Differential scanning calorimetry studies of crystalline morphology in bioerodible polyanhydrides for drug delivery

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Abstract

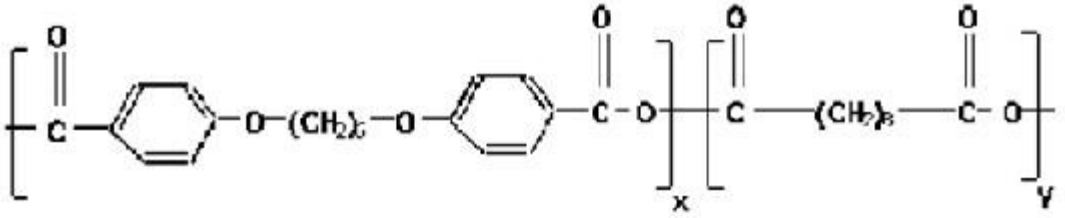
The overall goal of the research project is to design drug delivery systems with specifically tailored time-release profiles. The polymers of interest are polyanhydrides composed of 1,6-bis- (*p*-**c**arboxy**p**henoxy) **h**exane-co-**s**ebacic **a**nhydride, which are referred to as CPH:SA throughout the document. In order to design these drug delivery systems, we need to understand the morphology of the polymers, the polymer-drug interactions, and the polymer degradation kinetics. We investigate the thermal properties, degree of crystallinity, and crystal lamellar thickness of various compositions of CPH:SA using differential scanning calorimetry (DSC). Our results indicate that as the CPH content in the polymer increases, the crystal lamellar thickness increases and degree of crystallinity decreases. In addition, DSC studies of polymer/drug systems were performed using brilliant blue & p-nitroaniline as model compounds. The studies indicated that hydrophilic compounds (brilliant blue) are dispersed as particles while hydrophobic compounds (p-nitroaniline) form a solid solution with the polymer, leading to melting point depression.

Introduction

Controlled drug delivery has many significant advantages over treatments utilizing traditional repeated dosages. The controlled drug release profile is more constant in time than are the spiky profiles characteristic of repeated dosage delivery. As a result, controlled delivery may decrease the level of side effects. In addition, controlled delivery can provide localized release of 100-1000 times more drug than ordinary dosage forms.

The specific polyanhydrides of interest are poly (carboxyphenoxyalkane-co-alkanoic acids). An example of such a polymer is shown below, where x and y represent the number of repeating units of each co-monomer. The time-release profile is dependent on the ratio of x to y in the copolymer. Pure poly-sebacic anhydride has a short release

profile ranging up to a few weeks, depending on the value of y, while poly-CPH anhydrides, may have release profiles ranging up to several years.



1,6-Bis-(*p*-carboxyphenoxy)hexane Anhydride Sebacic Anhydride

The anhydride linkages of the copolymer are hydrolyzed when exposed to an aqueous environment, forming water-soluble degradation products. The hydrolytic degradation of these materials has been shown to occur at the surface of the bulk polymer [1]. Due to the surface degradation mechanism of polyanhydrides, water penetration is controlled by the system hydrophobicity [2].

Materials and Methods

The sebacic anhydride prepolymer was prepared using the following procedure: 40.0 grams of sebacic acid was refluxed in excess acetic anhydride for 30 minutes under a nitrogen sweep. The solution was evaporated to dryness in order to remove acetic acid and acetic anhydride. The sebacic anhydride residue was dissolved in 40 ml of chloroform, precipitated in 400 ml of a 1:1 mixture of ethyl ether to petroleum ether, filtered, and finally dried in a vacuum oven.

CPH anhydride prepolymer was synthesized by following procedures similar to those used in making SA, but with a few modifications. First, 1,6-bis-(*p*carboxyphenoxy)hexane diacid was synthesized as described by Conix [3]. 40 grams of the diacid was refluxed in excess acetic anhydride for 60 minutes under a nitrogen sweep. The solution was filtered to remove any unreacted diacid. The filtrate was concentrated to a volume of approximately 150 ml and refrigerated overnight. The CPH anhydride precipitated from solution and then was washed three times with 100 ml of ethyl ether and dried under vacuum. The powder was further purified by dissolution in chloroform. The impurities were filtered off and the filtrate was evaporated to dryness.

