Modification of poly(D,L-lactic acid)-co-poly(ethylene glycol) copolymer by low energy electron beam (EB) radiation

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Abstract: Poly(D,L-lactic acid)-co-poly(ethylene glycol) copolymer (D,L-PLEG) synthesized by melt polycondensation was irradiated using low energy electron beam (EB) in the presence of triallyl cyanurate (TAC) and tetraallyl pentaerythritol (TAPE) as crosslinking agents. The tensile strength of D,L-PLEG/TAC and D,L-PLEG/TAPE samples increases up to 48 MPa and 28 MPa at dose of 80 kGy and 60 kGy, respectively, and decreases with further increase of dose, whereas the elongation at break decreases continuously with increasing dose. The glass transition temperature ($T_g$) is improved to some extent due to the formation of molecular chain network. Degradation of D,L-PLEG is retarded with introduction of cross-linked network. The results suggest that the physical properties of crosslinked D,L-PLEG can be adjusted easily by varying irradiation dose.

Introduction

Poly(lactic acid) (PLA) is a typical biodegradable and biocompatible polymer, studied in a wide variety of applications, from implantable medical devices and drug release matrices to environmentally friendly packaging materials [1-4]. However, when PLA is used as drug delivery carrier and tissue engineering material, its hydrophilicity needs to be improved.

Poly(ethylene glycol) (PEG), well known for its water-solubility, lack of toxicity and excellent biocompatibility, has been authorized by USA Food and Drug Administration (FDA), usually chosen as the hydrophilic buoy block whose role is to provide a hydrated steric barrier [5]. Therefore, by introducing PEG into PLA through copolymerization, the synthesis of poly(lactic acid)-co-poly(ethylene glycol) (PLEG) becomes an important way to improve the hydrophilicity of PLA. Meanwhile, PEG-PLA copolymer usually degrades faster than PLA homopolymer, due to the hydrophilicity brought about by POE segments [6, 7]. Attention is also paid to the degradation of micro- and nanoparticles prepared from PEG-PLA, which have the most suitable combination of properties for use as drug delivery matrix [8, 9]. PLEG is synthesized by ring-opening polymerization of L(D)-lactide in the presence of PEG [10]. The process, however, requires very high purity lactide and is economical only for high priced medical and pharmaceutical applications. The tensile strength and heat resistance of PLEG are poor due to the presence of POE flexible chain, these properties cannot be adjusted easily by synthetic methods. To improve these properties and extend its application fields, it is a powerful method to introduce...
crosslink between polymer molecules, the physical properties can be controlled by adjusting the cross-linked degree. There are some reports about the PLEG derivative crosslinked by photopolymerization in the presence of photoinitiator [11, 12].

Electron beam (EB) irradiation has been well known as a very convenient, efficient and photoinitiator-free tool for modification of polymers through crosslinking, grafting and degradation techniques. Besides, irradiation can cause in parallel sterilization of the materials [13]. When the polymer is exposed to an EB, its mechanical and physical properties decrease due to reduction of the molecular weight of the polymer [14]. There are recent reports concerning improvement of mechanical properties and heat stability by employing polyfunctional monomers (PFM) as crosslinking agents to introduce crosslinking of some biodegradable polymers during irradiation [15]. PFM has been widely used for polyolefins and vinyl monomers. Because of its high reactivity, it has the capability to react with polymers and form cross-linked structure [16]. It is concluded that the cross-linking to scission ratio for aliphatic polyesters increases upon irradiation as a function of increasing \(-\text{CH}_2-\) to \(-\text{COO}-\) ratios in the main chain [17]. The overall effect of crosslinking is that the molecular weight of the polymer steadily increases with increasing irradiation dose, leading to branched chains, until ultimately a tridimensional network is formed when on the average each polymer chain is linked to another chain. The resulting structure corresponds to that of a polymer, which no longer melts above its normal melting temperature and does not dissolve in its usual solvents [18]. The use of PFM to prevent radiation degradation and induce radiation crosslinking of PLA-based materials has also been studied [19-21].

Therefore, crosslinking technology could be an effective method for the modification of D,L-PLEG by EB radiation. To the knowledge of authors, however, on investigation has been reported so far regarding the effects of low energy EB radiation on D,L-PLEG compounded with PFM. In this work, D,L-PLEG was synthesized by melt polycondensation, using low-cost D,L-lactic acid and PEG as raw materials. Triallyl cyanurate (TAC) and tetraallyl pentaerythritol (TAPE) were chosen as crosslinking agents, as shown in Fig 1. The effects of low energy EB radiation on the degradability, mechanical, thermal and water uptake properties of D,L-PLEG/PFM composite were investigated. It was expected that the introduction of crosslinking would not only overcome the low tensile and thermal properties of D,L-PLEG, but also extend the application fields of this material as a novel degradable plastic which can be used in industrial and biomedical fields.

