Effect of Terminal Sterilization on Bioresorbable Tyrosine Derived Polycarbonates for Medical Device Applications

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Statement of Purpose: In recent years, there has been an increase in the use of bioresorbable polymers for medical device applications. Terminal sterilization via heat, Ethylene Oxide (EO) or radiation is a prefered and superior way than aseptic processing. However, terminal sterilization can have a dramatic effect on the mechanical, chemical and surface properties of the polymers [1]. Our previous work has shown that EO sterilization changes the morphology of electrospun mats and porous scaffolds which could be detrimental [2]. This work, in collaboration with Johnson & Johnson Sterility Assurance (JJSA), is focused towards exploring the effects of mild, medium and severe conditions of EO, Gamma (γ), E-Beam (EB) and Vaporized Hydrogen Peroxide (VHP) sterilization on the chemical, structural and morphological properties of slow (E0000), medium (E1001(1k)) and fast (E5005(2k)) degrading tyrosine-derived polycarbonates (Fig. 1).

Methods: Thin films with 250 μm thickness were fabricated by compression molding of polylactic acid (PLA), E0000, E1001(1k) and solvent casting of E5005(2k) polymers. To evaluate the effect of dosage, humidity and exposure durations of EO, γ, EB, VHP sterilization, the polymer thin films were exposed to mild, medium and severe conditions specific to each sterilization method (Table 1). Weight and thickness were recorded for polymer films pre- and post-sterilization. The polymer films were also evaluated for (i) chemical degradation/ cross-linking by NMR/ATR; (ii) molecular weight loss by GPC; (iii) morphological changes by SEM; (iv) surface composition changes by XPS; (v) thermal characteristics by DSC and TGA; (vi) mechanical changes by MTS and (vii) surface energy (wettability) by contact angle measurements. All sample measurements were done in triplicates for statistical analysis.

Results: PLA, E0000, E1001(1k) and E5005(2k) thin films, ≈250 μm thickness, were fabricated on lab scale and sterilized in a controlled environment at JJSA as per Table 1. All films had a smooth surface texture free of air bubbles. Post-sterilization, no visual changes were observed in the polymer films. Previously, our group has shown that the micropores of the porous scaffolds collapse completely and electrospun fibers fuse together at medium and severe EO conditions [2]. SEM micrographs in Fig. 2 show no deformation or morphological changes in the surface texture of the ultra-fast degrading E5005(2k) films before and after EB sterilization under severe conditions. Similar results were obtained for other polymer films under EB and Gamma. The polymer films will further be evaluated for chemical degradation, molecular weight loss, thermal and mechanical properties and surface composition to give more detailed insight.

Table 1. Sterilization methods and conditions.

Sterilization	Process	Sterilization conditions	
Ethylene Oxide		Temperature (°C)	RH (%)
	Mild	35	35
	Medium	54	50
	Severe	54	75
Gamma		Temperature (°C)	Dose (kGy)
	Mild	4	15
	Medium-1	21	15
	Medium-2	21	25
	Medium-3	21	50
	Severe	37	50
Electron Beam (E-beam)		Temperature (°C)	Dose (kGy)
	Mild - 1	4	15
	Mild - 2	21	15
	Medium	21	25
	Severe	21	50
Vaporized Hydrogen Peroxide (VHP)		Temperature (°C)	Time (min)
	Mild	50	14
	Medium	50	28
	Severe	50	45

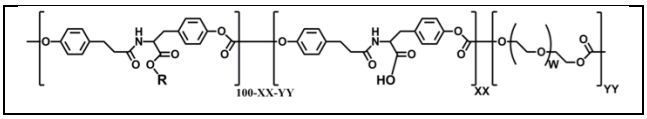

Fig. 1 Poly(DTE-*co*-DT-*co*-PEG carbonate), is abbreviated as Exxyy(nk). DTE: desaminotyrosyl-tyrosine ethyl ester; DT: desaminotyrosyl tyrosine, present at xx mole%; and PEG: polyethylene glycol of molecular weight nk (n is an integer and k = 1000 Da) present at yy mole%. For example, in E1001(1k): xx is 10% DT and yy is 1% PEG (1k).

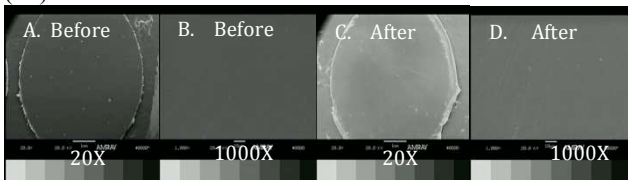

Fig. 2 SEM of E5005(2k) polymer films (A,B) before sterilization (C,D) after severe EB sterilization.

Conclusion: Sterilization can have detrimental effects on bioresorbable polymers and choosing an optimum sterilization condition is an important requirement. This study establishes a collaborative effort between New Jersey Center for Biomaterials and JJSA in finding optimal conditions for terminal sterilization of ultra-moisture sensitive polymers used in medical devices.

References:

[1] "Effect of various sterilization on the behavior of SR-PLLA fibers", J. P. Nuutinen et al.: J. Biomater Sci Polymer Edn (2002); 13(12): 1325–1336.

[2] "Ethylene oxide's role as a reactive agent during sterilization: Effects of polymer composition and device architecture", Phillips et al.; J Biomed Mater Res B: Appl Biomater. (2013); 101(4): 532-40.