Controlled hydrolytic degradation of polyglycolide–caprolactone-based bioabsorbable copolymer

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Polyglycolide–caprolactone (PGCL)-based copolymer was synthesized from glycolide and caprolactone by ring opening polymerization in the presence of stannous octoate catalyst and diethylene glycol initiator. The effects of prepolymerization time, monomer ratio, monomer-to-catalyst and monomer-to-initiator ratios on per cent weight conversion were optimized. The end-capped copolymer was synthesized to make absorbable sutures having controlled bioabsorbability at different pH levels. It was observed that end-capped absorbable copolymer was more stable at pH 10.0 compared to uncapped absorbable material. End-capped copolymer also retained higher tensile strength compared to uncapped copolymer after 21 days. This phenomenon of controlled hydrolytic degradation of PGCL-based bioabsorbable polymer having terminal group end-capping can be attributed to less availability of hydrophilic end groups facilitating hydrolytic degradation of polymers.

Keywords: Biocompatibility, bioabsorbable copolymer, hydrolytic degradation, polyglycolide–caprolactone, suture.

RECENT developments in the field of biomaterials have been focused on biodegradable polymers, e.g. polyglycolic acid, polylactic acid and polycaprolactone, as they degrade body metabolites having high level of biocompatibility, non-toxicity and easy processibility in different forms[1,2]. In addition, they have been accepted by the United States Food and Drug Administration (USFDA) for internal use in the human body. Their copolymers can be synthesized by ring opening polymerization of cyclic dimmers[2–5].

Most of the commercially available bioabsorbable synthetic polymers have ester linkages that get hydrolysed in the presence of moisture, under both *in vitro* and *in vivo* environments. The affinity towards moisture is expressed by the hydrophilic hydroxyl end groups facilitating the phenomenon of hydrolysis[6]. The carboxyl groups generated by hydrolysis further promote hydrolysis of ester bonds resulting in fast weight and strength loss as a result of which the synthetic bioabsorbable polymer becomes incapable of holding the wound edges during healing[7].

Polyglycolide–caprolactone (PGCL) copolymers are suitable for wound closure materials like sutures used to hold skin, internal organs, blood vessels and other tissues of the human body together during the healing period[8]. They must be strong, non-toxic, hypoallergenic and flexible in nature. Many complications such as infection, wound dehiscence and sinus formation occur in the wound closure line. The complexity involved in wound healing, such as the involvement of more than one type of tissue in the wound, the various degrees of wound strength during the process of healing, exposure of the materials to body fluids and the variety of surgical wounds each with its own healing problem, calls for different types of wound closure materials[4]. Sutures must not allow fluids to penetrate the body through them from the outside, which could easily cause infections.

The body environment such as pH level can affect the rates of degradation resulting into variable retention of strength of suture materials. The pH of gastric juice in the stomach goes as low as 0.9–1.5, while pancreatic juice in the duodenum ranges from 7.5 to 8.2 (ref. 5) and urinary pH ranges from 4.5 to 8.0 (ref. 6). Thus the effect of pH on retention of the weight and tensile strength of materials provides strong ground for the selection of suture materials for specific end-uses[7]. This article deals with the synthesis of copolymers based on glycolide and caprolactone (PGCL) by ring opening polymerization in the presence of stannous octate (SnOct) and diethyl glycol (DEG) as absorbable suture materials and their degradation behaviour under variety of pH environments of *in-vitro* studies.

Experiment

Materials used

Glycolide (1,4-dioxane-2,5-dione) having 99% purity, m.p. 82–86°C was procured from PURAC Asia Pacific Pvt Ltd, The Netherlands. ε-Caprolactone of 97% purity, b.p. 97–98°C was procured from Tokyo Chemical Industries Co Ltd, Japan. SnOct (tin (2+) *bis*(2-ethylhexanoate) having 92.5–100% purity was procured

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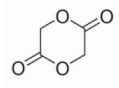
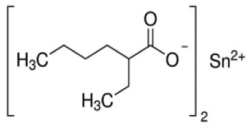
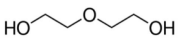
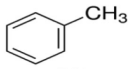
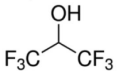
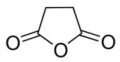
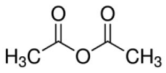
Table 1. Structure of the materials used

