Pharmacophore

ISSN-2229-5402

Journal home page: http://www.pharmacophorejournal.com

BIOCOMPATIBLE ELASTOMER WITH ADJUSTABLE MECHANICAL PROPERTIES AND DEGRADATION RATE AS A MIDLINE SEGMENT OF BIPARTITE SLING

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ARTICLE INFO

Received:
14 Apr 2021
Received in revised form:
03 Aug 2021
Accepted:
09 Aug 2021
Available online:
28 Aug 2021

Keywords: Biocompatible polymer, Poly (glycerol sebacate), Crosslinking, Microwave synthesis, Mechanical properties, *in vitro* degradation

ABSTRACT

Surgeries for suspending the urethra with synthetic porous tapes (sling) use are effective for curing stress urinary incontinence (SUI). The shortening of the urethral canal and urinary retention are recurrent postoperative problems caused by the tension exerted by the sling on the urethra. This study evaluated the behavior of a biocompatible, bioresorbable, and biodegradable poly (glycerol sebacate) (PGS) elastomer applied as a middle connection of the bipartite sling, which, when degraded, relieves the tension on the organ. Bipartite slings (BS) were fabricated with PGS as a median portion to interconnect their parts. PGS elastomers were synthesized in the common microwave, cured at different curing times in a vacuum oven, and evaluated regarding adhesion strength and mechanical properties by tensile test after *in vitro* degradation. Bothprepolymer (pre-PGS) and PGS elastomers (E) were assessed by Fourier transform infrared spectroscopy (FTIR) and nuclear magnetic resonance (NMR). The analyses revealed a higher degree of esterification (DE) and crosslinking for samples prepared by curing for 72 h, as well as better performance of mechanical properties over 45 days of *in vitro* degradation incubation. PGS elastomer prepared at 48 to 72 h curing times has proven suitable as a median portion of the bipartite slings used in surgeries for suspending the urethra in the SUI treatment.

To Cite This Article: Oliveira VD, Branciforti MC. Biocompatible Elastomer with Adjustable Mechanical Properties and Degradation Rate as a Midline Segment of Bipartite Sling. Pharmacophore. 2021;12(4):11-8. https://doi.org/10.51847/8IiDcNMrVE

Introduction

Stress urinary incontinence (SUI), the most common type of urinary incontinence, isthe involuntary urine leakage during sneezing, laughing, coughing, or exercising [1], which hampers daily activities and sexual acts, causing a negative psychological impact and possibly exposing the individual to public embarrassment [2]. It is often associated with pelvic organ prolapse (POP) of the urinary bladder and urethra [3]. A study carried out in the United States including women aged 18-89 years concluded that the lifetime risk of surgery for either SUI or POP in women is 20.0% by the age of 80 years [4-6]. SUI is more prevalent in women than in men. In 2008, around 127 million women and 10 million men were affected [7].
Porous synthetic tapes (sling) have been globally used in such surgeries [8]; although this procedure has a high cure rate for SUI after 12 months, severe complications as erosion has been associated with the poor biocompatibility and inadequate biomechanical properties of polypropylene mesh– as lack of elasticity and high stiffness– when it is implanted into the pelvic floor [9, 10]. Urinary retention has been a common postoperative complication [11, 12]. If urinary retention persists, it can damage surgical repair and cause urinary tract infection. Prolonged urinary retention requires a new surgery for dilating the urethra, stretching sling, or removing its central portion, for example [12].
This paper introduces a bipartite polypropylene sling interconnected by a biodegradable and flexible small midline segment designed as a potential solution to the above-mentioned problem. After some period, the synthetic parts of the implant must be fixed in both urethra and pelvic region by a natural fibrous tissue produced by the body, the median segment degrades, and is reabsorbed by the body. The urethra is decompressed while the support is maintained, unblocking the urine flow. To date, the continuous sling of polypropylene has been available on the health device market, but the development of a biomaterial suitable as a middle connection is still a big challenge.
Poly (glycerol sebacate) (PGS) is a relatively inexpensive biocompatible, bioresorbable, and biodegradable elastomer of adhesive properties, obtained by the polycondensation of glycerol and sebacic acid, with no catalyst, in two stages, pre-

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polymerization and crosslinking [13]. It has shown suitable for applications in vascular and nerve tissue engineering due to its Young modulus compatibility with soft tissues, flexibility, and resistance to cyclic deformations [14-16], and a promising candidate for use as a biodegradable midline segment of bipartite polypropylene sling.

