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Radiation effects on poly(lactide-co-glycolide) (PLGA) and poly(L-lactide) (PLLA)

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Abstract

The purpose of this study is to examine the effects of electron beam (e-beam) radiation on the thermal and morphological properties of biodegradable polymers (PLGA and PLLA), and to understand the radiation-induced degradation that these materials experience. PLGA(80:20) and PLLA polymer films were prepared by solvent casting, and were e-beam irradiated at doses of 5, 10, 20, 30 and 50 Mrad. The degradation of the films was studied by measuring the changes in their molecular weights, FTIR spectra thermal and morphological properties. The dominant effect of e-beam irradiation, in the presence of air, on both PLGA and PLLA is believed to be chain scission. The average molecular weight of PLGA decreases rapidly at low radiation dosage and remains relatively unchanged at high radiation dose (above 20 Mrad). Crystallinity increases with radiation dose for the non-irradiated amorphous PLGA. PLLA also undergoes chain scission upon irradiation but to a lesser degree compared to PLGA. The higher crystallinity of PLLA is the key factor in its greater stability to e-beam radiation compared to PLGA. The glass-transition temperatures (T_g) and melting temperatures (T_m) of both PLGA and PLLA decrease with increasing radiation dosage. Chain scission, though responsible for the reduction in the average molecular weight, T_g and T_m of both polymers, encourages crystallization. E-beam radiation enhances polymer degradation of PLGA and PLLA.

Keywords: Poly(lactide-co-glycolide); PLGA; Poly(L-lactide); PLLA; Biodegradable; Electron beam irradiation; Degradation; Chain scission; Cross-link

1. Introduction

Poly(lactide-co-glycolide) (PLGA) and poly(L-lactide) (PLLA) are extensively used in biomedical and pharmaceutical applications, and an example would be for controlled drug delivery purposes [1]. Like other biodegradable polymers, both PLGA and PLLA, whose chemical structures are illustrated in Figs. 1 and 2 respectively, have generated immense interest due to their favorable properties such as good biocompatibility, biodegradability and mechanical strength [2].

PLGA and PLLA are both hydrolytically unstable. Although insoluble in water, they degrade by hydrolytic attack of their ester bonds [3]. Through this hydrolytic attack, random chain scission occurs in the polymeric biomaterial, causing it to degrade into lactic and glycolic acids for PLGA and lactic acid for PLLA [3–9]. In the human body, lactic and glycolic acids enter the tricarboxylic acid cycle and are metabolized and subsequently eliminated from the body as carbon dioxide and water [4,6,7,9,10]. The rate of degradation of PLGA and PLLA is dependent on their degree of crystallinity (polymer morphology) and their glass transition temperatures (T_g) [6–8].

Radiation, at times used for polymerization purposes, has also been used for sterilization purposes. Radiation causes changes to the morphological properties of polymers, and can thus be used as a method to control the rate of degradation. The effect of ionizing radiation on polymers is generally divided into main-chain scission (degradation) and cross-linking (polymerization) [11,12]. Although both processes take place simultaneously in many polymers [13], if the scission predominates the cross-linking, it is termed as a degradation process. Polymer degradation, where chain scission is dominant, is associated with a reduction in the molecular weight [13]. On the other hand, cross-linking results in an increase in the molecular weight. Whether the process will be characterized predominantly by

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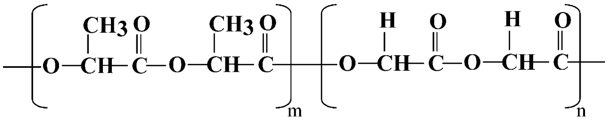

Fig. 1. Chemical structure of poly(lactic-co-glycolic acid) (PLGA).

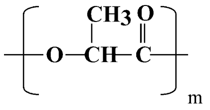

Fig. 2. Chemical structure of poly(L-lactic acid) (PLLA).

scission or by cross-linking depends on several factors, including the chemical structure of the polymer, the amount of dosage, the rate of dosage, the environment of the material during irradiation and the heat of polymerization [14]. The orientation and mobility of long chain polymeric molecules have also been reported to influence the direction of the overall radiation reaction [15]. As a result, ionizing radiation, through polymerization and degradation, affects the service life of products [16,17].

