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# Modification of a cyclo-olefin surface by radio-sterilization: Is there any effect on the interaction with drug solutions?

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ABSTRACT

A cyclo-olefin copolymer was subjected to an e-beam ionizing treatment. Two doses were studied: one corresponding to the recommended dose for the sterilization of pharmaceutical packaging (25 kGy), and a greater one to enhance the modifications caused by the treatment (150 kGy). The surface modifications were studied by X-ray photoelectron spectroscopy (XPS), contact angle measurements and atomic force microscopy (AFM). The roughness and the wettability of the surface were enhanced by the treatment. The consequences of the surface modifications on the drug interaction with the polymer were studied.


## 1. Introduction

Cyclo-olefins copolymers (COC) are more and more used in the biomedical applications and in the pharmaceutical packaging. For example, COC are used in the diagnostic field in micro-well plates and microfluidic devices (Fredrickson et al., 2006; Niles and Coassin, 2008; Nunes et al., 2010), and in a lot of pharmaceutical packagings such as syringes, bottles, blisters or parenteral nutrition bags (Makwana et al., 2011; Yamazaki, 2004). For these applications a minimal adsorption either of drugs or proteins is needed and the surface state is thus a major concern because it affects both the adhesion and the adsorption phenomena.

Moreover, all these devices have to be sterilized. One way to achieve sterilization is to use ionizing radiations. Many papers have been published for several decades on the modifications occurring in polymers upon ionizing radiations, which are known to be an efficient mean of sterilization; few of them were about cyclo-olefins polymers (Barakat et al., 2013; Saunier et al., 2008; Šećerov et al., 2008). Electron beam irradiation is known to induce chain scission, crosslinking, oxidation and grafting (Chapiro, 1988; Davenas et al., 2002). But, most of these studies focused on the changes in the bulk of the polymer; in comparison only few studies were done on the surface modification of the material, such as those of Zenkiewicz et al. on the modification of wettability and on the surface oxidation of polyolefines (Żenkiewicz, 2005; Żenkiewicz et al., 2003, 2007), and those of Nathawat (Nathawat et al., 2007, 2009) who studied the effect of electron beam on the polymer topography.

Two main parameters have to be considered to study the surface modification: the topography and the chemical composition of the surface. In the case of an ionizing radiation, one main attempted effect is the oxidation of the surface layer that will lead to an increase in wettability and that depends on the irradiation dose. To characterize the surface chemistry and to assess the surface oxidation level, XPS spectroscopy was used. The topographic modifications were achieved using AFM microscopy. As chemical and topographic modifications lead to a modification of the material wettability, contact angle measurements were used to characterize the surface properties. This last method is indeed one of the most sensitive methods that evidences the surface changes with a depth of analysis that concerns the only 0.5–1 first nanometers of the surface and allows quantifying the surface energy and the hydrophilic character of the surface.

Two e-beam irradiation doses were studied: the lower one (25 kGy) is the recommended dose for the sterilization of healthcare products (European Pharmacopeia). The higher (150 kGy) was used to enhance the degradation and modification of the surface submitted to an ionizing radiation.

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**Table 1**
Description of the different samples and analyses used in this study. The aging time $t$ of the sample is given for each analysis.

| | AFM | XPS | Contact angle | Adsorption tests |
|---|---|---|---|---|
| Commercial extruded films ($E$) | $t$ = 1 year | $t$ = 6 months | $t$ = 0, $t$ = 1 year | $t$ = 1 year |
| Spincoated films made with granulate-based solution ($S$) | $t$ = 0, $t$ = 1 year | Not analyzed | $t$ = 0 | Not analyzed |
| Spincoated films made with without additive polymer (SNA) | $t$ = 0 | Not analyzed | $t$ = 0 | Not analyzed |

The consequences of the surface modifications were evaluated in the case of a drug interaction. Three drugs were studied: benzalkonium chloride, phenylephrine and isoprenaline. Benzalkonium chloride is a mixture of alkylbenzyl dimethylammonium chlorides of various alkyl chain lengths and is used as an antiseptic and a spermicide in pharmaceutical formulations. It is found for example in leave-on skin antiseptics, contraceptive creams, and in some nasal sprays. It is quite lipophilic (log $P_{O/W}$ is between 2.5 and 3.5 depending of authors (Kopecký et al., 2007; Patlewicz et al., 2000; Pernak and Chwała, 2003)). Phenylephrine is a vasopressor drug that can be injected to patients suffering of hypotension in order to increase their blood pressure; isoprenaline is used to treat bradycardia and heart block. Both are hydrophilic (log $P_{O/W} = -0.3$ for phenylephrine (Pyka et al., 2006) and log $P_{O/buffer}$ is between −0.7 and −1.5 depending on the pH for isoprenaline (Gulyaeva et al., 2002; Mack and Bönisch, 1979)).