The synthesis of the prepolymer of poly (glycerol sebacate) in a common microwave was first reported in 2013 as a more efficient alternative energy than the conventional method that uses an inert gas atmosphere for at least 24 h. Moreover, its processing time can be reduced from days to minutes [17]. According to [18, 19], microwave processing is not only a green manufacturing technology but also sustainable, since it consumes less energy and processing time compared to conventional routes, even if in large-scale production. Microwave-assisted polycondensation has produced polymers of improved mechanical properties and higher molecular weight [20, 21].

This study investigated the performance of PGS as a midline segment of bipartite polypropylene sling. Elastomers were synthesized by microwave heating followed by curing at different times in a vacuum oven, for the evaluation of their mechanical behavior and *in vitro* degradation of the bipartite polypropylene slings.

Materials and Methods

Sebacic acid (SA) (99.8%purity) wassuppliedbyMetachem, Brazil, and reagent grade sodiumcloride (NaCl), potassium chloride (KCl), sodium phosphate dibasic dihydrate ($Na_2HPO_4.2H_2O$), and potassium dihydrogen phosphate (KH_2PO_4), whose purityexceeded 99%, were used in the preparation of phosphate-buffered saline (PBS) solution. Glycerol (G) (99.9% purity) and chloroform (99.8% purity) were purchased from Synth®, and slings of surgical Prolene® polypropylene (PP) meshes were suppliedbyEthicon.

Synthesis of Prepolymer

The prepolymer (pre-PGS) was synthesized according to [15], with modifications. A mixture of sebacic acid and glycerol (1:1) was prepared and treated in a domestic microwave oven (Brastemp 27 liters, BSM27ABHNA model, 1.7 kW, and 2.4 GHz). It was irradiated for 1 min (microwave irradiation cycle), and the microwave door was then kept open for 1 min for internal ventilation so that the gases produced could escape and prevent the overheating of the mixture. During the ventilation interval, the reaction temperature was measured by a simple analog thermometer. The total microwave irradiation time was 1 h. The microwave was set to provide an output of 340, 510, and 680 W at each microwave irradiation cycle, according to the temperature measured, 110-120, 100-110, and 90-100 °C, respectively, for maintaining the maximum reaction temperature ≤120 °C.

Preparation of Bipartite Slings and Curing

The surgical PP meshes were cut to the dimensions of the bipartite sling (BS), according to ASTM F2255−05 standard, as shown in **(Figure 1)**.

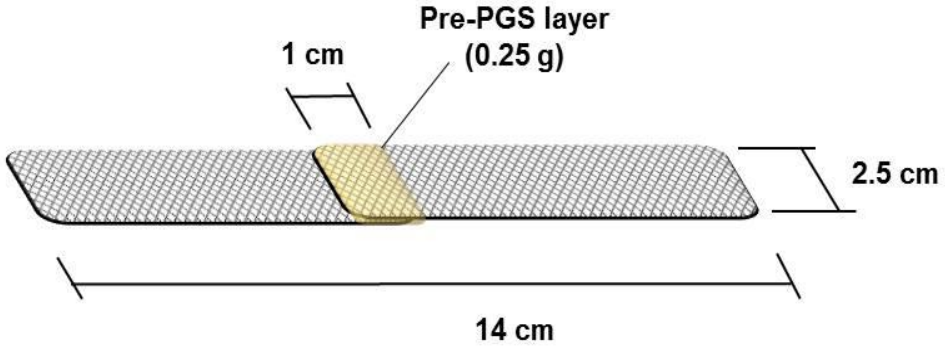


Figure 1. Bipartite sling (BS) interconnected by the pre-PGS layer (highlighted in yellow).

