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The effect of gamma irradiation on physical–mechanical properties and cytotoxicity of polyurethane–polydimethylsiloxane microfibrillar vascular grafts

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Abstract Poly(ether) urethane (PEtU)–polydimethylsiloxane (PDMS) based materials have been processed by a spray, phase-inversion technique to produce microfibrillar small-diameter vascular grafts; however the effect of sterilization upon these grafts is still unknown. This study investigated the effect of gamma irradiation on grafts made of PEtU–PDMS materials containing different PDMS concentrations. Sterilisation-induced changes in surface chemical structure and morphology were assessed by infrared spectroscopy, light and scanning electron microscopy. Tensile tests were used to examine changes in mechanical properties and the cytotoxicity evaluation was performed on L929 fibroblasts. The study demonstrated that physical–chemical and mechanical properties of PEtU–PDMS grafts, at each PDMS concentration, were not significantly affected by the exposure to gamma irradiation, moreover no sign of cytotoxicity was observed after sterilisation. Although in vitro experiments have been promising, further in vivo studies are necessary to evaluate the biodegradation behaviour of PEtU–PDMS graft after gamma irradiation, before any clinical application.

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1 Introduction

Synthetic vascular grafts with an internal diameter >6 mm, are an acceptable alternative to autologous vessels for vascular reconstructions above-the-knee in patients with peripheral arterial disease (PAD). However, the rate of occlusion of synthetic graft, due to early thrombotic complications and/or late myointimal hyperplasia, is significantly higher (up to 60% at 5 years) when used for revascularization below-the-knee, where smaller diameter grafts are necessary [1, 2]. To face these limitations, investigators have turned their attention toward the development of new graft materials, with reduced thrombogenicity and inflammatory response and improved mechanical properties.

Poly(ether) urethane–polydimethylsiloxane (PEtU–PDMS) based materials yield the good biological and mechanical properties of polyurethane, and the good resistance to oxidation and environmental crackings of siloxane. PEtU–PDMS materials have been processed by a spray, phase-inversion technique to produce small-diameter vascular grafts (<5 mm) with diverse structures and properties [3]. Previous in vitro and in vivo studies have validated the biocompatibility and the good mechanical properties of microporous PEtU–PDMS vascular grafts [4–7], suggesting their potential clinical application for vascular reconstructions in general and specifically for below-the knee applications.

Since sterilization is required for every material or device made available for clinical use and its effect may adversely affect material properties [8–10], it is important that any changes will be fully characterized and considered in the manufacturing process. So far the effect of sterilization procedures on the properties of PEtU–PDMS grafts, obtained by the spray, phase-inversion technique, has never

been investigated. Therefore, in view of a clinical application of these grafts below-the-knee, the aim of this study was to determine the changes in the chemical, physical, mechanical and biological properties of PEtU–PDMS vascular grafts, containing different PDMS concentrations, following sterilisation by gamma irradiation at a standard dose of 25 kGy.

2 Materials and methods

2.1 Graft material preparation

The materials used for graft fabrication were composed of two commercially available elastomers: (1) a medical-grade, aromatic poly(ether) urethane (PEtU) (Estane 5714F1, Lubrizol Advanced Materials, Inc., Cleveland, OH, USA) (AMW 150,000–175,000 Dalton), supplied in grain form, and (2) a diacetoxy silyl terminated (tetra-acetoxy functional) PDMS (AMW 77.292 Dalton) (United Chemical Technologies, Inc, Bristol, PA, USA), supplied as a 55% solution in tetrahydrofurane (THF) and 1,4-dioxane (DX) (2:1, v/v). The PEtU is composed of: (1) a soft segment made of polytetramethylene oxide (PTMO); (2) an isocyanate hard segment made of methylene bis (p-phenylisocyanate) (MDI); (3) a chain extender made of 1,4-butandiol. The PEtU material was further purified using a Soxhlet apparatus in a 1:1 (v/v) methanol:acetone mixture before being dissolved in THF:DX 1:1 to a concentration of 3% (w/v). Solvents were purchased from Carlo Erba Reagenti (Milano, Italy) and were purified by distillation before use. The reaction between the PEtU and PDMS was performed in a three neck flask reactor, equipped with a reflux condenser, at 82°C for 6 h, in a mixture of 1:1 THF:DX, under stirring and in a nitrogen atmosphere [11]. Nitrogen atmosphere was used to avoid, in this phase, moisture initiated reactions between acetoxy groups of PDMS molecules. PDMS was added to the reaction mixture by an addition funnel at concentrations of 0% (pure PEtU), 10, 20, 30, 40, 50, 60 and 80%, (henceforth termed S0, S10, S20, S30, S40, S50, S60 and S80), respect to the PEtU component. In these conditions hydrogen bonding are possible between hydrogen atoms in urethane groups and oxygen atoms in the PDMS backbone. The resulting PEtU–PDMS homogeneous solution, at a final concentration of 3% (w/v), were stored at room temperature and protected from light until its use for graft fabrication by the spray, phase-inversion process.

