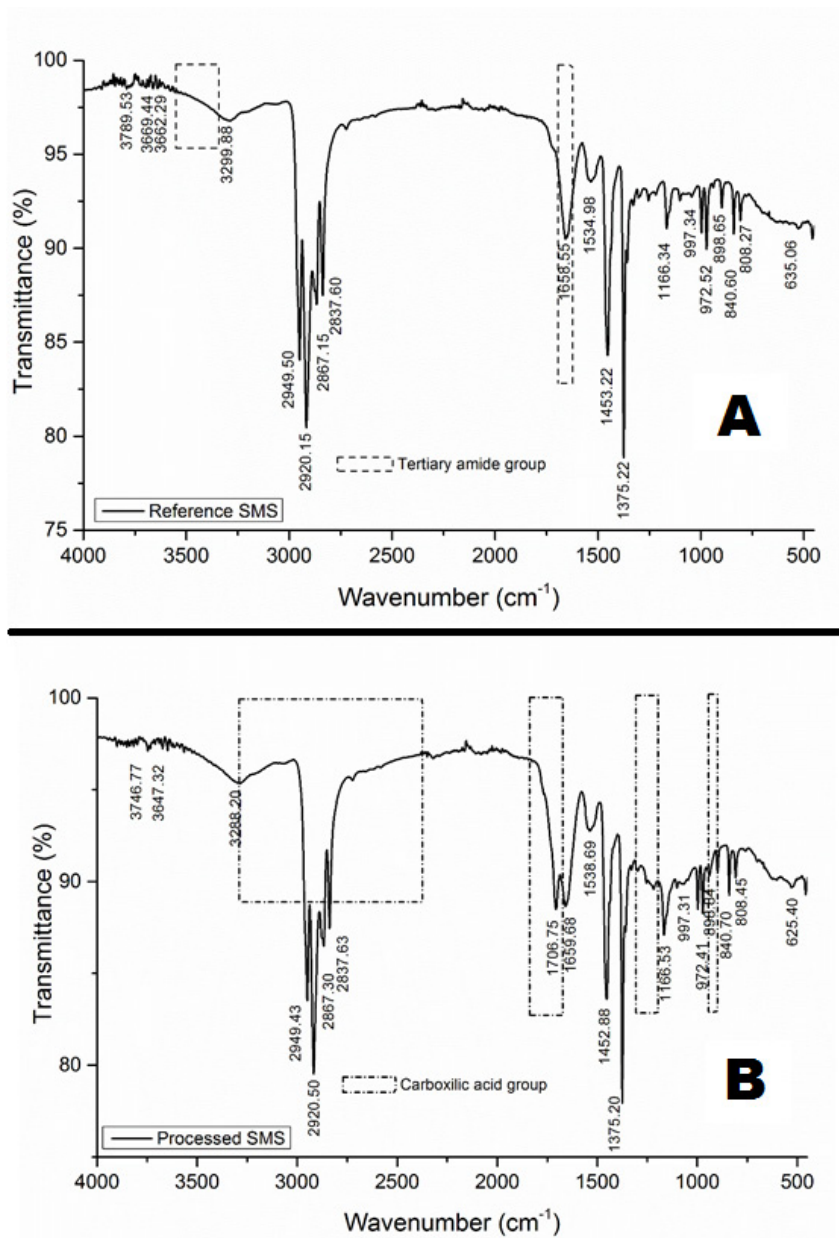


Figure 5. The FTIR spectra of the SMS: (A) = non-sterilized sample with peaks values and tertiary amide groups regions that were removed after the sterilization; (B) = sterilized sample with peaks values and carboxylic acid groups regions that were added after the sterilization.

Table 1. Results of the tensile test in the plastic and paper portion of the plastic-paper pouch.

	Force				Displacement			
	Mean (N/mm)	Min (N/mm)	Max. (N/mm)	σ_x	Mean (N/mm)	Min (N/mm)	Max. (N/mm)	σ_x
Non-sterilized plastic	44.6	41.0	47.0	2.6	16.0	11.8	19.3	3.2
Sterilized plastic	41.2	38.0	42.0	1.6	12.7	9.4	16.4	2.4
Difference (%)		7.6				20.8		
Non-sterilized paper	76.1	72.9	78.6	2.1	2.4	2.2	2.6	0.2
Sterilized paper	64.4	60.7	68.5	2.5	2.2	2.0	2.3	0.1
Difference (%)		15.4				10.6		

N=5 according to the ASTM D882-02 standard (American..., 2002).