The principles of polymerization and degradation by irradiation can be described according to the principles of radiation chemistry. Firstly, macromolecules of polymer materials will be excited under ionizing radiation to form active species, such as cations, anions or radicals [18]. These active species can either react with one another or are able to initiate further reactions among the polymeric chains, thus giving rise to changes in the material properties. The combination of two radicals leads to cross-linking, while the chain transfer and subsequent splitting lowers the molecular weight [19]. Degradation can also occur when energy from the radiation exceeds the attractive forces between the atoms, thus disrupting the molecules [20]. This radiation energy breaks the chemical bonds causing chain scission. As a result, a radiation source of shorter wavelength and higher frequency or energy, often packs sufficient energy to cause chain scission through the breaking of these chemical bonds.

It is widely accepted that PLGA and PLLA undergoes hydrolytic degradation, but not much is known of their degradation due to e-beam irradiation effects. This paper studies the effects of e-beam radiation on the morphological and thermal properties of both PLGA and PLLA films, and their degradation behaviours.

2. Materials and methods

2.1. Preparation of biopolymer films

The biopolymer films were prepared by a simple solvent casting method. PLGA(80:20) and PLLA were purchased from Purac Far East, Singapore, and the solvent used was dichloromethane (DCM) from E. Merck, Germany. The polymer was first dissolved in DCM at a weight ratio of 1:12. The polymer solution was spread over a glass plate to give a film of approximately 0.7032 mm in wet thickness. The solvent was evaporated slowly in air at room temperature for 48 h to prevent the formation of air bubbles.

The polymer films were cut into rectangular strips of dimensions 8 cm×3 cm for further tests. Each strip was then placed in an oven at 40 °C for a week to evaporate any remaining solvent, leaving behind dried polymer films.

2.2. Electron beam (e-beam) radiation

Each of the PLGA and PLLA film samples was irradiated using the Energy Sciences Inc. (ESI) Electron Beam Accelerator at room temperature (25 °C) and humidity, and in the presence of oxygen. The accelerating voltage used was 175 kV. The film samples were irradiated at radiation doses of 5, 10, 20, 30 and 50 Mrad.

2.3. Gel permeation chromatography (GPC)

The number average molecular weight (M_n) of each of the irradiated sample was determined using GPC (Agilent 1100 series). GPC was performed at 30 °C with 80%-tetrahydrofuran and 20%-DCM as solvents, using RID (Reflective Index Detector) as the detector. The calibration is done in accordance to polystyrene standards and the flow rate used was 1 ml min^{-1}. The GPC results are plotted using a logarithmic molecular weight (MW) scale.

2.4. Modulated differential scanning calorimeter (MDSC)

DSC measurements were performed on a TA Instrument DSC 2920 Modulated DSC apparatus. To avoid oxidative degradation, the sample and reference pans were purged with nitrogen at a constant flow rate of 48 ml min^{-1}. The samples were heated from −40–250 °C at a scan rate of 5 °C min^{-1}. Approximately 5 mg of each sample was used in the analysis. The presence of a T_g reveals the presence of an amorphous region, and the presence of a T_m reveals the presence of a crystalline phase in the sample. The area under the melting peak gives the enthalpy heat of fusion per gram of sample. During the heating process, some of the polymer crystallizes resulting in a crystallization peak. The difference between the enthalpy of fusion and the enthalpy of crystallization from the DSC is used as an indication of the original level of crystallinity within the sample [21].

2.5. Fourier transformed infrared spectroscopy (FTIR)

The infrared spectra of the films before and after irradiation were obtained to verify the polymerization and degradation of the monomers using Fourier transformed infrared spectroscopy (FTIR). The Perkin Elmer system 2000 FTIR was used to characterize the polymeric films. The FTIR spectra were obtained with 16 scans per sample over the range of 4000–400 cm^{-1}.

3. Results

3.1. Gel permeation chromatography

The number average molecular weight (M_n) of each of the irradiated samples was plotted against radiation dose. The GPC plots for PLGA and PLLA are illustrated in Figs. 3 and 4 respectively.

An initial drastic drop in the number average molecular weight of PLGA is observed during the initial dose of e-beam irradiation at 5 to 20 Mrad (Fig. 3). This is followed by relatively unchanged (within experimental error) average molecular weight at higher radiation dose (30 Mrad and above).

