Degradation of poly(lactide-*co*-glycolide) (PLGA) and poly(L-lactide) (PLLA) by electron beam radiation

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Abstract

This paper seeks to examine the effects of electron beam (e-beam) radiation on biodegradable polymers (PLGA and PLLA), and to understand their radiation-induced degradation mechanisms. PLGA (80:20) and PLLA polymer films were e-beam irradiated at doses from 2.5 to 50 Mrad and the degradation of these films were studied by measuring the changes in their molecular weights, FTIR spectra, thermal and morphological properties. The dominant effect of e-beam irradiation on both PLGA and PLLA is chain scission. Chain scission occurs first through scission of the polymer main chain, followed by hydrogen abstraction. Chain scission, though responsible for the reduction in the average molecular weight, T_c, T_g and T_m of both polymers, encourages crystallization in 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. A linear relationship is also established between the decrease in molecular weight with respect to radiation dose.
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1. Introduction

Poly(lactide-*co*-glycolide) (PLGA) and poly(L-lactide) (PLLA) have been extensively used as a controlled release carrier for drug delivery due to their good biocompatibility, biodegradability and mechanical strengths [1,2]. PLGA and PLLA are both hydrolytically unstable, and although insoluble in water, they degrade by hydrolytic attack of their ester bonds [3], resulting in the formation of lactic and glycolic acids [3–9]. Conventionally, the rate of hydrolytic degradation for these biopolymers is controlled by altering their physical properties; such as their molecular weights, degree of crystallinity and glass transition temperature (T_g) [6–8].

Radiation has been known to alter the physical properties of polymers through main-chain scission and cross-linking [10,11]. According to the principles of radiation chemistry, free radicals are formed when macromolecules of polymers are excited under ionizing radiation [12], where they are then free to react with one another or initiate further reactions among the polymeric chains, thus giving rise to changes in material properties. The combination of two radicals leads to cross-linking or recombination in the amorphous and crystalline regions, respectively [13], whereas chain transfer and the subsequent splitting results in chain scission [14]. Usually both these processes take place simultaneously for many polymers [15].

Semi-crystalline polymers, such as PLLA, are non-homogenous with a two-phase system consisting of amorphous and crystalline regions. During irradiation, energy is deposited uniformly and radicals are formed throughout the polymer in both the amorphous and crystalline regions [16]. However, crystalline regions consist of chains that were more oriented and closely packed compared to the more open amorphous regions. As a result, oxygen, stabilizers and specific active radical species are excluded from the crystalline phase, and the irradiation chemical reaction paths in the amorphous and crystalline phases will therefore be different. The close proximity of the polymer chains in the crystalline

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structure also encourage trapped free radicals to recombine, thus reducing the number of effective chain scissions, through an effect known as the "cage effect" [17].

Although some work has been reported on the effects of gamma radiation on poly(lactic acid) [18], little is known of the effects of electron beam (e-beam) radiation on the morphological, thermal and degradation behaviour of PLGA and PLLA. This paper reports on the investigation into the effects of e-beam radiation on the morphological, thermal and degradation behaviour of both PLGA (amorphous) and PLLA (semi-crystalline) films, establishes a relationship between the changes in molecular weight and radiation dose of these biopolymers, and suggests the possible radiation degradation mechanisms. The motivation behind this work is to investigate into the use of e-beam radiation as a possible means of controlling the rate of hydrolytic degradation of PLGA and PLLA.

2. Materials and methods

PLGA (80:20) and PLLA were purchased from Purac Far East, Singapore (manufactured by Purac, Holland). Films of PLGA and PLLA were prepared by a solvent casting method, in which the biopolymers are first dissolved in dichloromethane (DCM), purchased from E. Merck, Germany, using a weight ratio of 1:12 (polymer: DCM). The solution was then spread over a glass plate to give a film of approximately 0.7 mm in wet thickness, and the solvent slowly evaporated in air at room temperature for 48 h to prevent the formation of air bubbles. The remaining solvent was then removed in an oven at 40 °C for a week.

Thermogravimetric analysis (TGA) conducted on the films show no significant amount of DCM present in the films after drying. The dry thickness of the film was then measured to be about 0.055 mm, which was below the maximum film thickness (0.065 mm) allowed for a 100% full depth penetration of the electron beam.

Each of the PLGA and PLLA film samples was irradiated using the Energy Sciences Inc. (ESI) Electron Beam Accelerator at room temperature (25 °C), humidity and in the presence of air. The maximum accelerating voltage used was 175 kV, with the radiation dose ranging from 2.5 to 50 Mrad.

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

Ionizing radiation causes the formation and breaking of polymer bonds as a result of intermolecular cross-linking and scission in the polymer. The radiation chemical yields for chain scission (G_s) and cross-linking (G_x), which is defined as the number of such reactions per 100 electron volts of absorbed energy, therefore determines the extent of chain scission or cross-linking during irradiation, and can be calculated from the following equations [19]:

$$1/M_w = 1/M_{w,0} + (G_s/2 - 2G_x)D_x 1.038 \times 10^{-6}, \quad (1)$$

$$1/M_n = 1/M_{n,0} + (G_s - G_x)D_x 1.038 \times 10^{-6}, \quad (2)$$

where $M_{w,0}$ and $M_{n,0}$ are the weight and number average molecular weights of non-irradiated samples. M_w and M_n are the corresponding values following exposure to irradiation dose, D. A ratio of G_s/G_x greater than 4 would indicate that chain scission is more dominant [19].

Changes in the thermal properties and enthalpy of fusion and crystallization were investigated with the use of TA Instrument DSC 2920 Modulated DSC apparatus. The use of the Modulated DSC allows the heat capacity of the sample to be measured in one run with an error of 1% or less. 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 °C to 250 °C at a scan rate of 5 °C min^{-1}, with approximately 5 mg of each sample used in the analysis. The difference between the enthalpy of fusion and the enthalpy of cold crystallization [20] was used as an indirect measurement of the level of sample crystallinity for PLGA with respect to radiation dose. Cold crystallization is defined as the crystallization of the amorphous chains during heating. This enthalpy difference was taken as the true portion that crystallizes upon immediate irradiation. The degree of crystallinity for PLLA was calculated as the percentage of the enthalpy heat of fusion over the enthalpy heat of fusion for a 100% crystalline PLLA ($\Delta H_{f(100\%)} = 95$ J/g [21]).

Wide-angle X-ray diffraction (WAXD) was performed using the Shimadzu XRD-6000 employing Cu Kα radiation ($\lambda = 1.5406$ Å), with a thin-film attachment that rotates at a speed of 50 rpm. A scan axis of 2θ was used to obtain diffraction patterns of a scan range between 5° and 40°, with a scan rate of 0.2° deg/min. The θ-fixed angle was kept at 0.5°; and the voltage used was 40 kV and the current was 30 mA. The degree of crystallinity was calculated as the percentage of the scattered intensity of the crystalline phase over the scattered intensity of the crystalline and amorphous phase. The full-width at half maximum (FWHM), B, is related to the mean dimension of crystallites perpendicular to the *hkl* planes, t, by Scherrer's equation [22],

$$B = 0.9\lambda/t \cos \theta, \quad (3)$$