In each curing test, the bipartite sling (BS) was interconnected by the pre-PGS layer (0.25 ± 0.02 g), as highlighted in yellow in (Figure 1), and the samples were supported on a steel sheet. Teflon®'s adhesive prevented PGS from adhering to the steel sheet. A 200 g aluminum weight bar was positioned over the median segment of the slings, in accordance with ASTM F2255−05. 2g of pre-PGS were then deposited in an aluminum container to be used in Fourier transform infrared spectroscopy (FTIR) and nuclear magnetic resonance (NMR) characterization analysis of the elastomers. The materials were cured in a vacuum oven (27 in.Hg) at 130ºC for 24, 48, 72 and 96 h, generating the elastomers denoted as E24, E48, E72, and E96, and the BS specimens interconnected by the PGS layer denoted as BS/E24, BS/E48, BS/E72, and BS/E96.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectroscopy inferred polymerization and cure and compared the degree of crosslinking among pre-PGS and

elastomers (E, i.e., cured PGS samples). A Spectrum 100 (Perkin Elmer) spectrometer was used and FTIR spectra were recorded according to an attenuated total reflectance (ATR) mode, with zinc selenide crystal, 16 scans, 4000 to 500 cm^{-1} wavenumber, and ± 4 cm^{-1} spectral resolution.

Nuclear Magnetic Resonance (NMR)

^{1}H NMR spectra were taken for the pre-PGS and the elastomers (E) samples by an Avance III HD600 Bruker spectrometer at 600.27 MHz and 23 ºC. Chloroform (99.8% purity) was used as a deuterated solvent. **(Figure 2)** illustrates the PGS synthesis reaction and the proton positions employed in the ^{1}H NMR analyses.

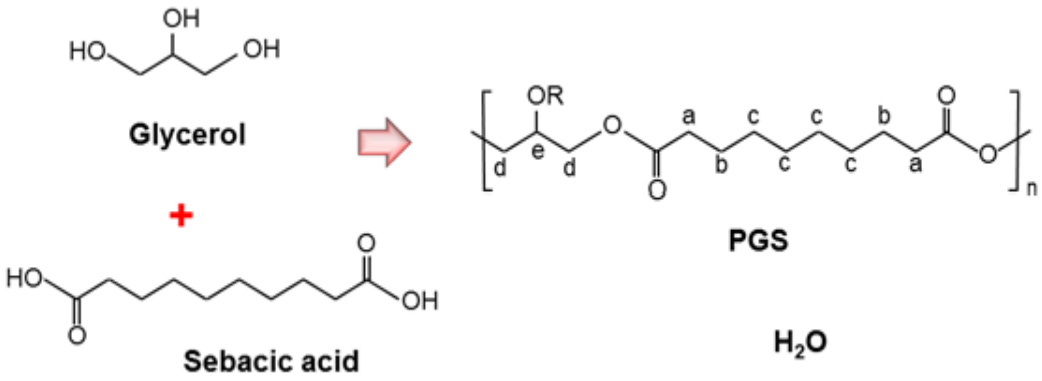


Figure 2. PGS synthesis with ^{1}H protons positions, where R = H, or polymer chain. Categories a, b, and c are associated with sebacic acid, whereas d and e refer to the contribution of glycerol.

The molar ratio of the glycerol/sebacic acid (G/SA) reactants in the pre-PGS and elastomers (E) was calculated by Equation 1 [22].

$$G/SA=\frac{N_{a,b,c}\times Am_{d,e}}{N_{d,e}\times Am_{a,b,c}} \quad (1)$$

where $N_{a,b,c}$ and $N_{d,e}$ are the numbers of protons in the -CH_2- and -CH- groups from the sebacic acid (16H) and glycerol (5H) reacted, respectively, and $Am_{a,b,c}$and$Am_{d,e}$are the integral areas of the peak of the respective protons.
The partial degrees of esterification of the carboxyl groups in positions “d” (DE-d) and “e” (DE-e) are given by Equations 2 and 3, respectively [22].

$$DE\text{-}d(\%) = \frac{N_f \times Am_{d,e}}{N_{d,e} \times Am_f} \times 100 \quad (2)$$

$$DE\text{-}e(\%) = \frac{N_e \times Am_{d,e}}{N_{d,e} \times Am_e} \times 100 \quad (3)$$

Where $N_f$is the number of protons in the -CH_2-OH group of glycerol (OH-CH_2- and -CH_2-OH = 6 H) and $Am_f$is the integral area of their peak (4.0 - 4.4 ppm), N_e is the number of protons in the -CH-OR group of cross-links (-CH-OCH_2- = 3 H), and $Am_e$is the integral area of their peak (4.9 – 5.3 ppm). Finally, the degree of esterification (DE) was obtained from the sum of both partial degrees of esterification, i.e., DE = DE-d + DE-e.