![Triallyl cyanurate (TAC) and Tetraallyl pentaerythritol (TAPE)](image)

**Fig. 1.** The structure of polyfunctional monomers (PFM) as crosslinking agents.
Results and discussion

Composition of D,L-PLEG copolymer

The FTIR spectrum of D,L-PLEG is shown in Fig. 2. An absorption band at 3502 cm\(^{-1}\) is representative of the terminal hydroxy group (OH). The bands at 2995, 2945, 2877 cm\(^{-1}\) and 1456, 1384 cm\(^{-1}\) are attributed to the saturated C-H stretch in copolymer. The bands at 1186 and 1089 cm\(^{-1}\) are attributed to the (C-O-C) stretch in ester and ether groups. A strong absorbance was seen at 1758 cm\(^{-1}\) which confirms the presence of the ester via the (C=O) stretch. The typical \(^1\)H-NMR spectrum of D,L-PLEG copolymer is shown in Fig. 3. The bands at 1.56 and 5.17 ppm are attributed to the methyl and methine protons of PLA blocks, respectively, while the bands at 3.64 ppm is characteristic of main chain methylene in the PEG blocks. The existence of a covalent bond between PLA and PEG block is evident from a low-intensity multiplet at 4.25 ppm, which represents methylene protons of the acylated end unit of PEG chain (-CH\(_2\)-O-CO-). The number average molecular weight of D,L-PLEG is 20,952, its polydispersity index (PDI) (\(M_w/M_n\)) is 1.77 as evaluated by GPC. These data indicate the feasibility of preparing well defined D,L-PLEG copolymer under controlled conditions.

![Fig. 2. The FTIR spectra of D,L-PLEG synthesized by melt polycondensation.](image1)

![Fig. 3. The \(^1\)H-NMR spectra of D,L-PLEG synthesized by melt polycondensation.](image2)
**Gel behavior and water uptake of samples**

Crosslinking and chain scission of polymers induced by EB radiation are generally simultaneous phenomena, the ratio of these two events determines the net effect of the process. Usually, in most polymers, one of the general processes dominate, either crosslinking or degradation [14]. It is reported that the irradiated polymer containing 3 wt.% TAC can give higher gel content [22]. Therefore, in this study, the amount of TAC and TAPE are both 3 wt.% relative to D,L-PLEG.

The changes of the gel fraction of D,L-PLEG/PFM samples versus irradiation dose are shown in Fig. 4. It can be seen that gel is not formed for irradiated pure D,L-PLEG within the dose range of 20-100 kGy. However, the gel fraction of D,L-PLEG containing PFM increases significantly. The gel fraction of D,L-PLEG/TAC and D,L-PLEG/TAPE samples are 68.5 % and 27.5 % at dose of 80 kGy, respectively. This is probably contributed to the sufficiently high amount of polymer radicals produced that can react with monomers at dose of 80 kGy. The effect of TAC accelerates initial increase in gel fraction of D,L-PLEG. After approximately 80 kGy, the effect begins to level off. However, the gel fraction of D,L-PLEG containing TAPE is low and varies indistinctively before the dose of 60 kGy. It is also observed that D,L-PLEG/TAC sample gives much higher gel fraction compared to D,L-PLEG/TAPE sample at the same dose. This is due to the presence of three functional groups (C=C) and a cyclic unit (cyanuric ring) of TAC that achieves a greater steady three-dimensional network by irradiation than that of aliphatic TAPE [16]. It is well known that when bulk polymers are irradiated, the dominant reactions and the final products depend strongly on the geometrical arrangements of the polymer molecules [14].

![Fig. 4. Gel fraction of D,L-PLEG/PFM hybrid films prepared by EB radiation.](image)

The reaction degree of TAC upon the radiation crosslinking reaction was investigated by the FTIR spectra of the sample. As shown in Fig. 5, the absorbance due to carbon-carbon double bonds [23] falls with increasing irradiation dose. This indicates the consumption of TAC via grafting or crosslinking on PLEG chain upon EB radiation.

As shown in Fig. 6, the double bonds in the TAC monomer are very active under radiation to experience crosslinking reaction, which is true in the FTIR spectra of the
sample during radiation crosslinking as shown in Fig. 5, where the characteristic absorption band of the double bonds become weak with increasing irradiation dose.