Material	Formula	Structure
Glycolide	$C_4H_4O_4$	
ε-Caprolactone	$C_6H_{10}O_2$	
Stannous octoate	$[CH_3(CH_2)_3CH(C_2H_5)CO_2]_2Sn$	
Diethylene glycol	$(HOCH_2CH_2)_2O$	
Toluene	$C_6H_5CH_3$	
Hexafluoroisopropanol	$(CF_3)_2CHOH$	
Succinic anhydride	$C_4H_4O_3$	
Acetic anhydride	$(CH_3CO)_2O$	

from Sigma Aldrich Chemicals Pvt Ltd, Germany. DEG having auto-ignition temperature 442°C was procured from RFCL Ltd, India. Toluene (methylbenzene) having B.P. 111°C was procured from S.D. Fine Chemical Ltd, India. Hexafloro isopropanol (1,1,1,3,3,3-hexafluoro-2-propanol) having 99% purity, b.p. 59°C, m.p. –4°C and density 1.596 g/ml at 25°C was procured from Sigma Aldrich Chemicals Pvt Ltd, Germany. Succinic anhydride (dihydro-2,5-furandione) having 99% purity, b.p. 261°C and m.p. 118–120°C was procured from Fluka, Switzerland. Acetic anhydride having 99% purity, mol wt 102.1 and vapour density 3.5 was procured from S.D. Fine Chemical Ltd, India.

All these materials were used as such without further purification in the process (Table 1).

Method

Synthesis of PGCL copolymers: The polymerization of PGCL was carried out in a reaction vessel containing 0.22 mol glycolide and 0.11 mol e-caprolactone. A catalyst, SnOct diluted in toluene and DEG (initiator) was added to the reaction vessel using a micro syringe under stirring conditions. The reaction vessel was purged with nitrogen and reaction mixture was heated at 185°C for 6–8 h.

Further, 0.22 mol of molten glycolide was added to the prepolymer in the reaction vessel and the temperature of the reaction mixture was raised to 210°C for 2–3 h. End-capping of copolymer was done with molten succinic anhydride or acetic anhydride, and the reaction was further continued for 1 h. The copolymer was separated, ground and dried at 110°C under vacuum for 8 h to remove any unreacted monomers. The effect of various process variables, e.g. initiator-to-monomer ratio, catalyst-to-monomer ratio and reaction time of synthesis of PGCL copolymer was studied. Figure 1 represents the reaction scheme for the synthesis and end-capping of copolymer.

Spinning of suture: Melt spinning was selected for spinning the polymer as PGCL has its melting point much below the decomposition temperature. In the present process, synthesized PGCL copolymer was ground and dried in vacuum oven at 110°C for 8 h and extruded through a typical melt spinning line (Figure 2). The filament was cooled through a quenching chamber where cool air was passed through the filament when it emerged from a tiny hole known as the spinneret. The filament produced was stretched and taken up to the winder[9,10].

Standard melt spinning parameters were used: 165°C feed temperature, 173°C compression temperature, 175°C melt temperature, 187°C die head temperature, 25 feed rpm, 35 extruder rpm and 35 metering rpm.

Characterization: Molecular weight and molecular weight distribution of the copolymers after and before end-capping were determined by gel permeation chromatography (Make-Waters) using 2414 RI detector. The sample was prepared in duplicate by dissolving in tetra hydrofuran (THF) and dimethy formamide (DMF) in

the ratio of 1 : 3, and used as mobile phase at a flow rate of 1 ml/min for elution purposes. The molecular weights were calibrated with polystyrene as standards[11] whereas inherent viscosity of PGCL copolymer was measured in 1,1,1,3,3,3-hexafluoroisopropanol with a concentration of 0.1d l/g at 25°C using Ubblehode viscometer.

FTIR spectra were taken at ambient conditions using ABB-FTIR FTLA2000-100 analyzer (Swiss-make) with a wavenumber resolution 2 cm^{-1}; the recorded wavenumber range was 400–4000 cm^{-1}. Sample for FTIR was prepared by pasting thin membrane on KBr pellets.