In vitro Degradation and Mechanical Characterization

All cured bipartite sling (BS) samples were soaked in phosphate-buffered saline (PBS) solution, at pH = 7.4 and 37 ºC, thus generating the samples denoted as BS/E24, BS/E48, BS/E72, and BS/E96, respectively, and removed at different stages of 1 h, 7, 21, and 45 days *in vitro* degradation. After degradation, their mechanical behavior was evaluated by tensile tests in a model 5969 Instron universal tensile testing machine at 5mm.min^{-1} speed, according to ASTM F2255−05. At least five BS specimens were tested for each degradation stage.

Results and Discussion

Polymerization, Cure, and Degree of Esterification

(Figure 3) shows the FTIR spectra of prepolymer (pre-PGS) and elastomers cured for 24 h (E24 sample), 48h (E48 sample), 72 h (E72 sample), and 96 h (E96 sample). The dashed lines indicate the 3500, 1740, and 1160 cm^{-1}main peaks.The broad

peak at approximately 3500 cm^{-1}corresponds to the hydroxyl groups (O – H)stretching peaks, and those around 1740 and 1160 cm^{-1} are attributedto the ester groups (C = O and C – O, respectively) stretching vibrations [23].

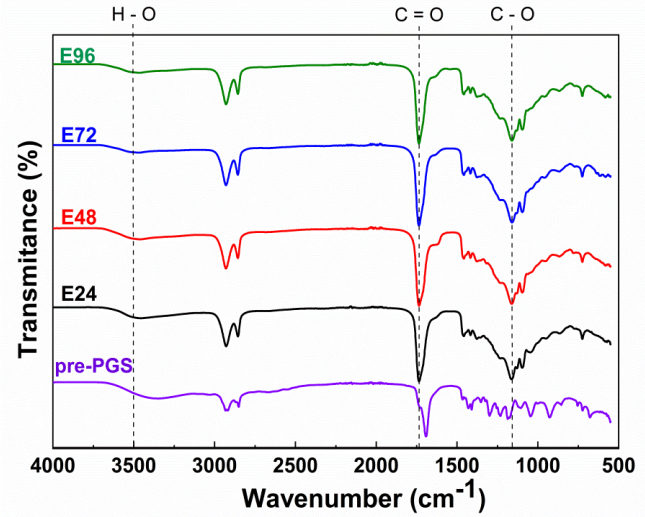


Figure 3. FTIR spectra of pre-PGS and E24, E48, E72, and E96 cured elastomers. Dashed lines indicate the 3500, 1740, and 1160 cm^{-1}peaks.

As the degree of esterification (DE) increases, the intensities of C = O bond-induced peaks increase, whereas peaks from O − H bonds decrease, indicating an increased density of cross-links [13-15, 23].

As expected, the pre-PGS spectrum exhibited a broader O – H peak and the lowest intensity of C = O and C – O peaks, followed by the E24 sample. The E72 spectrum showed the lowest intensity at 3500 cm^{-1} and the highest intensities at 1740 and 1160 cm^{-1}, indicating the highest degree of esterification among all samples. However, this trend was not observed in the E96 sample, which exhibited lower intensities ofC = O and C – O peaksin comparison to E72. PGS also exhibited peaks for the alkane group (– CH_2) between approximately 2800 - 3000 cm^{-1}.

The chemical shifts between 1.3 – 2.4 ppm in the ^{1}HNMR spectra **(Figure 4)** are attributed to the shielded methylene protons **(**a, b, c) in **(Figure 2)** of the sebacic acid unit, while signals of the methylene and methane protons of the glycerol unit and various glycerides **(**d, e, f) in **(Figure 2)** appear between 3.5 – 4.5 ppm (– CH_2 –) and 4.9 – 5.3 ppm (– CH –), respectively [22, 24-26].