**Fig. 5.** ATR-FTIR spectra of PLEG mixed with TAC irradiated at different doses.

**Fig. 6.** Possible radiation-induced crosslinking of TAC between D,L-PLEG chains.
Fig. 7 shows the variation of water uptake of samples with irradiation dose. It is found that before irradiation, D,L-PLEG, D,L-PLEG/TAC and D,L-PLEG/TAPE samples almost have the same water uptake. But after irradiation, the water uptake of D,L-PLEG decreases slightly. But this has a reverse effect on the water uptake of the irradiated D,L-PLEG/PFM samples, it decreases significantly with increasing irradiation dose, the water uptake of irradiated D,L-PLEG/TAC decreases more rapidly than that of irradiated D,L-PLEG/TAPE. Thus, the tighter cross-linked network can lead to the lower percent of the water uptake.

![Graph showing water uptake vs. irradiation dose](image)

**Fig. 7.** Water uptake of D,L-PLEG/PFM hybrid films prepared by EB radiation.

**Tensile properties**

EB radiation of PLA with a relatively high concentration of ester groups in the backbone does not result in crosslinking of the polymer. During irradiation there is a strong decrease in the molecular weight. The embrittlement of the irradiated PLA is most likely to be a combined result of the molecular weight decrease and the formation of gaseous degradation products in the polymer matrix. But these problems can be overcome by its copolymerization with the polymers which have a lower concentration of ester groups in the backbone [24]. Fig. 8 shows the variation of tensile strength of the samples with irradiation dose. It is found that before irradiation, the tensile strength of D,L-PLEG/TAC and D,L-PLEG/TAPE compounds is lower than that of D,L-PLEG due to the plasticizing function of TAC and TAPE. But after irradiation, the tensile strength of D,L-PLEG decreases slightly with increasing irradiation dose, which is in accordance with the results mentioned above [24]. The tensile strength of irradiated D,L-PLEG/TAC sample increases more obviously compared to that of irradiated D,L-PLEG/TAPE sample. This is attributed to the formation of cross-linked structure, which can improve the tensile strength of D,L-PLEG/PFM samples. The tensile strength of D,L-PLEG/TAC and D,L-PLEG/TAPE increases with the increase of irradiation dose, they are up to 48 MPa and 28 MPa at dose of 80 kGy and 60 kGy, respectively. However, this property decreases with the further increase of dose. This is probably due to the increase of crosslinking density at early stage, after reaching a maximum, the higher irradiation dose leads to degradation and destroys the network structure. Therefore, electron beam (EB)
radiation is a very convenient and efficient method to improve the tensile strength of D,L-PLEG through crosslinking technique, this property can be controlled by varying irradiation dose.

**Fig. 8.** The effect of irradiation dose on the tensile strength of samples.

The variation of elongation at break versus irradiation dose is shown in Fig. 9. It is found clearly that the elongation at break of D,L-PLEG/TAC and D,L-PLEG/TAPE decreases rapidly with the increase of irradiation dose. This is attributed to the formation of radiation cross-linked network in the polymer, which can restrict the mobility of the molecular chain during drawing [25]. For D,L-PLEG, its elongation at break also decreases with the increase of irradiation dose due to main chain scissions of D,L-PLEG molecules.

**Fig. 9.** The effect of irradiation dose on the elongation at break of samples.
**Thermal properties**

The quantitative evaluation of the thermal transitions of irradiated D,L-PLEG/TAC and D,L-PLEG/TAPE samples with various doses was investigated by DSC. Fig. 10 shows the DSC heating curves of the crosslinked D,L-PLEG. The original D,L-PLEG (a) shows a glass transition temperature ($T_g \sim 28 \, ^\circ C$), then a small exothermic peak of crystallization around $101 \, ^\circ C$, followed by a weak melting peak ($T_m \sim 131 \, ^\circ C$), which is similar to the results reported by Wang et al. [26]. However, Curve (b) and (c) show only a endothermic peak around $T_g$, without any peak of crystallization and melting. Besides, $T_g$ is found to be $30 \, ^\circ C$ and $31 \, ^\circ C$ for D,L-PLEG/TAPE and D,L-PLEG/TAC compounds irradiated at 60 kGy, respectively. This means that the irradiated D,L-PLEG samples mixed with TAC and TAPE are crosslinked at dose of 60 kGy, D,L-PLEG molecules are mostly fixed by cross-linked network in amorphous region. Therefore, $T_g$ of samples increases with an increasing number of crosslinks.