2.2 Graft fabrication

The diluted PEtU–PDMS solutions, were brought to the point of precipitation by the addition of 17% (v/v) distilled water. The thermodynamically unstable solutions were processed by a "spray-machine", described in detail elsewhere [12], that using the phase-inversion principle allows to manufacture microporous grafts [13]. Briefly, polymeric solutions and distilled water are simultaneously sprayed to intersect on a rotating mandrel, inducing a sudden material precipitation which results in a tubular microfibrillar structure that can be fabricated with different porosity along the wall thickness. In these watery conditions the acetoxy terminal groups of PDMS react with other acetoxy terminal groups of other PDMS molecules forming a polymeric network which produce acetic acid as by-product. This reaction is initiated by water during the graft fabrication and continue during the graft curing in water until its completion in about 24 h. During this phase the 1:1 THF:DX solvent is exchanged with water by diffusion and the microporous structure of the graft become consolidated. The resulting graft material can be considered made of a non-covalent semi-interpenetrating polymeric network (semi-IPN) in which only one of the polymer systems (the PDMS) is cross-linked, interacting via hydrogen bonding with the PEtU macromolecule.

In this study, grafts (12 cm length and 5.0 mm I.D.) were made featuring two different layers in the wall thickness: an highly porous internal layer and a low porosity external layer obtained, respectively, with a 0.2 and 2% (w/v) PEtU–PDMS material solutions.

Grafts were maintained for a minimum of 16 h in distilled water to allow the solvent exchange with water and the graft structural consolidation. Finally, grafts were washed with deionized water in an ultrasonic bath and stored in water at room temperature until used.

2.3 Gamma irradiation

Half of each PEtU–PDMS graft was used as control, the other half immersed in distilled water was packed in polypropylene tube and irradiated with a dose of 25 kGy at room temperature, using a ^{60}Co gamma-ray source (Gammarad Italia S.p.a., Bologna, Italia).

2.4 Visual inspection

Visual inspection of all samples was performed before and after sterilization to examine any color changes or structural deformations.

2.5 Morphological analysis

Grafts microgeometry was highlighted by Sudan Black staining with a procedure previously described [14]. Briefly, graft samples were dipped in staining solution

(0.12% w/v in absolute ethanol) for 10 min at room temperature and then rinsed in distilled water. The stained surfaces were observed by stereo-microscope (SZH0, Olympus, Milano, Italy) and representative images were acquired by a JVC CCD camera at ×70 magnification. The acquired images were analysed by a computerized image analysis system (KS300-3.0, Carl Zeiss, Jena, Germany) to measure wall thickness and internal diameter values of both gamma irradiated and unsterilised grafts.

The surface topography of all grafts was characterized using a scanning electron microscope (SEM) (Jeol 5600, Jeol Italia, Milano, Italy) after gold–palladium metallization (Sputter coater S150B, Edwards, Irvine, CA). The SEM images of graft surface were taken with an acceleration gun voltage of 12 kV.

2.6 Chemical analysis

Attenuated Total Reflectance Fourier Transform Infrared Spectroscopy (ATR-FTIR) was used to analyse changes in the surface chemical structure of all grafts following exposure to gamma rays. Analysis was conducted using a Perkin Elmer Spectrum One (CPU32) equipped with ATR. Spectra were recorded between 650 and 4000 cm^{-1} and peak intensities normalized with respect to the aromatic absorbance peak at 1414 cm^{-1}. Attention was focused on the spectral regions corresponding to the carbonyl groups (non-hydrogen-bonded urethane carbonyl stretching at 1730 cm^{-1} and hydrogen-bonded urethane carbonyl stretching at 1703 cm^{-1}), urethane (N–H bending and C–N stretching at 1530 cm^{-1}), urethane (C–N stretching 1120 cm^{-1}) and the ether groups (aliphatic asymmetric C–O–C stretch near 1110 cm^{-1}).