The molar ratio of the glycerol/sebacic acid (G/SA) reactants and the partial and total degrees of esterification (DE) of all samples were calculated by Equations 1-3 with the use of the integrated areas of^{1}H NMR peaks **(Table 1)**.

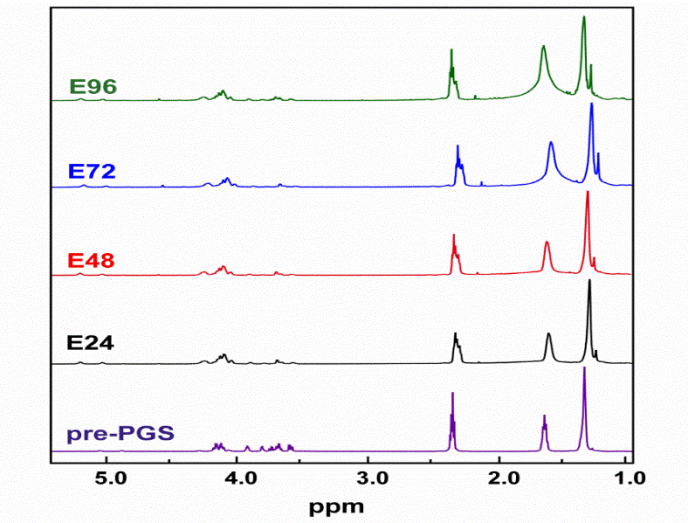


Figure 4. ^{1}H NMR spectra of pre-PGS and E24, E48, E72, and E96 cured elastomers.

Table 1. Glycerol/sebacic acid (G/SA) molar ratio and partial (DE-d, DE-e) and total degrees of esterification (DE) of pre-PGS and E24, E48, E72, and E96 cured elastomers.

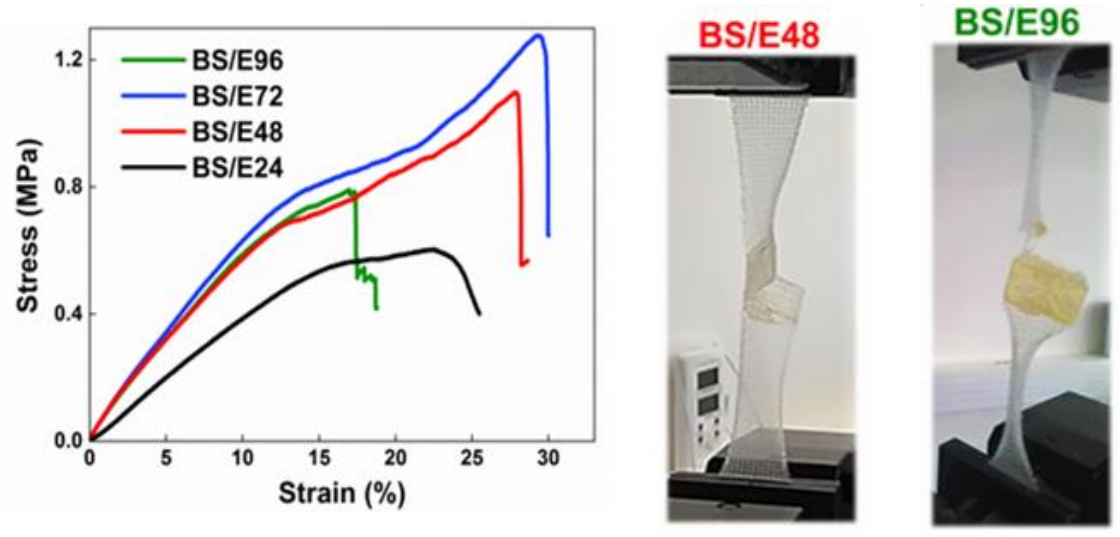
Sample	G/SA	DE-d (%)	DE-e (%)	DE (%)
pre-PGS	0.85/1	34	4	38

E24	0.72/1	59	14	73
E48	0.66/1	61	15	76
E72	0.59/1	52	27	79
E96	0.36/1	57	14	71

DE is expected to increase in function of the curing time increase. Such behavior was exhibited by E24, E48, and E72 samples; however, this trend was not observed in E96, corroborating the FTIR results **(Figure 3)**. E96 showed a 39% lower G/SA molar ratio and an 8% decrease in DE in comparison to E72, indicating degradation during the long curing time. Moreover, this decrease can be observed specifically in DE–e, revealing the degradation occurs mainly in the cross-links (–CH –OR). E72 showed the highest DE among the elastomers, while the smallest loss of glycerol (G/SA) was observed for E24.