The thermal properties of copolymer were determined using differential scanning calorimeter (DSC; SDT 2960, TA Instruments, USA) over a temperature range 100°C to 250°C at a scan rate of 5°C/min under inert atmosphere. The dry samples were sealed in crucible inside the glove box. The sealed samples were taken out of the glove box only at the time of DSC experiments. Samples were kept at 250°C for 3 min to remove the heat history and cooled up to –50°C at the cooling rate of 5°C/min. Finally, they were reheated at the rate of 5°C/min up to 250°C to obtain heat flow change with increasing temperature. All the thermograms were base line-corrected and calibrated against indium metal. Thermo-gravimetric analysis (TGA) of synthesized copolymer was carried out using SDT-TGA analyzer (TA Instrument, USA) with a scan rate of 5°C/min until 700°C under nitrogen atmosphere.

In vitro degradation characteristics of monofilament suture were evaluated by measuring weight loss and tensile strength. The immersion solution consists of phosphate buffer saline (PBS) of four different pH levels (3.2, 6.4, 7.4 and 10.0). End-capped and uncapped sutures were cut into uniform length of 80 cm each to be immersed in four different pH levels of PBS (refs 12–18). After 7, 14, 21, 28 and 42 days absorbable sutures were removed, rinsed with distilled water and evaluated for tensile strength (using Tinius Olsen) at 5 cm grip length and 100 cm/min speed.

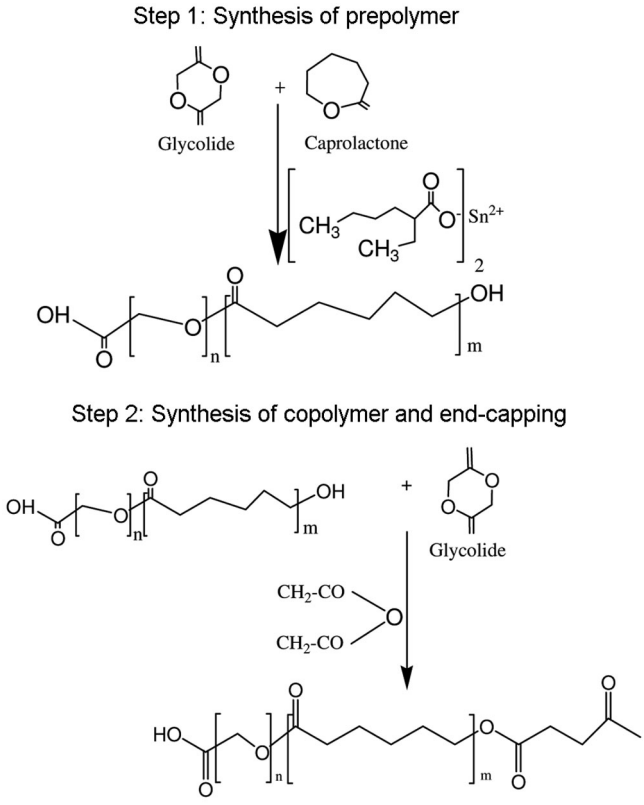


Figure 1. Schematic representation of synthesis and end-capping.

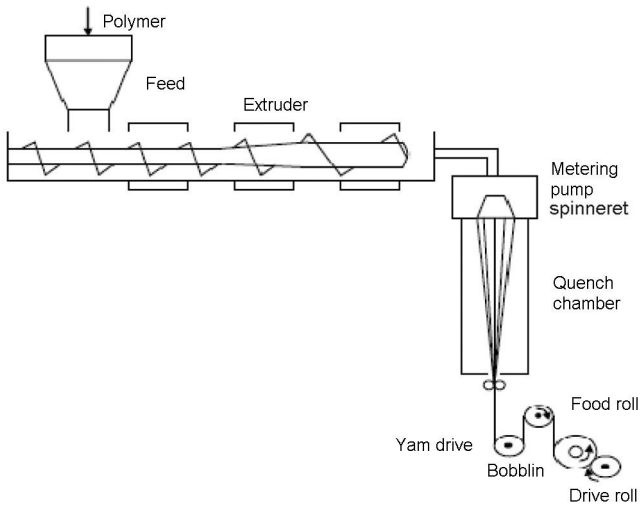


Figure 2. Melt spinning line.

Results and discussion

Optimization studies

SnOct was preferred as a catalyst for synthesis of PGCL copolymer due to its very low toxicity for products being used in biomedical applications[2]. The polymerization reaction was carried out in different conditions by varying the reaction time, concentration of catalyst and concentration of initiator in order to determine the optimum polymerization conditions. Figures 3–5 show the effect of these parameters on inherent viscosity of copolymer. Figure 3 shows that the maximum inherent viscosity could be achieved in 6 h of reaction and also there is not much difference in percentage of conversion. On the basis of these results, 6 h of reaction time was found optimum for pre-polymerization.