2.7 Mechanical test

Tensile tests were performed to examine changes in mechanical properties of gamma irradiated grafts. Uniaxial stress–strain data were obtained using a dynamometric tension/compression machine (10HKT, Tinius Olsen, R&D, Milano, Italy) equipped with a 100 N load cell. For each PDMS concentration at least three unsterilised and three gamma irradiated samples were tested. The tests were performed both on strips and on rings: two strips and three non consecutive rings were obtained from each graft. Hysteresis loops were performed before stress–strain measurement to stabilize the materials. The tests were carried out according to ASTM D 412-98a ("Standard test methods for vulcanised rubber and thermoplastic elastomers-tension", 2002) at a crosshead velocity of 500 mm/min.

2.7.1 Strips

The length of strips was measured with a digital caliper (RS, ± 0.03 mm), their thickness with a digital micrometer (Mitutoyo, serie 293-IP65, ± 0.001 mm). The strips were positioned on the testing machine by pneumatic grips and tested at constant velocity up to rupture. Ultimate tensile strength (UTS, [MPa]), elongation at UTS (ε_{UTS}, [%]) and Young's modulus (E, [MPa]) were measured.

2.7.2 Rings

The thickness and diameter of the rings were determined by the KS300-3.0 software (Carl Zeiss), the width was measured with the digital micrometer. The rings were positioned onto special hooked grips lubricate with vaseline oil to avoid the eccentricity of the samples. UTS and elongation at UTS (ε_{UTS}) were measured during the test.

Results are presented as absolute value and as well as percentage variation (Δ, [%]) between non sterilised and gamma-irradiated samples.

2.8 Cytotoxicity test

2.8.1 Cell culture

The in vitro cytotoxicity test was performed with L929 immortalised mouse cell-line fibroblasts from Interlab Cell Line Collection (ICLC, ATL 95001, Genova, Italy). Cells were maintained in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum (FBS), 2 mM L-glutamine, 100 μg/ml streptomycin and 100 U/ml penicillin and were subcultured when at confluence (split ratio 1:3) by trypsinization (0.5% trypsin/0.2% EDTA). The medium was changed every three days and cell viability was routinely checked by vital staining with trypan blue. The cell cultures were kept at 37°C in a humidified atmosphere of 5% CO_2 in air. Culture media were supplied by BioWhittaker Europe, sera and all culture reagents were from Sigma Chemical Co., St. Louis, MO, USA.

2.8.2 Preparation of sample extracts

The cytotoxicity of gamma sterilized grafts were performed with the extraction method. For the extract preparation, samples of each graft were immersed in the complete culture medium that was chosen as extraction vehicle. The ratio of sample surface area to extracting medium volume was 3 cm^2/ml, according to ISO 10993-12 ("Biological evaluation of medical devices—Samples preparation and reference materials"). The surface area

was calculated on the basis of the overall sample dimensions, not taking into account surface porosity. The extraction was performed in chemically inert containers at 37 ± 1°C for 72 ± 2 h with agitation (40 rpm). An inert container with the same extractant and no added material was processed according to the same conditions providing the negative control for the testing procedure. The extract of copper obtained after 24 h of incubation in the conditions described above, diluted 1:10 with complete culture medium, provided the positive control of toxicity. At the end of each extraction period, samples were aseptically removed and the extracts were stored at 4°C and used within 24 h.

2.8.3 MTT assay

The MTT assay is based on the reduction of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), a water-soluble yellow dye by the mitochondrial succinate dehydrogenase to form a water-insoluble dark blue formazan product. Only viable cells with active mitochondria reduce significant amounts of MTT to formazan. L929 cells were seeded into 96-well plates at a density of 8×10^3 cells per well. After 24 h of seeding, when cells were in the logarithmic phase of growth, the medium was carefully decanted and replaced with 200 µl per well of sample extracts and controls. Following an exposure time of 24 h, the surviving cells number was determined by MTT dye reduction. MTT salt (20 µl of a 5 mg/ml MTT solution, filter-sterilized, Sigma) were added to each well and incubated for 3 h at 37°C. At the end of this time, the MTT reaction medium was removed and formazan crystals were solubilized with the addition of 100 µl per well of dimethylsulfoxide (DMSO). The optical densities were measured in a microplate reader (SpectrafluorPlus; TECAN, Austria GmbH) at 550 nm. These determinations were carried out in 3–6 replicates and three independent experiments were performed.

2.9 Sterility test

All grafts were tested for sterility after gamma irradiation using a procedure previously described [15] with slight modifications. Briefly, sterilized samples were immersed in a Mueller–Hinton broth for cultivation of microorganisms (Oxoid S.p.A., Milano, Italy) and maintained under agitation at 37°C for 5 days. Sterile broth was used as negative control, while unsterilized graft was used as positive control. Clouding of the broth after 5 days indicated contamination and inefficient sterilization, while a clear, uncontaminated broth indicated efficient sterilization, producing a sterile device.