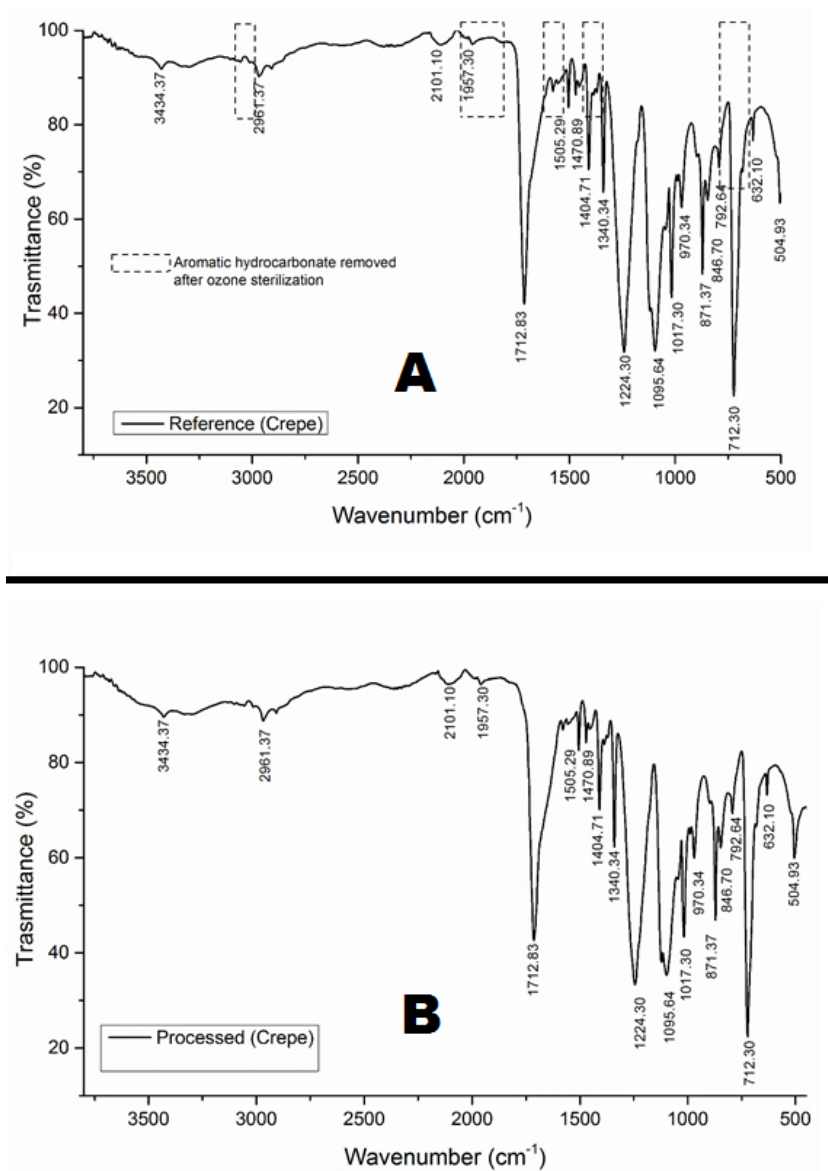


Figure 6. The FTIR spectra of the crepe paper: (A) = non-sterilized sample with peaks values and aromatic hydrocarbonate groups regions that were removed after sterilization; (B) = sterilized crepe paper sample with peaks values.