Three monomer-to-catalyst ratios (36,875, 53,636, 80,821) were used and the inherent viscosity of 1.0, 1.3 and 0.9 dl/g respectively was observed (Figure 4). The monomer-to-catalyst ratio of 53,636 provides the highest inherent viscosity of 1.3 and thus it was optimized for polymerization.

Various ratios of monomer-to-initiator were used (491 to 7007), wherein inherent viscosity ranging from 1.3 to

2.3 dl/g was observed. The monomer-to-initiator ratio of 3933 gave the best inherent viscosity of 2.3 dl/g, and thus was optimized for polymerization (Figure 5).

Characterization studies

Weight average molecular weight of the copolymers was determined and calibrated with polystyrene as standard. The samples prepared by dissolving in THF and DMF in the ratio 1 : 3, and used as mobile phase at a flow rate of 1 ml/min for elution purposes. The weight average molecular weight of copolymers was found to increase gradually with increasing reaction time between 7,482 and 24,688 Da (Figure 6).

The IR spectra of PGCL copolymer showed absorbance peaks at 2959 (CH_2 asymmetrical), 2861 (CH_2 symmetrical stretching), 1743 (aliphatic ester), 1413 (CH bend), and 1093 cm^{-1} (C–O stretch) and PGCL copolymer with end-capping 2964 (CH_2 asymmetrical), 2866 (CH_2 symmetrical stretching), 1743 (aliphatic ester), 1418 (CH bend), 1093 cm^{-1} (C–O stretch). The IR spectra of PGCL copolymer were found to be similar to the IR spectra of PGCL copolymer with end-capping. The characteristic broad hump of terminal hydroxyl groups present in PGCL

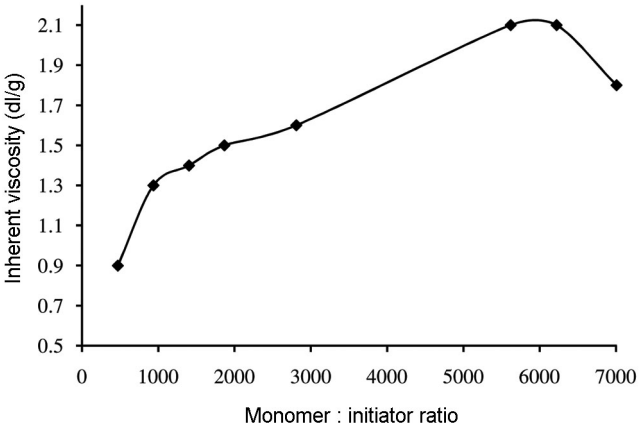


Figure 5. Effect of initiator concentration on inherent viscosity of copolymer.

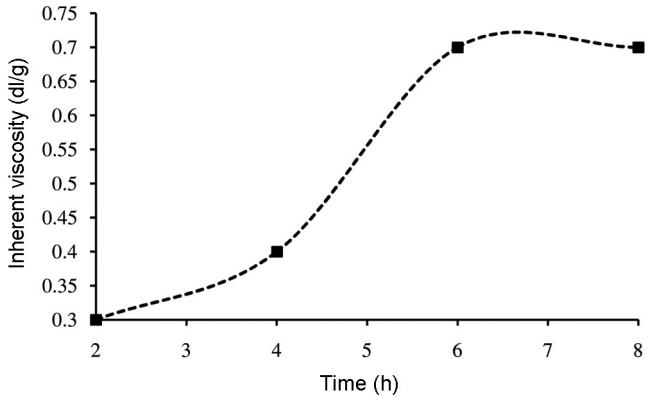


Figure 3. Effect of prepolymerization time on inherent viscosity of copolymer.