2.10 Statistical analysis

Statistical analysis was carried out using the post hoc paired Student's two-tailed *t*-test. The level of statistical significance used to determine whether the difference between the means was significant when $P < 0.05$.

3 Results

3.1 Visual inspection

During visual inspection, no obvious colour change or structural deformation were observed in any of the samples gamma irradiated with a dose of 25 kGy respect to the relative control (unsterilised graft).

3.2 Morphological surface examination

Stereo-microscope observation of graft, after Sudan Black staining, revealed the presence of an highly porous internal surface and a dense external surface (Fig. 1). No significant difference in the wall thickness and internal diameter values between gamma irradiated and unsterilised graft was measured (data not shown). Moreover, SEM images showed no

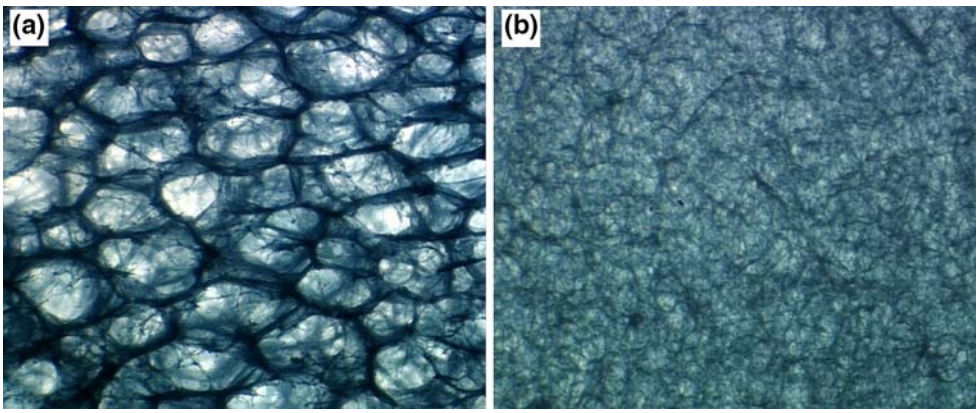

Fig. 1 Stereo-microscopical observation, after Sudan Black staining, of the internal (**a**) and external (**b**) PEtU–PDMS graft surfaces (×70 original magnification)

changes in the surface topography of samples exposed to gamma irradiation compared to unsterilised samples.

3.3 Chemical analysis

No significant changes were observed in the IR spectra between sterilized samples and their controls on all spectral regions analysed. In particular, no effect on the soft segment ether band at 1110 cm^{-1} and on hard segment ether band at 1080 cm^{-1} were observed for all grafts following exposure to the gamma rays (Fig. 2).

3.4 Mechanical test

Data obtained from mechanical tests are showed in Figs. 3 and 4 for strip and ring shaped PEtU–PDMS samples respectively. The increase of PDMS percentage affected mechanical properties of PEtU–PDMS material inducing a decrease of UTS (Figs. 3a, 4a) and Young Modulus (Fig. 3e) and an increase of elongation at UTS (Figs. 3c, 4c).

For both strip and ring shaped samples, UTS decrease was significant among 0, 10, 20, 30% PDMS and 60 and 80% PDMS, while elongation at UTS increase was significant for PDMS percentage variations $\geq$10%. Young modulus reduction was significant for PDMS percentage variation $\geq$20%.

The sterilization treatment produced minimal changes in mechanical properties: in gamma irradiated samples a small decrease of tensile strength (Figs. 3b, 4b) and elongation at UTS (Figs. 3d, 4d) was observed, as compared with non irradiated samples, as well as a low increase of stiffness (Fig. 3f). These changes were not statistically significant for all the PDMS percentages tested.

3.5 Cytotoxicity evaluation of gamma irradiated grafts

The results of the MTT assay are reported in Fig. 5, as the percentage of cell viability related to the control medium (assumed as 100%) after 24 h of extracts incubation. Extracts of 72 h prepared from gamma irradiated PEtU–PDMS grafts with increasing percentages of PDMS (0, 10, 20, 30, 40, 50, 60 and 80) did not depress mitochondrial activity in the L929 cells with respect to the control medium. On the contrary, cells treated with copper extract (positive control) revealed a statistically significant decrease of formazan production; in fact copper extract inhibited L929 mitochondrial activity to about 20% of the control medium.