![DSC heating curves of D,L-PLEG and D,L-PLEG mixed with 3 wt.% of TAC and TAPE irradiated at 60 kGy.](image)

**Degradation test of samples**

The degradation test is a convenient method for evaluating the rate of degradability of polymers. The effect of irradiation dose (40 kGy and 60 kGy) on the degradation of samples is shown in Fig. 11. Weight remaining of the unirradiated D,L-PLEG treated for 480 h is 68 wt %, this value of D,L-PLA reported by Proikakis et al. is about 80 % at the same conditions [27]. This is attributed to the hydrophilic natures of PEG, which can solubilize larger molecular weight fragments [30]. PEG also increases the accessibility of water to the polymer matrix, this ensures bulk degradation of D,L-PLEG. However, weight remaining of the irradiated D,L-PLEG compounded with TAC and TAPE increases obviously. It can be seen that weight remaining of D,L-PLEG/TAC sample increases more significantly than that of D,L-PLEG/TAPE sample at the same irradiation dose. Meanwhile, at the same incubation time, weight remaining of D,L-PLEG/TAC and D,L-PLEG/TAPE samples irradiated at 60 kGy is higher than that of samples irradiated at 40 kGy. This is probably due to the introduction of cross-linked network between molecular chains, which can retard...
degradation [16], because the PBS solution could hardly enter into the polymer gels. On the other hand, the sample could obtain much more gels to form three-dimensional cross-linked network at a higher dose. Furthermore, TAC can provide D,L-PLEG with much higher cross-linked network than TAPE. This can be seen from the variation of gel fraction with irradiation dose (Fig. 4).

Fig. 11. Degradation curves of D,L-PLEG and D,L-PLEG mixed with 3 wt.% of TAC and TAPE irradiated at 60 kGy.

Conclusions
The study has demonstrated that D,L-PLEG copolymer is synthesized successfully using low-cost raw materials and simple melt polycondensation, it is feasible that D,L-PLEG is radiation-induced crosslinking using low energy EB in the presence of TAC and TAPE as crosslinking agents. The gel fraction and water uptake results indicate that D,L-PLEG/TAC sample can form cross-linked network more efficiently than D,L-PLEG/TAPE sample. Compared with the pure D,L-PLEG, the mechanical and thermal properties of crosslinked D,L-PLEG are improved due to the wide formation of radiation-induced cross-linked network in polymer. The introduction of cross-linked network also retards the degradation of D,L-PLEG. These properties can also be controlled more easily by varying irradiation dose compared to the synthetic methods. Besides, one can possibly combine crosslinking and sterilization in one single technological step by EB radiation.

Experimental part

Materials
D,L-Lactic acid (85-90 wt.% aqueous solution) and poly(ethylene glycol) (PEG) with weight average molecular weights of 6000 (PEG 6K) were purchased from Tianjin Bodi Chemical Co., Ltd. (China). Tin(II) chloride dihydrate (SnCl₂·2H₂O) was purchased from Chongqing Chemical Reagent Company (China). p-Toluenesulfonic acid (TSA) was purchased from Chengdu Kelong Chemical Reagent Company (China). Acetone, dichloromethane (DMC) and methanol were laboratory reagents. Triallyl cyanurate (TAC) and tetraallyl pentaerythritol (TAPE) were synthesized...
according to the literatures [28, 29]. All reagents were analytical grade and used without further purification.

**Synthesis of D,L-PLEG**

A total of 100 g of D,L-lactic acid (85-90 wt.% aqueous solution) was dehydrated at 100 °C, first at atmospheric pressure for 1 h, then at a reduced pressure of 20 torr for 1 h, finally under a pressure of 5 torr for another 4 h at 150 °C. Then, a viscous liquid of oligo(D,L-lactic acid) (ODLLA) was formed quantitatively.

A 200 mL pear-shaped three-necked flask was equipped with a mechanical stirrer and a reflux condenser that was connected to a vacuum system through a cold trap. A total of 40 g of ODLLA, 3.60 g of PEG 6K, 0.16 g of SnCl₂·2H₂O (0.4 wt.% relative to ODLLA), and 0.12 g of TSA (an equimolar ratio to SnCl₂·2H₂O) were charged into the flask. The reaction mixture was stirred under a pressure of 5 torr at 180 °C for 18 h and was subsequently cooled to room temperature. The resulting copolymer was dissolved in acetone, precipitated in a mixture of methanol and distilled water (v/v=1:6), filtered, then dried under vacuum (yield 72%).