In vitro Degradation and Mechanical Characterization

As shown in **(Figure 5a)**, an increase in toughness occurs as the curing time increases up to 72 h. Overall, the samples resisted until a complete detachment of the parts, i.e. cohesive failure of the adhesive, represented by BS/E48 sample **(Figure 5b**). An exception was observed for BS/E96, whose failure occurred prematurely at the PP sling-elastomer border, i.e. a cohesive failure of the adherent (PP sling), as shown in **(Figure 5c)**. The irregularity at the end of the BS/E96 stress-strain curve **(Figure 5a)** is related to the successive breakings of the sling wires in the fragile region. Such fragility results from the combination of high glycerol loss, as evidenced in the ^{1}H NMR results, and possible degradation in the crosslinking step.



a) b) c)

Figure 5. Mechanical behavior of BS specimens interconnected via PGS after incubation in PBS for 1 h at 37 ºC: (a) Average stress-strain curves of BS/E24, BS/E48, BS/E72, and BS/E96; (b) BS/E48 and (c) BS/E96 images taken near the failure occurred in the tensile test.

BS/E96 showed the highest Young modulus after the incubation period **(Figure 6a)**. Only a 14.3% modulus reduction after 45 days of incubation was detected, whereas BS/E48 and BS/E72 exhibited 46.9% and 26.1% Young modulus reductions, respectively. However, BS/E96 showed lower values of tensile strength and elongation at break in comparison to BS/E48 and BS/E72 **(Figure 6b and 6c)**, respectively. After 21 days of incubation, the tensile strength of BS/E72 was still equivalent to that of BS/E48 after 1 hof incubation, and after 45 days it was still equivalent to 21 days of degradation of BS/E48. BS/E24 showed the lowest mechanical properties, and after 45 days, the degradation was sufficient to detach the parts of the slings.