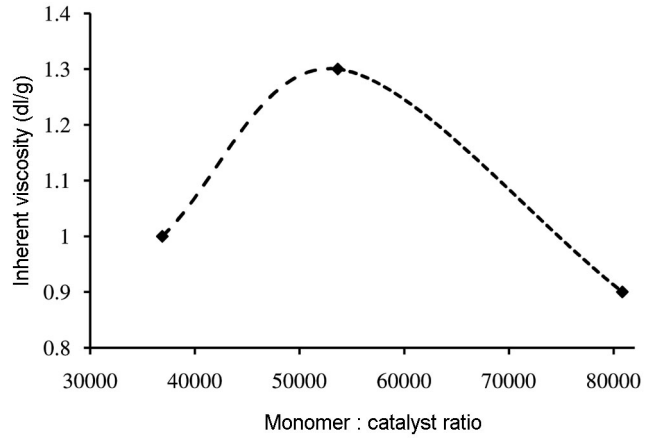


Figure 4. Effect of catalyst concentration on inherent viscosity of copolymer.

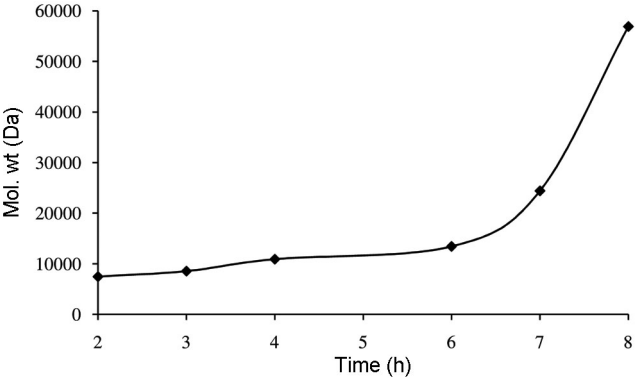


Figure 6. Weight average molecular weight at different reaction times.

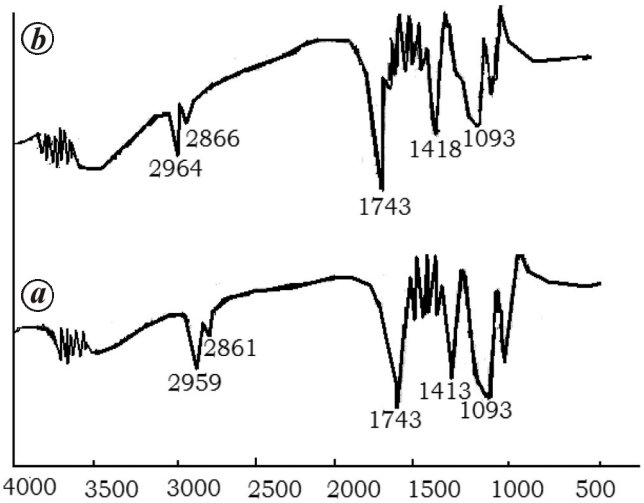


Figure 7. FTIR spectra of polyglycolide–caprolactone (PGCL) (***a***) and PGCL with end-capping (***b***).

copolymer at 3500 cm^{-1} reduced slightly in the end-capped copolymer indicating partial end-capping of terminal hydroxyl groups (Figure 7).

Thermal analysis: Figure 8 shows that the melting point of end-capped polymer is higher than that of uncapped copolymer. Thermal stability of end-capped and uncapped PGCL copolymers was measured at a scan rate of 5°C/min up to 700°C under nitrogen atmosphere (Figure 9). It was observed that uncapped PGCL copolymer was comparatively better in stability than end-capped copolymer.

In vitro degradation kinetics

In vitro degradation characteristics of developed end-capped and uncapped PGCL monofilaments were evaluated by measuring the losses in weight and tensile strength at four different pH levels (3.2, 6.4, 7.4 and 10.0; Figures 10–13 and Table 2). Monofilaments of end-capped and uncapped PGCL copolymers of uniform length (80 cm each) were immersed in four different pH levels of PBS solution. After 7, 14, 21, 28 and 42 days, absorbable fibres were removed, rinsed and evaluated for tensile strength. From the results it was observed that ester linkages allow gradual hydrolytic degradation in the copolymer backbone. Table 2 shows the tensile properties

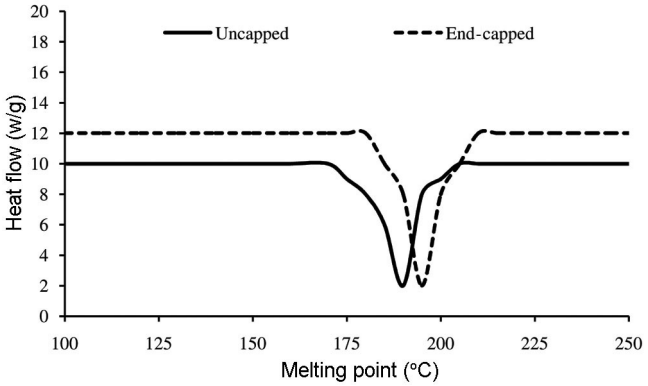


Figure 8. Melting point of end-capped and uncapped PGCL copolymer.