**Preparation of samples and irradiations**

D,L-PLEG and polyfunctional monomer (PFM) were dissolved in DCM. The content of D,L-PLEG was 40 wt.%, the amount of PFM was 3 wt.% relative to D,L-PLEG. Then, the sample was treated to form the film with thickness of 48 μm by solution casting method. Finally, the film was dried in a vacuum oven at 40 °C for 36 h. For comparison, D,L-PLEG without any PFM was treated with the same procedure.

The film samples were irradiated by a Curetron® EBC-200-AB-TW electron beam accelerator (NHV Corporation, Japan). The accelerating voltage was 150 kV with a beam current of 5 mA. A transport system was used with a conveyor speed of 27 m min⁻¹. The dose rate was 20 kGy per pass. The irradiation doses of the samples were calculated by multiplying 20 kGy by the number of passes irradiated. The irradiations of the no vacuum-degassed samples were performed at room temperature under the nitrogen atmosphere with the content of oxygen of less than 100 mg L⁻¹. Dosimetry was performed using cellulose triacetate (CTA) film dosimeters (ASTM 2000, E1650-97el).

**Measurements**

FTIR spectra were measured on Thermo Nicolet 380 Fourier Transform Infrared Spectrometer (Thermo Electron Corporation) in KBr pellets at 4000-400 cm⁻¹ in air atmosphere. The attenuated total reflection infrared spectroscopy (ATR) of the irradiated film was also recorded on a Nicolet 380 FTIR Spectrometer. ¹H-NMR spectra were recorded at room temperature using a 300 MHz Bruker spectrometer. CDCl₃ was used as the solvent. Chemical shifts (δ) are given in ppm using tetramethylsilane (TMS) as internal reference.

Average molecular weight and its distribution were determined by a Waters gel permeation chromatograph (GPC). The analyzer composed of a Waters 1515 isocratic HPLC pump and a Waters 2415 refractive index detector. Samples were dissolved in tetrahydrofuran (THF) at a concentration of 1 mg mL⁻¹. A Waters Styragel HT 4 THF column (7.8 × 300 mm) with linear range of molecular weight from 5,000 to 600,000 g mol⁻¹ was used in series with HPLC grade THF as eluent at a flow rate of 1.0 mL min⁻¹. The internal and column temperature were kept constant at 35 °C.
Calibration was accomplished with polystyrene standards. Molecular weight was determined by Empower 2 software.

Gel fraction of the irradiated samples was estimated by measuring its insoluble part in dried sample after immersion in DCM for 48 h at room temperature. The gel fraction was calculated according to the following equation:

\[
\text{Gel fraction (\%)} = \left( \frac{G_d}{G_i} \right) \times 100
\]

where \(G_i\) is the initial mass of the dried sample after irradiation and \(G_d\) is the mass of dried insoluble part of sample after extraction with DCM.

The amount of water retained in the samples radiated by various doses was determined gravimetrically. The dried samples were immersed in the 7.4 pH phosphate-buffered saline (PBS) solution maintained at a temperature of 37 °C [31]. At the end of 24 h, the samples were removed from solution, all surface water was wiped off with filter paper. Water uptake was calculated as follows:

\[
\text{Water uptake (\%)} = \left( \frac{W_d - W_i}{W_i} \right) \times 100
\]

where \(W_d\) is the weight of wet sample in bulk for 24 h and \(W_i\) is the initial weight of dried sample.

Tensile tests were carried out according to ISO 1184 using the KDIII-500 electron tensile testing machine (Shenzhen Kaiqiangli Testing Instruments Co., Ltd, China) at room temperature. The rectangular strip-shaped specimens were extended at a crosshead speed of 50 mm min\(^{-1}\). The tensile property values reported represent an average of the results from tests run on three specimens.

Calorimetric studies were carried out on a DSC Q200 thermal analyzer (TA Instruments) using N\(_2\) as a purge gas (50 mL min\(^{-1}\)) at scan rate of 10 °C min\(^{-1}\) from -10 to 180 °C. The instrument was calibrated with an indium standard (melting temperature 156.6 °C, \(\Delta H_f = 28.45 \text{ J g}^{-1}\)) and an empty pan was used as reference. The samples (~5 mg) were tested in hermetic TA aluminium pans. Thermograms were analyzed with Universal Analysis 2000 software (Version 4.4A, TA Instruments).

Degradation of the samples was carried out in PBS solution at 37 °C [32]. At various intervals of time, the film was taken out and washed with distilled water and dried to a constant weight in vacuum. Mass loss was monitored gravimetrically and determined using the following equation:

\[
\text{Weight remaining (\%)} = \left( \frac{M_d}{M_i} \right) \times 100
\]

where \(M_i\) is the initial mass of dried sample and \(M_d\) is the final mass of dried sample after incubation.

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