The number average molecular weight of PLLA decreases linearly with radiation dose as illustrated in Fig. 4. The ratio of the molecular weight of the non-irradiated film ($M_{n,0}$) to the molecular weight of the irradiated film ($M_{n,t}$) suggests the degree of degradation due to e-beam radiation. A greater deviation of $M_{n,t}$ from $M_{n,0}$ will imply that a greater degree of degradation has occurred, resulting in a larger $M_{n,0}/M_{n,t}$ ratio. It can be observed from the plot of $M_{n,0}/M_{n,t}$ against the radiation dose (Fig. 5) that the $M_{n,0}/M_{n,t}$ ratio for the PLGA samples is larger than the PLLA samples at all radiation doses.

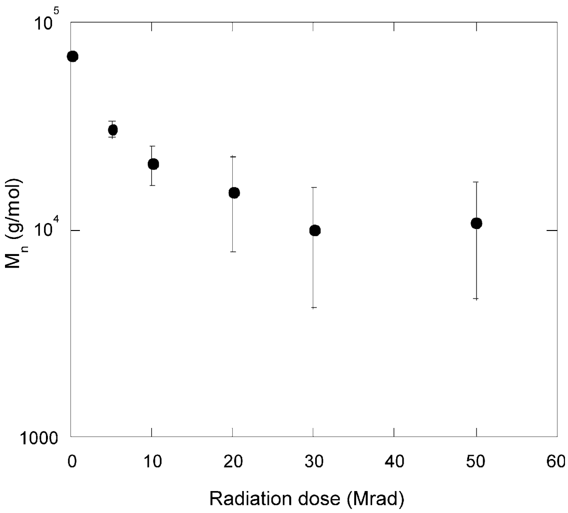

Fig. 3. Number average molecular weight (M_n) with respect to radiation dose for PLGA films.

3.2. Modulated differential scanning calorimeter (MDSC)

From the MDSC, it was observed that the non-irradiated PLGA sample does not exhibit a melting peak. The irradiated samples, on the other hand, exhibit a crystallization peak and a melting peak. Partial crystallization occurs prior to melting, which contributes to part of the endotherm. The PLLA films, on the other hand, exhibit both crystallization peaks and melting peaks.

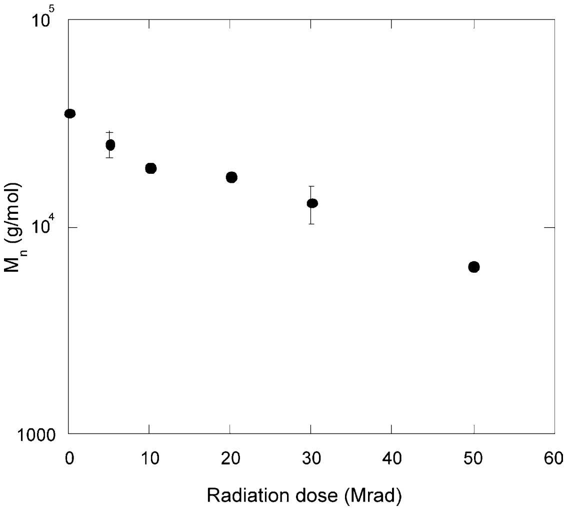

Fig. 4. Number average molecular weight (M_n) with respect to radiation dose for PLLA films.

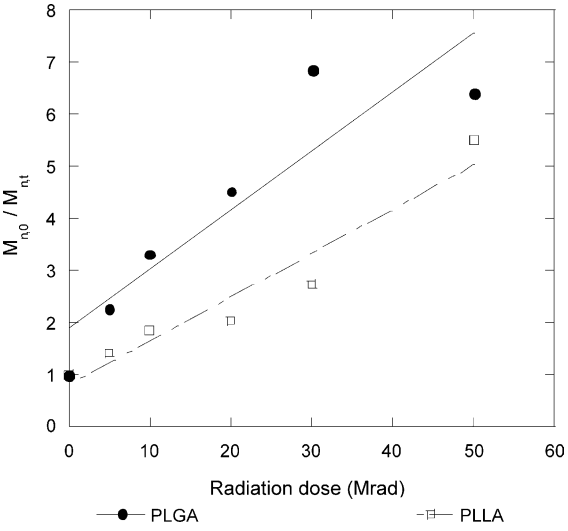

Fig. 5. Ratio of M_n of non-irradiated to irradiated films indicating the extent of radiation degradation.