3.6 Sterility testing

Following gamma irradiation with a dose of 25 kGy all graft samples were made sterile. Only the unsterilised graft (positive control) has determined the clouding of the Mueller–Hinton broth in the sterility test, indicating contamination of microorganisms.

4 Discussion

Poly(ether) urethane (PEtU) elastomers are widely used in medical devices because they have good biocompatibility, good processability and excellent mechanical properties including toughness, durability, flexibility, high tensile strength and abrasion resistance [16]. However devices fabricated using these elastomers are known to undergo hydrolytic and/or oxidative degradation after in vivo implantation, restricting their application for long-term implants [17, 18].

On the other hand, siloxane polymers are resistant to biological degradation such as autoxidation and hydrolysis, moreover they show good blood compatibility and low toxicity [19]. Unfortunately, they do not have the mechanical properties necessary for many chronically implanted devices, and they are subject to mechanical failure.

For these reasons, it would be desirable to have a material which combines, in one step, the mechanical and tissue-compatibility features of PEtU and the blood compatibility and biostability properties of siloxane.

To reach this goal, a standard aromatic PEtU was modified with the addition of increasing quantities of a reactive siloxane, the polydimethylsiloxane (PDMS), to realise PEtU–PDMS materials with suitable properties for medical implantable devices. The PEtU–PDMS materials have been processed by the spray, phase-inversion technique to manufacture vascular grafts with small internal diameters ($\leq$5 mm) and different structural properties. In vitro and in vivo studies have shown that PEtU–PDMS materials, with different PDMS percentages, are not cytotoxic, and exhibit good hemocompatibility and biocompatibility [6, 20]. In vivo biostability studies, performed in rat and rabbit animal models, demonstrated that the degradation rate of PEtU–PDMS materials can be modulated by varying the siloxane concentrations, moreover, for all the PDMS concentrations, only a little inflammation response to degradation products was observed at the site of implantation [21]. Mechanical tests, showed the possibility to modulate elastic properties and volumetric compliance of PEtU–PDMS grafts as a function of the polymer solution concentrations and of the fabrication parameters. As expected, the material evidenced anisotropic viscoleastic properties, with linear behaviour at low stress and high elongation at rupture. In vitro fatigue test performed under physiological conditions on PEtU–PDMS grafts and in vivo implants in the sheep