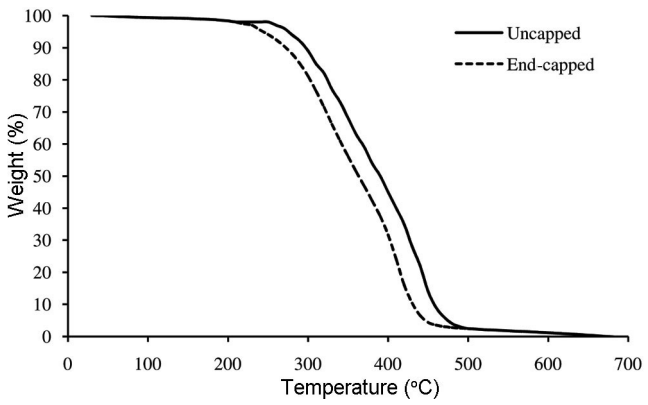


Figure 9. Thermogravimetric analysis–differential thermal analysis (TGA–DTA) of end-capped and uncapped PGCL copolymer.

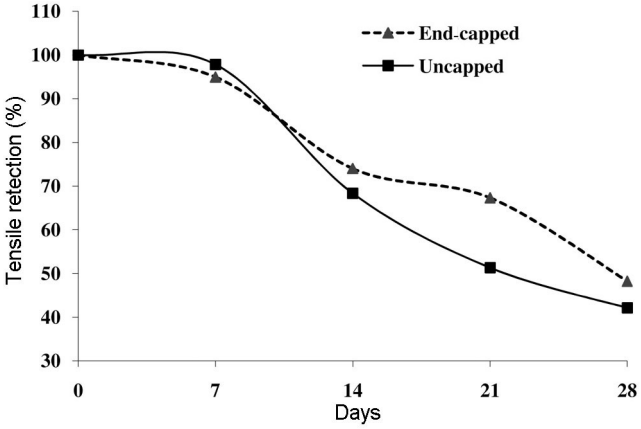


Figure 10. Retention (%) of tensile strength at pH 3.2.

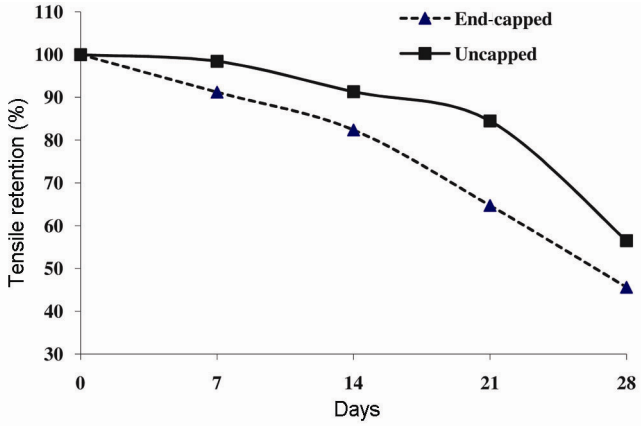


Figure 11. Retention (%) of tensile strength at pH 6.4.

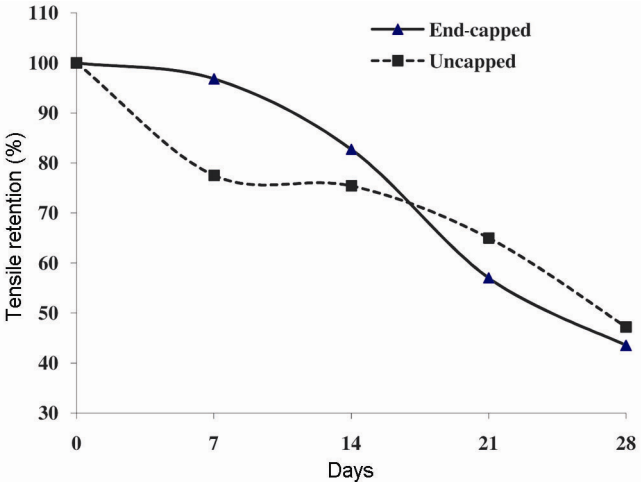


Figure 12. Retention (%) of tensile strength at pH 7.4.