## 2. Materials and methods

### 2.1. Polymer

Topas® COC 8007 from Topas Advanced Polymer (Frankfurt, Germany) was used for this study. It is an ethylene-norbornene copolymer with a 65% molar ratio of ethylene. Its glass transition temperature is around 80 °C and was established by differential scanning calorimetry measurements published in a previous study (Saunier et al., 2007). Molecular weights are determined by Size Exclusion Chromatography in another paper (Barakat et al., 2013): $M_n$ was around 68 000 g mol$^{-1}$ and $I_p$ = 1.2. This polymer was available as 100 μm thick extruded films or as granulates.

Spincoated films were obtained by dissolving the polymer granulates in hot toluene (5% in weight solutions) and by casting the solution onto silicone wafers (Neyco, Paris, France). The acceleration was set to 2000 rpm/s and the speed of 2000 rpm was maintained during 60 s with a SPS spincoater (Putten, The Netherlands) SPIN 150.

In order to extract the small molecular weight compounds from the polymer – especially Irganox 1010® used as an antioxidant – a dissolution process was performed: the polymer granulates were dissolved in hot toluene and then precipitated by methanol. This polymer will be called in the text "without additive polymer". Table 1 gives the different samples and the analysis used in this study.

### 2.2. Drugs

Phenylephrine and isoprenaline in the hydrochloride form, benzalkonium chloride, sodium metabisulfite, and sodium chloride were provided by Sigma–Aldrich (St Quentin Fallavier, France). The solutions of phenylephrine and isoprenaline were prepared at a concentration around 100 ppm of the drug in a solution of ppi water containing 0.1% of sodium metabisulfite (preservative) and 0.9% of NaCl, that is to say solutions closed to what is found in injectable pharmaceutical formulations. The solutions of 100 ppm of benzalkonium chloride were prepared in a 0.9% NaCl ppi water solution.

### 2.3. Irradiation

The irradiation by electron beam was performed by the Ionisos Company (Chausmenil, France). E-beam was produced by a high power generator (10 MeV) with a 20-kW power accelerator. Two different irradiation doses were used: 25 and 150 kGy.

### 2.4. Contact angle measurements

Four probe liquid were used: glycerol and ethylene glycol (Merck KGaA, Darmstadt, Germany), diiodomethane (Merck Schuchardt OHG, Hohenbrunn, Germany) and milliQ water. The liquid properties are given in Table 2. Contact angle measurements were carried out using a Digidrop® apparatus from GBX (Bourg de Péage, France) by doing static contact angle measurements. The contact angle measurements were done on three different spincoated films ($n$ = 3). For each film and each liquid, ten drops were deposited ($n$ = 10).

A spherical cap model was assumed for the drop. Different parameters of the drop were studied as a function of the time of deposit: the contact angle $\theta$, the radius of the drop spherical cap $R$, its height $H$ and its volume $V$. The volume was calculated either by using $\theta$ and $R$ or $\theta$ and $H$. In the case of the water drops, the receding contact angle $\theta_r$ was calculated by using the "stick-slip" phenomenon that occurs during the drop evaporation (Shanahan, 1995): once the drop is deposited, the evaporation proceeds with a pinned contact radius and the contact angle decreases with time, but, after some time, the radius recedes and the contact angle stabilizes (Bourges-Monnier and Shanahan, 1995). The receding contact angle is considered to be the one obtained when the contact line begins to recede (Erbil et al., 1999).

### 2.5. XPS analysis

The chemical analysis of the surface was carried out using a Escalab 220XL spectrometer (Thermo-scientific, Courtaboeuf, France). A twin anode Al Kα source was used. A step scan interval of 1 eV (survey scan) and of 0.1 eV (high resolution spectra of the C1s and O1s) was used. The pass energy was of 200 eV for the survey scans and of 50 eV for the high resolution scans. All the spectra were recalibrated in order to have a C1s peak's maximum at 285 eV. The survey scans were used to quantifying the atomic percentage

**Table 2**
Properties of the solvents used in contact angle measurements.

| | Viscosity (mPa s) (25 °C) | Vapor (mmHg) (20 °C) | Surface tension (mN m$^{-1}$) (20 °C) | Polar component (mN m$^{-1}$) (20 °C) |
|---|---|---|---|---|
| Water | 0.9 | 17.5 | 72.8 | 51 |
| Diiodomethane | 2.8 | 0.68 | 51.8 | 0 |
| Ethylene glycol | 16.1 | 0.05 | 48 | 19 |
| Glycerol | 934 | 0.00015 | 64 | 30 |