The melting temperatures (T_m) of the irradiated PLGA and PLLA samples were plotted against radiation dose as illustrated in Fig. 6. It is observed that the melting temperatures of both PLGA and PLLA decrease with increasing radiation dose. The polydispersity index (M_w/M_n) also increased from 1.5 (0 Mrad) to 3.9 (50 Mrad) with increasing radiation dose, which indicates that the chains have become less uniform due to branching.

The melting temperature of PLGA is observed to be lower than PLLA (Fig. 6) at all radiation doses, suggesting poorer packing capability of PLGA chains as compared to PLLA chains.

The crystallization temperature (T_c) decreases with radiation dose for both PLGA and PLLA, as illustrated from Fig. 7. The crystallization temperature of PLLA at all radiation doses is observed to be much lower than PLGA.

As with the decrease in the crystallization temperature, the glass transition temperature (T_g) of PLGA and PLLA also decrease with increasing radiation dose, as illustrated in Fig. 8. This decrease in the glass transition temperature corresponds to the decrease in molecular weight with radiation dose.

The change in the difference between the enthalpy of fusion (ΔH_f) and crystallization (ΔH_c) was used as an indirect measurement of the level of sample crystallinity with respect to radiation dose [21]. This was taken as the true portion that crystallizes upon immediate irradiation. The degree of crystallinity increases with respect to radiation dose for PLGA, as observed in Fig. 9. For PLLA, the degree of crystallinity was found to decrease

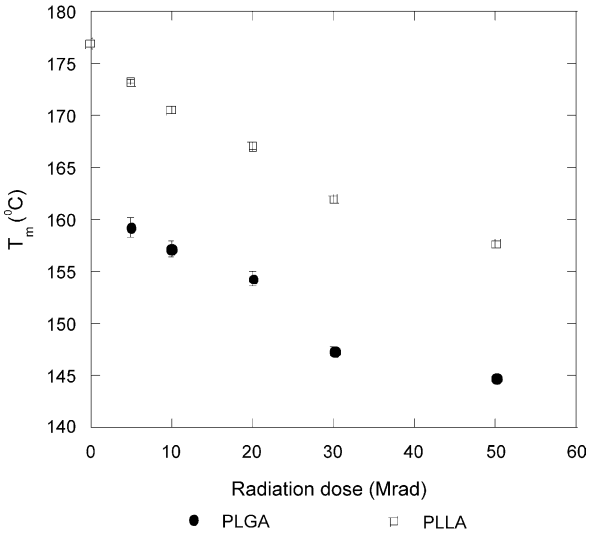

Fig. 6. Melting temperature (T_m) of PLGA and PLLA as a function of radiation dose. A heating rate of 5 °C/min was used.

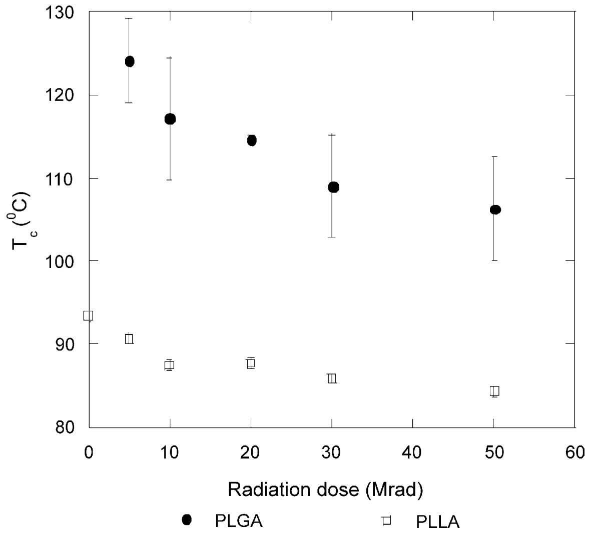

Fig. 7. Changes in crystallization temperature (T_c) of irradiated PLGA and PLLA films as a function of radiation dose.