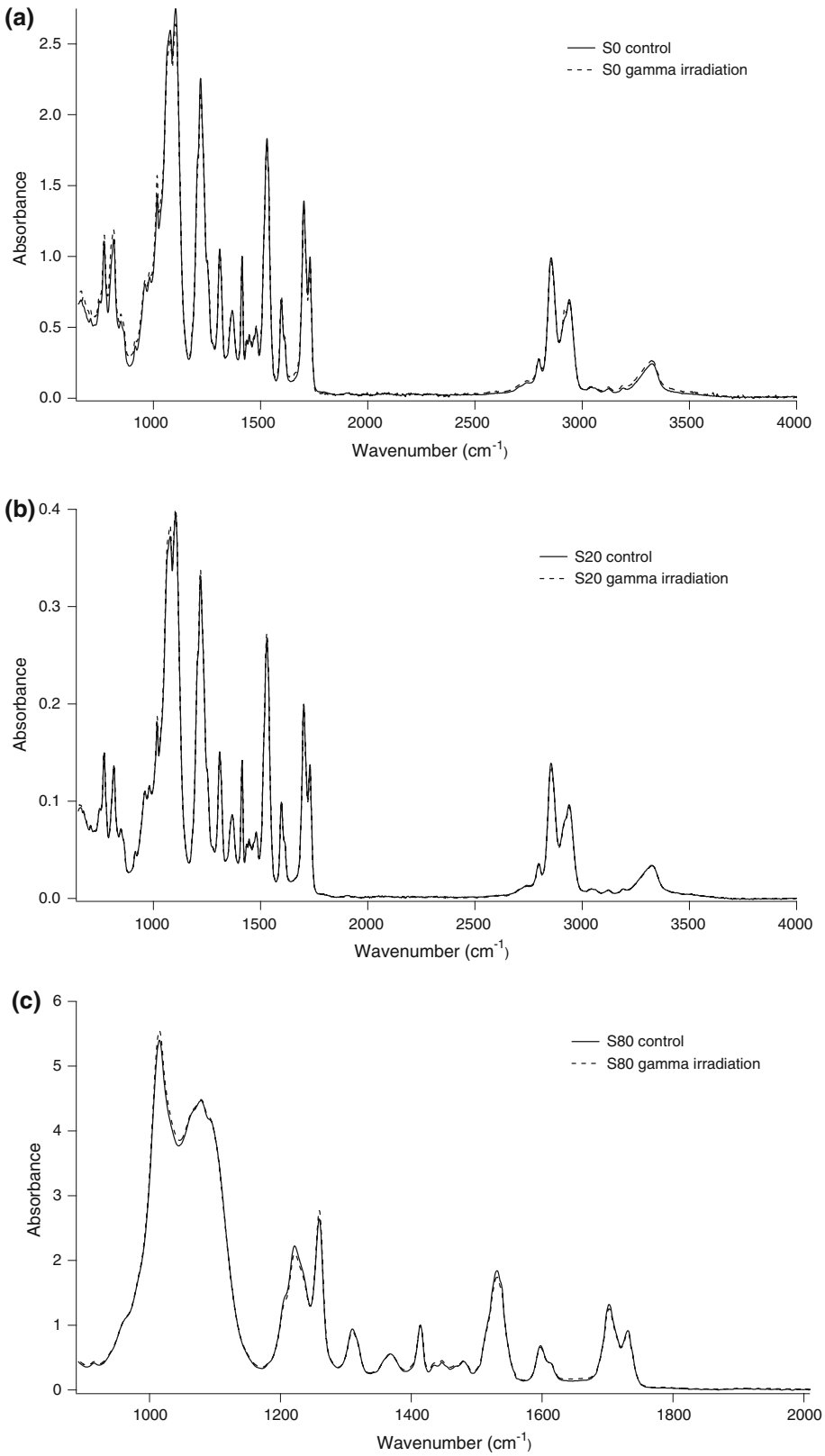

Fig. 2 Representative ATR-FTIR spectra for S0 (**a**), S20 (**b**) and S80 (**c**) graft samples gamma irradiated and not treated (control)

carotid artery by-pass model demonstrated good medium/long-term performances: neither rupture nor aneurismatic events were observed [4].

The overall biological and mechanical properties of PEtU–PDMS vascular grafts make them potentially suitable for cardiovascular applications, in particular for