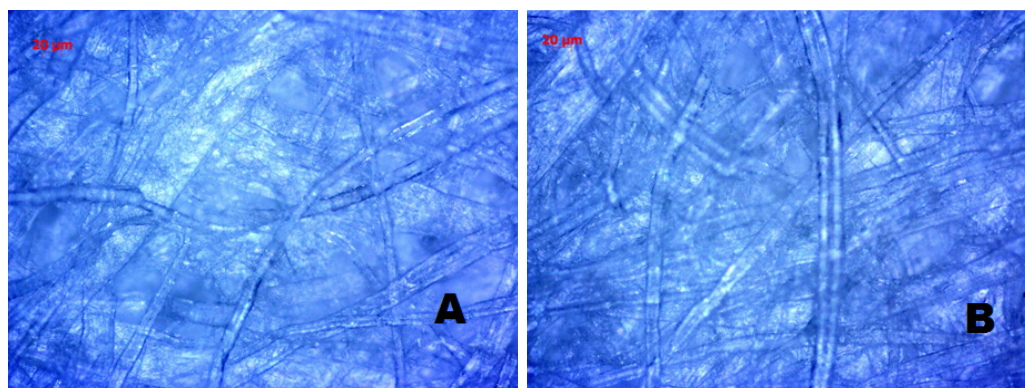


Figure 7. Optical micrograph of the surface of the non-sterilized paper sample (A) and sterilized paper sample (B).

Discussion

Sterilant permeability, non-toxic residues after sterilization, color preservation, microbiological barrier integrity and mechanical resistance were considered as evaluation criteria for ozone sterilization compatibility. The four materials demonstrated penetrability to ozone sterilant according to the microbiological challenge: the biological indicator was negative for processed materials reaching the sterile assurance level (Von Woedtke and Kramer, 2008). Crepe paper and SMS showed changes in their appearance and surface color before and after sterilization. SMS and Tyvec® had changes in the mechanical resistance, presenting a brittle surface when touched. The result of the SMS degradation is in agreement with the pertinent literature, if compared to data presented for a series of synthetic materials used in packaging (Ozen et al., 2002). In disagreement with our results, Tyvec® was applied by Ohkawa et al. (2004) in disinfection by ozone and no changes were observed. The manufacturer of the Tyvec® mentions in the technical guide the compatibility with EtO, gamma radiation, electron-beam, steam (under controlled conditions) and sterilization oxidation processes at low temperature (specifically compatible with hydrogen peroxide from a particular manufacturer) (DuPont, 2011). The differences between our results and other works demonstrate that exposure time and ozone concentration enhance material degradation.

Paper-plastics showed no variations either in color or in the visual appearance, and it was not possible to observe structural changes through tactile examination. FTIR analysis of the non-sterilized and sterilized papers shows the same results or, in other words, the ozone has not changed the chemical structure. The literature demonstrates similar peaks in the FTIR spectrum of the reference and treated material. This result agrees with the studies of Polovka et al. (2006) that investigated a similar material. In microscopy analysis, it was possible to observe that the medical grade paper preserved the fibers and macro barrier after the ozone sterilization process. As in the literature, Tyvec® did not present aggregations nor superficial chemical changes. FTIR analysis revealed chemical alteration in crepe paper and in SMS, while no changes in paper-plastic and Tyvec®-plastic pouch. The tensile test demonstrates that the paper-plastic pouch's mechanical resistance decreases in 20.8% after the ozone sterilization. By considering that, in the bag construction, paper and plastic are fixed together, the tensile and displacement are limited by the paper. As far as we know, no other studies were conducted to determine the best result for this purpose. But, by considering the requirements of BS EN 868-5 "Packaging for terminally sterilized medical devices - Part 5: Sealable pouches and reels of porous materials and plastic film construction -

Requirements and test methods" (British..., 2009) for the tensile test in sealed portion paper-plastic (determined with limit of 1.5N/15mm), sterilized paper and plastic portion could resist the procedure. The experiment revealed that SMS, crepe paper and Tyvec®-plastic pouch were more affected by ozone sterilization than medical grade paper-plastic pouch and that this last one, despite a decrease in the tensile resistance, maintained the characteristics for a convenient disposable packaging system for medical devices when sterilized by ozone.

As a final remark, we conclude that ozone is an efficient sterilant with effective penetration in all studied materials and strong sporicidal activity but, as other chemical agents, affects some materials used in disposable medical device packaging. It is important to highlight some limitations: the applied profile cycle promotes a strong oxidation on the materials, with high ozone concentration, low humidity and large cycle time that maximizes the effects in packaging material. For lower time and concentration and high humidity the results could be different.

The results suggest that medical grade paper-plastic pouch is the most appropriate disposable medical device packaging to be sterilized by ozone when compared to the other materials analyzed in this study. Further study with an adequate sample size is necessary in order to show that the observed effects are statistically significant. Despite the limitations, the present work can contribute with the correct application of ozone sterilization of materials in the medical and research areas, since the correct choice of packaging material can maintain medical device sterile and avoid subsequent contamination after sterilization.

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