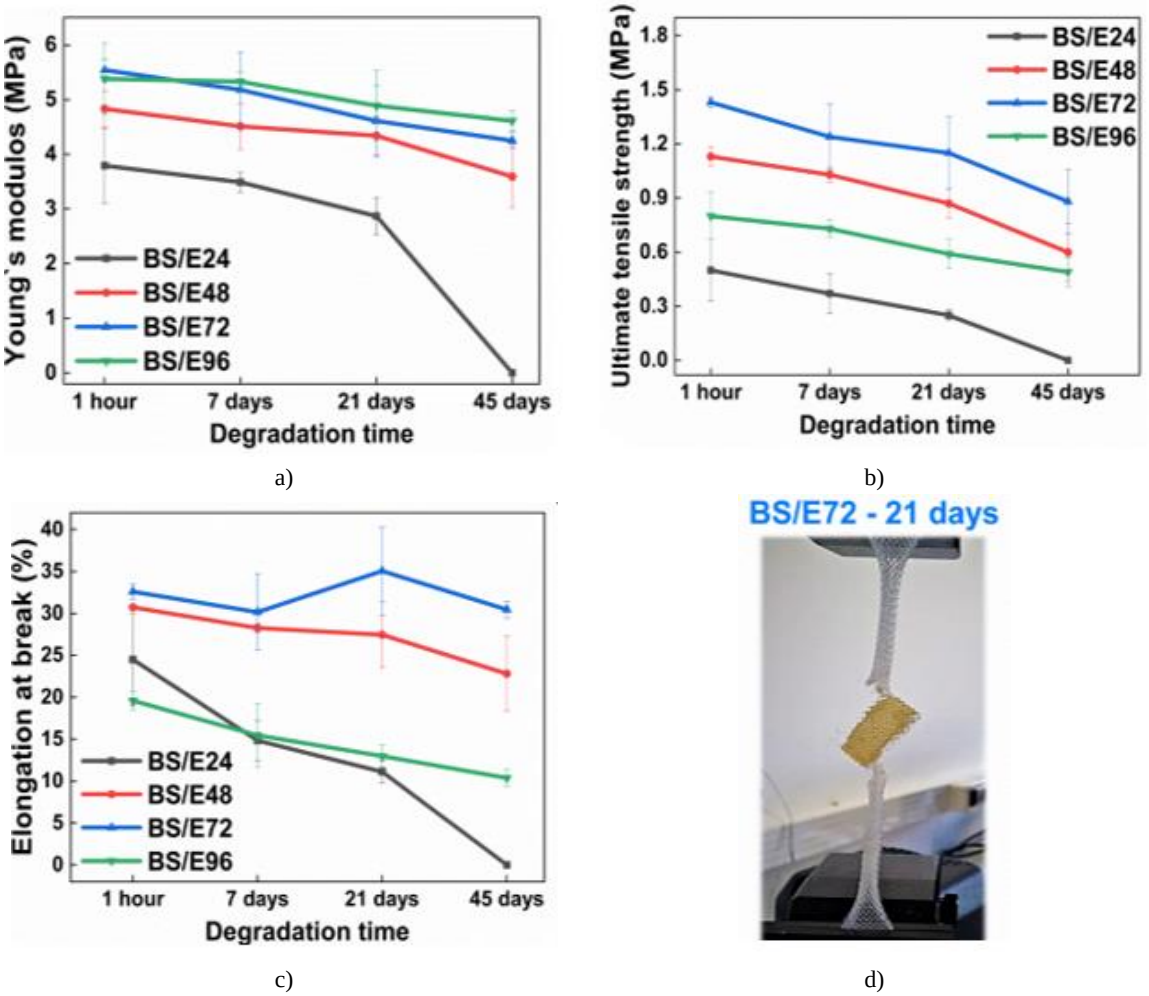


Figure 6. (a) Young modulus, (b) ultimate tensile strength and (c) elongation at break of BS/E24, BS/E48, BS/E72, and BS/E96 specimens after incubation in PBS for 1 h, 7, 21, and 45 days at 37 ºC. (d) BS/E72 specimen near the failure occurred in the tensile test after incubation for 21 days.

BS/E48 showed only a 10.7% reduction in elongation at break after 21 days of degradation, and BS/E72 showed an unreal 7.6% increase in elongation after 21 days **(Figure 6c)** due to a failure at the fragile points at the PP sling-elastomer border, as shown in **(Figure 6d)**, - an increase in the distance between the grips of the tensile testing machine inducesa false elongation measurement.

BS/E72showed the slowest degradation rate. After 45 days of incubation, it maintained an elongation at break similar to that exhibited by the samples with 7 days of incubation **(Figure 6c)**. However, unlike the other specimens (BS/E24, BS/E48, and BS/E96), which show a cohesive failure of the adhesive after 21 days of degradation **(Figure 5b)**, BS/E72 showed a cohesive failure of the adherent (PP sling), as displayed in **(Figure 6d)**, whose rupture occurs at the PP sling-elastomer border.

Conclusion

PGS elastomers were successfully synthesized and used as a midline segment of the synthetic bipartite sling. Elastomer E72, obtained by 72 h of cure and used in BS/E72, showed the highest degree of esterification, followed by elastomer E48, used in BS/E48. Such results indicate BS/E48 and BS/E72 as the best alternatives for the intended application - the latter maintained superior mechanical properties for longer. Although the minimum resistance conditions for the sling have not been defined, the resistance and elasticity of the samples even after *in vitro* degradation for the minimum of 45 days demonstrate the feasibility of the application, i.e., the degradation time can be adjusted according to the remodeling time of the pelvic tissue and motivatethe continuity and deepening of studiesunder*in vivo* conditions.

Acknowledgments: The authors acknowledgeurologist N. Neumayr for making this study possible, F. Gomes (Metachem) for the polymer donation, and Prof. J. R. Tarpani for the use of the vacuum oven.

Conflict of interest: None

Financial support: This study was financed by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) – Brazil – Finance Code 001.

Ethics statement: None

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