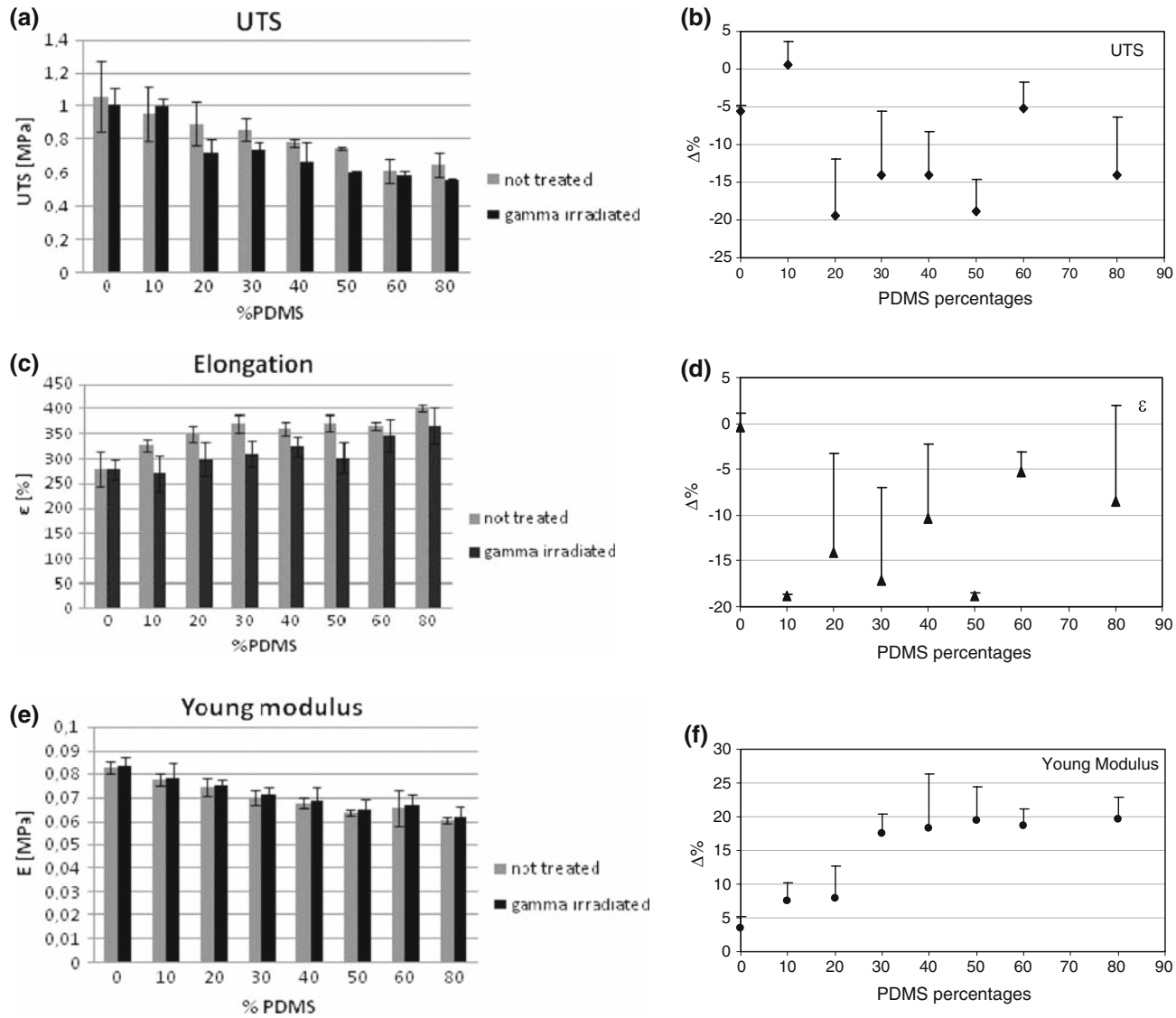

Fig. 3 Mechanical properties of strip shaped samples obtained from PEtU–PDMS grafts containing increasing PDMS concentrations. Ultimate tensile stress—UTS (**a**), elongation at UTS—εUTS (**c**) and Young Modulus—E (**e**) of gamma irradiated and not treated PEtU–PDMS samples versus PDMS percentages. Results are expressed also as percentage variation (Δ) of UTS (**b**), elongation at UTS (**d**) and Young modulus (**f**) between gamma irradiated and not treated samples for different percentages of PDMS. Values are the mean $\pm$ SD of six measurements

vascular reconstructions below-the knee in patient affected by PAD. However, the translation of the pre-clinical results into clinical applications requires the choice and validation of an optimal sterilisation procedure for PEtU–PDMS vascular grafts.

Sterilisation of medical devices can be achieved using a range of techniques including steam, ethylene oxide (EtO) and gamma irradiation. Depending on the polymer chemical nature and processing methods, the different sterilization procedures can cause different degrees of changes in material properties. Devices prepared from polyurethane elastomers are not suitable for steam sterilisation, due to the extensive deformation of the device, and accelerated polymer degradation caused by the high temperature and pressure developed during the process. EtO molecules can interact with the urethane and urea groups through alkylating reactions, which can modify the hydrogen bonding interactions and consequently thermal and mechanical properties of polyurethane based materials. On the other hand, polyurethanes are generally considered to be resistant to the effects of high energy radiation and in general aromatic polymers are more resistant than aliphatic ones [22]. Although polyurethanes are considered to be relatively resistant to gamma irradiation, previously published studies have provided conflicting and often inconsistent results. The high-energy radiation, in addition to killing bacterial