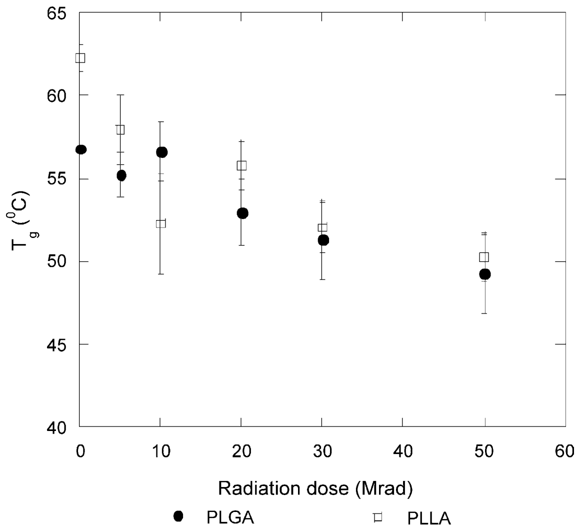

Fig. 8. Glass transition temperature (T_g) of PLGA and PLLA as a function of radiation dose. A heating rate of 5 °C/min was used.

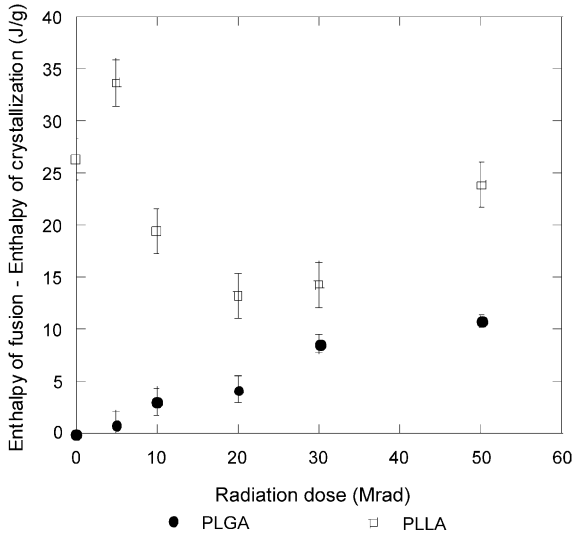

Fig. 9. Difference in the heat of fusion and heat of crystallization of irradiated PLGA and PLLA films as a function of radiation dose.

at initial radiation doses, up to 30 Mrad. Beyond 30 Mrad, the degree of crystallinity was then observed to increase.

3.3. Fourier transformed infrared spectroscopy (FTIR)

There are some distinctive differences in the FTIR spectra of PLGA and PLLA non-irradiated films. One of the differences is the existence of the 1424 cm^{-1} peak present in PLGA, which is absent in PLLA. This peak corresponds to the C–H deformation in the –O–CH_2– structure that is present only in the glycolic acid structure of PLGA. The highly crystalline non-irradiated PLLA also exhibits a crystalline peak at 920 cm^{-1}, which is absent in the non-irradiated amorphous PLGA films.

Upon irradiation, it was observed that two new peaks were formed in both PLGA and PLLA films at 3290 and 2340 cm^{-1}. The peak at 3290 cm^{-1} indicates the formation of alcohol groups during the irradiation process [Fig. 10 (a)], while the peak at 2340 cm^{-1} indicates the presence of trapped carbon dioxide gas upon irradiation [Fig. 10 (b)]. A change in intensity of the hydroxyl groups (3540 and 3650 cm^{-1} peaks) was also observed upon irradiation [Fig. 10 (a)].