Table 2. Retention (%) of tensile strength of monofilament at different pH levels

Days	pH	Retention (%) of tensile strength	
		End-capped	Uncapped
3.2	7	94.9	97.8
	14	74.0	68.3
	21	67.3	51.3
	28	48.2	42.1
6.4	7	91.2	98.4
	14	82.4	91.3
	21	64.7	84.5
	28	45.6	56.5
7.4	7	96.8	77.5
	14	82.7	75.4
	21	57.0	65.0
	28	43.5	47.2
10.0	7	91.5	80.0
	14	76.9	77.8
	21	56.7	42.8
	28	48.0	36.0

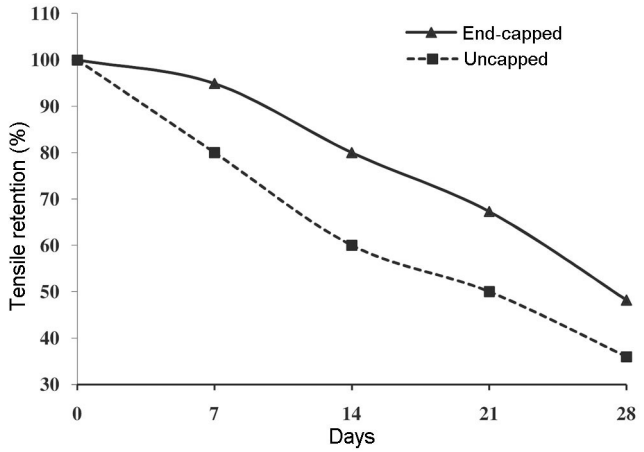


Figure 13. Tensile retention (%) of end-capped and uncapped PGCL-copolymer at pH 10.0.

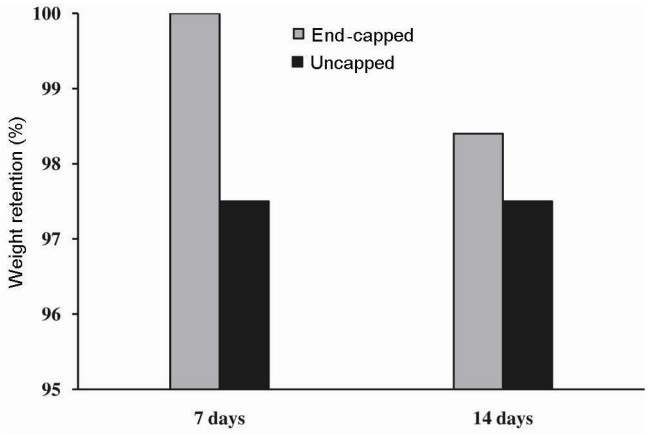


Figure 14. Percentage of weight retention after 7 and 14 days.

and their retention (%) for both end-capped and uncapped absorbable monofilaments at four different pH levels (3.2, 6.4, 7.4, 10.0). It was established that end-capped absorbable fibre was more stable at pH 10.0 compared to uncapped absorbable material. End-capping also retained more tensile strength (48%) compared to uncapped filaments (36%) after 28 days[19–23]. Percentage of weight retention of end-capped and uncapped filaments was compared after 7 and 14 days at pH 10.0 (Figure 14). From the figure it can be observed that endcapped suture material exhibits better weight retention capacity after 7 and 14 days, when immersed in PBS solution of pH 10.

Conclusion

In order to arrest the hydrolysis of polyester resin, an attempt was made to synthesize copolymers using two-step synthesis processes at an optimum ratio of glycolide to caprolactone monomers (2 : 1). The polymerization parameters such as reaction temperature (185°C) and time (6–8 h), catalyst concentration, initiator concentration, etc. were optimized to achieve the highest level of inherent viscosity (2.3 dl/g) in hexafluoroisopropanol at 25°C. An innovative approach of blocking the hydroxyl end groups of synthesized bioabsorbable polyester copolymers of glycolide and caprolactone was used. The synthesis involved the ring opening polymerization of cyclic esters and then end-capping of terminal hydroxyl groups. The end-capping with succinic anhydride, a biocompatible molecule was found effective in terms of improved tensile retention behaviour under different pH conditions.

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