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Effect of isothermal annealing on the hydrolytic degradation rate of poly(lactide-*co*-glycolide) (PLGA)

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Abstract

Isothermal crystallization through annealing at 115 °C was conducted to increase the degree of crystallinity of poly (lactide-*co*-glycolide) (PLGA). The maximum increase in the degree of crystallinity (~21%) was achieved after 60 min of annealing. The crystal size/perfection was observed to increase with annealing time. The annealed PLGA films were then hydrolytically degraded in phosphate buffered saline solution of pH 7.4 at 37 °C for up to 150 days. Minimal mass loss was observed throughout the time investigated, suggesting that the samples were still in the first phase of degradation. The increase in the degree of crystallinity of the PLGA samples annealed at 15 and 30 min was found to retard their overall rate of hydrolytic degradation, when compared to those samples with higher initial crystallinity (annealed for 45 and 60 min) that had faster degradation rates. The increased degradation rate at higher crystallinity was associated with the loss of amorphous material and the formation of voids during annealing, which decreases the glass transition temperature and increases the average water uptake in the samples annealed for longer times. Therefore, the increase in degree of crystallinity is found to retard hydrolytic degradation but only to a certain extent, beyond which the formation of voids through annealing increases the rate of hydrolytic degradation.

Keywords: Poly(lactide-*co*-glycolide); PLGA; Biodegradable; Hydrolytic degradation; Crystallinity; Isothermal annealing

1. Introduction

The use of biodegradable polymers in the biomedical field has become increasingly important in the recent years due to their special ability to degrade. Poly(lactide-*co*-glycolide) (PLGA) is an example of such a biodegradable polymer, and has been extensively used in various biomedical applications [1]. It has been an excellent candidate for such applications because of its good biocompatibility, low toxicity, satisfactory mechanical strengths and excellent biodegradability [2].

PLGA is hydrolytically unstable, and its degradation mechanism in vivo has been credited to the random hydrolytic chain scission of ester bonds in its backbone, with possible enzyme catalytic effects [2]. This continual ester hydrolysis reaction forms carboxylic acid end groups that further catalyze the hydrolysis reaction, and leads to the eventual formation of lactic and glycolic acids [2–4]. In vivo, lactic and glycolic acids enter the tricarboxylic acid cycle and are metabolized and subsequently eliminated from the body as carbon dioxide and water [2,4]. It is generally accepted [5–7] that the hydrolysis of most polyesters, such as PLGA, proceeds according to the reaction shown in Fig. 1.

The kinetics of this reaction are given by

$$\mathrm{d[COOH]}/\mathrm{d}t = k'[\mathrm{ester}][\mathrm{H_2O}][\mathrm{COOH}] = k[\mathrm{COOH}] \quad (1)$$

where [COOH], [ester] and [H_2O] are the concentrations of carboxyl end groups, ester and water in the polymer matrix respectively, and it is assumed that in the early stages of the reaction the concentration of water and ester are constant. By assuming that $[\mathrm{COOH}] = 1/M_n$,

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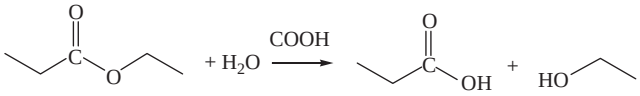

Fig. 1. Hydrolysis of ester bonds in biodegradable polyesters.

it can thus be shown that,

$$\ln M_n = \ln M_{n,0} - kt, \quad (2)$$

where $M_{n,0}$ is the initial number-average molecular weight of the polymer. The rate of degradation of PLGA is dependent on several factors [2,8], one of which includes its degree of crystallinity.

The percentage or degree of crystallinity reflects the extent of formation of crystalline regions within a polymer matrix. The degree of crystallinity has been shown to affect mechanical strength and swelling behaviour of the polymer, properties that influence the polymers suitability for end applications [9]. The formation of crystals in lactic/glycolic acid polymers is mainly dominated by the monomer used. Apart from the intrinsic susceptibility of a given polymer to form crystalline regions, the processing history of a polymer, such as its heating and cooling rate, also has significant effects on its crystallinity [10].

The driving force for crystallization is an increase in the (negative) interaction energy achieved by efficient molecular packing and by maximization of the number of strongly interacting groups that are in direct contact (e.g. forming hydrogen bonds). Once the molecules discover the most efficient arrangement, they repeat it endlessly in a crystalline lattice, where the smallest repeating entity is the unit cell [11]. The creation of a three-dimensional ordered phase from a disordered state is a two-stage process. The first step in crystallite formation is the creation of a stable nucleus brought about by ordering of chains in parallel array, stimulated by intermolecular forces, followed by the stabilization of long range order by the secondary valence forces which aid the packing of molecules into a three-dimensional ordered structure. The second stage is the growth of the crystalline region, the size of which is governed by the rate of addition of other chains to the nucleus. As this growth is counteracted by thermal redispersion of the chains at the crystal-melt interface, the temperature must be low enough (below T_m) to ensure that this disordering process is minimal. Yet, the temperature should be above T_g to enable sufficient thermal energy for the diffusion of chains into suitable orientations. For polymers in general, measurable rates of crystallization occur between ($T_m - 10$ K) and ($T_g + 30$ K), a range in which thermal motion of the polymer chains is conducive to the formation of stable ordered regions [12].

It is widely accepted that the degree of crystallinity affects the rate of hydrolytic degradation of PLGA but there is a lack of data that relates the degree of crystallinity of PLGA to its hydrolytic degradation rate. The ability to control the degree of crystallinity of PLGA through annealing therefore becomes an attractive study. This paper seeks to study the effects of isothermal annealing on the morphological properties of PLGA films and its subsequent hydrolytic degradation behaviour.

2. Materials and methods

2.1. Preparation and annealing of PLGA films

PLGA(80:20) (IV = 4.8) was purchased from Purac Far East, Singapore (manufactured by Purac Holland). Films of PLGA were prepared using a simple solvent casting method. The polymer was first dissolved in dichloromethane (DCM) at a weight ratio of 1:25. This weight ratio would give a polymer solution with good flow properties, without compromising on solubility. The polymer solution was then poured into a Teflon mould and the solvent was evaporated slowly in air at room temperature for 48 h to prevent the formation of air bubbles. The films were then placed in an oven at 40 °C for a week to evaporate any remaining solvent, leaving behind dried films with thickness about 0.055 mm.

The polymer films were then cut into rectangular strips of dimensions 8 cm × 3 cm and isothermally annealed at 115 °C, which is approximately the crystallization temperature of PLGA [13], for various lengths of time. Different annealing times resulted in different degree of crystallinity in PLGA. The percentage crystallinity (from WAXD) and enthalpy of fusion (from MDSC), for these films were then plotted with respect to annealing time.

2.2. Hydrolytic degradation of annealed PLGA films

PLGA films annealed for 15, 30, 45 and 60 min were used for the in vitro degradation studies, with the non-annealed films (0 min) used as the control sample. Prior to in vitro hydrolytic degradation, the initial mass (m_0) of each PLGA film was recorded. The samples were then placed in 10 ml screw top bottles containing phosphate buffered saline (PBS) solution (pH 7.4) and incubated at 37.0 °C for various lengths of time (up to 150 days). Samples were removed once every 3 days for the first 2 weeks and subsequently once every 10 days. The pH of the solution was monitored over time to ensure a stable pH 7.4 was maintained at all times.

At the designated time intervals, the films were removed from the PBS solution, rinsed with distilled