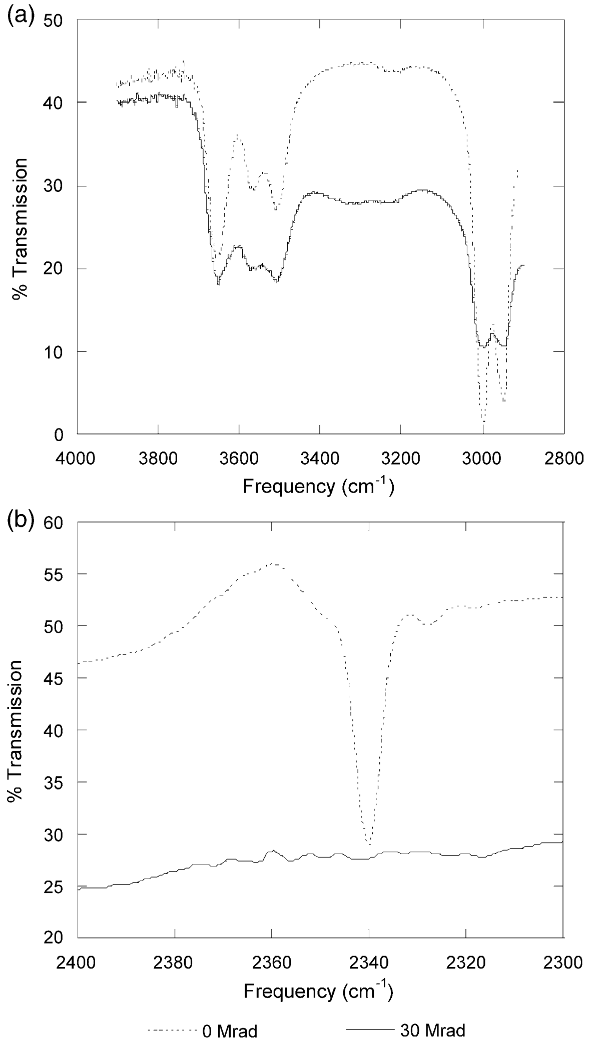

Fig. 10. (a) FTIR spectra of irradiated and non-irradiated PLGA film showing formation of alcohol groups. (b) FTIR spectra showing the formation of a carbon dioxide peak upon irradiation.

4. Discussion

The number average molecular weight of PLGA and PLLA generally decreases with increasing radiation dose as seen in Figs. 1 and 2 respectively. The decrease in molecular weights indicates that chain scission is the dominant process upon irradiation. Under e-beam radiation, PLGA and PLLA molecules are excited to form active species, such as free radicals [18]. Since the irradiation here is carried out in the presence of oxygen, peroxyl free radicals are also formed [22,23]. These active species will then react with one another and initiate further reactions among the polymeric chains, causing chain scission through chain transfer and splitting of the polymer chains [19]. The high energy from the e-beam radiation may at the same time cause chain scission through breaking of the chemical bonds between monomers [20]. This chain scission process lowers the molecular weight of these polymers. The degradation of PLGA and PLLA, through chain scission, emits carbon dioxide gas, which is trapped in the irradiated films. This trapped carbon dioxide gas gives rise to the infrared peak at 2340 cm^{-1}, in all the freshly irradiated samples [Fig. 10 (b)].

The rate in which the average molecular weight decreases with radiation dose differs for PLGA samples irradiated below 20 Mrad and above 20 Mrad (Fig. 3). The decrease in molecular weight is significant for PLGA samples irradiated below 20 Mrad, while at 20 Mrad and above, the molecular weights are somewhat constant, within experimental errors. Chain scission occurs readily within the open amorphous regions, giving rise to shorter polymer chains, which are able to reorientate and crystallize. With increasing radiation dose, more chains in the amorphous regions are scissioned, thus promoting crystallization and increasing the degree of crystallinity. This is illustrated in Fig. 9 where the difference between the enthalpy of fusion and crystallization ($\Delta H_f - \Delta H_c$) of PLGA increases with radiation dose. As the degree of crystallinity increases, the molecular weight of PLGA continues to decrease, but at a slower rate, until it remains constant with radiation (Fig. 3).

At higher radiation doses (above 20 Mrad), the molecular weight of PLGA remains constant within experimental error. This can be attributed to the formation of the crystalline phase within the polymer upon irradiation. The crystalline regions formed consist of chains that are more oriented and closely packed compared to the amorphous regions. The close proximity of the polymer chains in the crystalline structure encourages the trapped free radicals to recombine, thus reducing the number of effective chain scission. This effect is also known as the "cage effect" [24], a concept which involves the recombination of initial radicals before they can diffuse out of the active region and undergo reactions other than recombination elsewhere. Hence, the presence of a crystalline phase inhibits or retards the chain scission process. This causes the molecular weights to remain approximately constant with radiation dose.

Another possible reason for the constant molecular weights is because cross-linking is in competition with chain scission [25] at higher radiation doses (20 Mrad and above). When the PLGA is irradiated in the presence of air, oxygen molecules act as free radical scavengers, thus resulting in a higher number of chain scission and little cross-linking. However, at high radiation doses, the number of free radicals formed is larger than the number of free radical scavengers present. This is because most of the oxygen dissolved in the film would have been used up in forming free radical scavengers during the initial radiation doses. Hence, these active free radicals, which are greater in number compared to the free radical scavengers, are able to react and cause cross-linking.

In the case of PLLA, the decrease in the molecular weight with increasing radiation also indicates that chain scission is the dominant process upon irradiation. However, the decrease in the molecular weight was found to be linear with radiation dose (Fig. 4). The degree of e-beam radiation degradation was also lower for PLLA than PLGA (Fig. 5). This observation can be attributed to the "cage effect", since PLLA is a semi-crystalline polymer, and has a higher degree of crystallinity compared to PLGA (Fig. 9 and 920 cm^{-1} peak on FTIR). A semi-crystalline PLLA is better able to retard degradation compared to an amorphous PLGA, or a lower crystallinity PLGA.