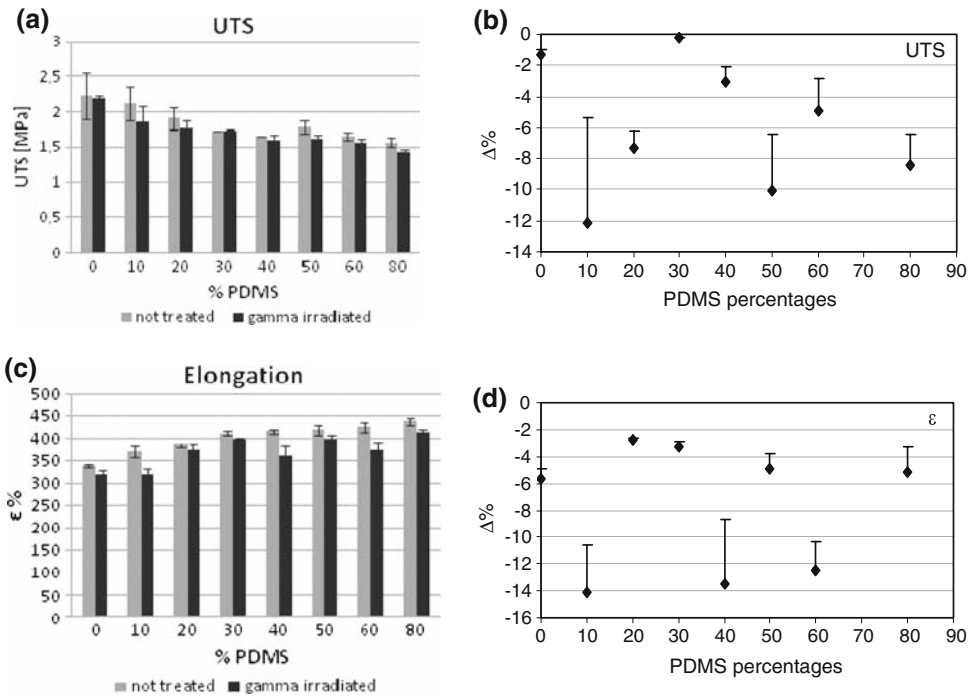

Fig. 4 Mechanical properties of ring shaped samples obtained from PEtU–PDMS grafts containing increasing PDMS concentrations. Ultimate tensile stress—UTS (**a**) and elongation at UTS—εUTS (**c**) of gamma irradiated and of not treated PEtU–PDMS samples versus PDMS percentages. Results are expressed also as percentage variation (Δ) of UTS (**b**) and elongation at UTS (**d**) between gamma irradiated and not treated samples for different percentages of PDMS. Values are the mean ± SD of six measurements

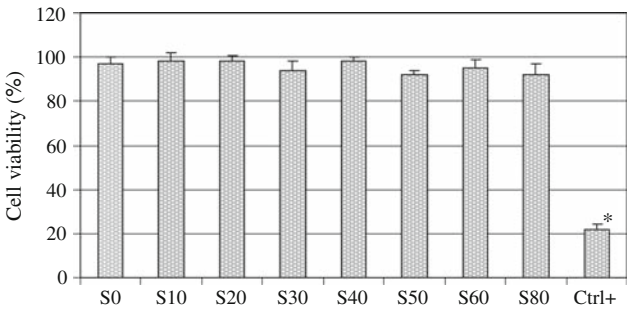

Fig. 5 Cell viability (%) for L929 fibroblasts after 24 h of incubation with extracts of gamma sterilized grafts as determined by the MTT assay. Ctrl+: positive control ($n = 3$, mean ± standard deviation are reported). * $P < 0.05$ versus control medium

life, may also affect material properties; the primary changes can be chain scission, that leads to a loss of mechanical properties, and/or cross-linking that results in an increase in tensile strength [8].

Moreover, because sterilisation process on polyurethane could determine the release of highly toxic degradation products, such as the methylene dianiline [23–25], great attention have to be given to the possible formation of toxic products.

This study investigated the effects of gamma irradiation at a standard dose of 25 kGy on PEtU–PDMS vascular grafts fabricated by the spray, phase-inversion technique in terms of morphological, chemical and mechanical properties.

The stereo-microscopy and scanning electron microscopy analysis showed no changes of the 3-D graft geometry and surface topography of the sterilized samples in comparison to the unsterilized ones, moreover no colour changes was observed by visual inspection.

The infrared analysis revealed that gamma sterilisation did not have effect on the surface chemistry of the PEtU–PDMS grafts; no chain scission and/or crosslinking in the sterilized samples occurred. This result is in agreement with Zhang et al. [26] who demonstrated that neither silicone nor polyurethane elastomers degraded or cross-linked to any appreciable extent after sterilisation by high-energy radiation.

Influence of PDMS percentage on mechanical properties variations was maintained after gamma irradiation, respect to not sterilized samples. Mechanical tests showed a little reduction in ultimate tensile strength and deformation, both for strips and for rings samples, and a slight increasing of Young modulus for strips, as a consequence of the sterilization process. Anyhow, no statistically significant differences were observed between sterilised and unsterilised graft samples.

Finally, no cytotoxic effects of extracts obtained from PEtU–PDMS graft were found in comparison to the culture medium, evidencing the absence of any toxic products release following treatment by gamma irradiation.

5 Conclusions

This study has demonstrated that the gamma irradiation method, at a standard dose of 25 kGy, was optimal for the

sterilisation of PEtU–PDMS grafts containing different PDMS concentrations and manufactured by a spray, phase-inversion technique. Grafts resulted sterile, as confirmed by the sterility test, without any significant changes in their physical–chemical and mechanical properties.

However, although interesting, these results were obtained in vitro and further in vivo studies will be necessary to evaluate the biodegradation behaviour of PEtU–PDMS graft sterilized with gamma irradiation.

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