The thermal and morphological properties of a polymer are very much affected by the changes in its molecular weight. Hence, scission of the polymer chains will cause the thermal and morphological properties of the irradiated PLGA and PLLA samples to change. The absence of a melting peak in the originally non-irradiated PLGA film indicates the absence of a crystalline phase in the PLGA control sample. In other words, the original PLGA film is completely amorphous. Irradiated films, on the other hand, displayed an endotherm and crystallization peak (Figs. 6 and 7). During irradiation, chain scission occurs and the molecules become shorter. These shorter chains are less entangled and have better mobility, thus allowing re-orientation of the molecules. The re-orientation of the molecules results in the formation of a crystalline phase. This explains the existence of the endotherm in all the irradiated PLGA samples. The heating process in the MDSC also encourages crystallization, giving rise to a crystallization peak. The decrease in the crystallization temperature with radiation dose (Fig. 7) further supports that chain scission has taken place during irradiation, since shorter chains are better able to re-orientate and re-crystallize than longer chains. The decrease in the molecular weights of the polymers (Figs. 1 and 2) also decreases the T_g, as illustrated in Fig. 8. Since the glass transition temperature, T_g, is dependent on the molecular weight of the polymer, the higher the molecular weight, the higher the T_g [26]. The decrease in T_g suggests that the polymer chains have gained better mobility brought about by chain scission. Further re-crystallization decreases the amount of amorphous material and this in turn, increases the brittleness of the irradiated PLGA and PLLA films. The decrease in melting temperatures of both PLGA and PLLA with increasing radiation dose further suggests that cross-linking is occurring simultaneously with chain scission (Fig. 6). The decrease in melting temperature together with the increase in the polydispersity index (from 1.5 to 3.9) indicates possible branching of the chains through the recombination of free radicals. The decrease in melting temperature also indicates the increase in the flexibility of the chains with radiation dose, which may be due to side chain branching [27].

Chain scission of PLGA and PLLA results in changes in the FTIR spectrum of the non-irradiated compared with the irradiated samples. The two observable changes in the FTIR spectra for PLGA and PLLA were observed to be the formation of a new peak at 3290 cm^{-1} and changes in the intensity of the peaks between 3540 and 3650 cm^{-1}, indicating that there is an increase in the alcohol groups formed upon irradiation; though a small contribution could also be from water and hydroperoxides produced in the course of oxidation. The formation of these alcohol groups is the result of the peroxyl free radicals undergoing degenerate chain branching. The formation of peroxyl free radicals causes chain scission resulting in the decrease in the molecular weights of PLGA and PLLA with increasing radiation dose (Figs. 1 and 2). The chain scission process encourages the formation of crystalline phases within both PLGA and PLLA, which retard the radiation degradation process, through "cage effect".

5. Conclusion

PLGA and PLLA degrade through chain scission when exposed to e-beam irradiation in the presence of air. E-beam irradiation causes a decrease in the average molecular weight (M_n), glass-transition temperature

(T_g), melting temperature (T_m) and crystallization temperature (T_c) of the biopolymers. Irradiation also causes the formation of a crystalline phase within the originally amorphous PLGA. The degree of crystallinity in PLGA increases with radiation dose. The formation of crystalline regions arrests PLGA degradation by balancing chain scission and cross-linking at high radiation dose. The higher degree of crystallinity in PLLA compared to PLGA decreases the degree of e-beam degradation in PLLA to PLGA. The higher degree of crystallinity in PLLA compared to PLGA makes PLLA implants more suitable for sterilization using radiation compared with PLGA. It has also been shown that the degree of crystallinity changes with radiation dosage. Since the rate of hydrolytic degradation of a biodegradable polymer is dependent on its degree of crystallinity, the ability to control the degree of crystallinity through irradiation will help control the rate of hydrolytic degradation of the polymer.

6. Future work

Since the reaction observed is a hydro-peroxidative degradation, irradiation will be carried out in an inert gas atmosphere to investigate the irradiation effect of e-beam through this complex degradation. The rate of hydrolytic degradation of these polymers after irradiation will also be examined.

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