Pure polySA and molar compositions of 20:80, 50:50, and 80:20 CPH:SA were synthesized by melt polycondensation using the above-specified prepolymers at 180^{o}C under high vacuum for 90 minutes. The polymer was dissolved in methylene chloride, precipitated in petroleum ether, and dried in a vacuum oven. The polymers and prepolymers were stored under argon in a dessicator under vacuum to prevent premature hydrolysis.

A ± 1^{o}C/min modulated differential scanning calorimeter (MDSC 2910, TA Instruments, New Castle, DE) with a temperature ramp of 10^{o}C/min was used to measure

the thermal properties (glass transition temperature, T_g, melting point, T_m, and latent heat of fusion, ΔHm) and degree of crystallinity. DSC was also used to characterize polymer/drug interactions.

The degree of crystallinity, X_{waxd}, was calculated from wide angle X-ray diffraction data by taking the area under the crystalline peaks (A_c) divided by the total area under all peaks in the diffraction pattern (A_t)

$$X_{WAXD} = \frac{A_c}{A_t} \qquad (1)$$

An alternative measure of the degree of crystallinity, X_{DSC}, was calculated using DSC and WAXD.

$$X_{DSC} = \frac{\Delta H_{copolymer}}{W_{CPH}\Delta H_{CPH,pure} + W_{SA}\Delta H_{SA,pure}} \qquad (2)$$

The term Δ $H_{copolymer}$ is the heat of fusion for the copolymer that is obtained from the DSC. Wi is the mass fraction of the monomer *i* and $\Delta H_{i,pure}$ is the heat of fusion of a pure polymer with complete crystallinity. It is calculated from the latent heat of fusion of a homopolymer from DSC divided by the degree of crystallinity of the pure polymer from WAXD. The WAXD studies have been performed in our group and we use those results directly here.

The crystal lamellar thickness was calculated using the Thomson-Gibbs equation

$$T_{ml} = T_{m\infty}\left(1 - \frac{2\sigma_e}{\Delta H\, l}\right) \qquad (3)$$

where T_{ml} = observed melting temperature of a crystal of thickness (l),$T_{mi\hat{U}}$ = equilibrium melting temperature of an infinitely thick crystal, the surface free energy per unit area of the chain folds σ_e = 70 x 10^{-7} J/cm^2 [4] and ΔH = latent heat of fusion per unit volume of crystal. Annealing studies were conducted at temperatures T_c between the glass transition and melting temperatures for 90 minutes. $T_{mi\hat{U}}$ is the point at which T_c = T_{ml}.

Results and Discussion

Polymer Characterization:

The molecular weight of the polymers was determined using gel permeation chromatography (GPC). Briefly, the polymer sample was dissolved in methylene chloride and eluted into chloroform on a Waters 410 Differential Refractometer equipped with a 510 HPLC pump set at a rate of 1.0 ml/min. The weight average molecular weights ranged from 20,000 to 40,000 with polydispersities between two and four (Table 1). The desired mechanical properties exist within this range of molecular weights. The latent heat of fusion, area above the melting point in figure 1, of the polymers decreased as the CPH content increased and as a result the degree of crystallinity, calculated from equation 2, decreased from 60.8% for 0:100 to 25.8% for copolymer 80:20 CPH:SA. This is because as the rigidity in the system (ie., amount of CPH) increases, the ability to crystallize decreases.

Annealing studies were performed for all the copolymers and lamellar thicknesses were calculated using equation 3. We observed that the lamellar thickness, *l*, increased with increase in the CPH content. This increase can be explained by examining the CPH and SA molecules. The CPH molecule is more rigid and sterically hindered than SA, making it more difficult for the polymer chains to fold and to arrange themselves into crystals. Pure polySA is the most crystalline polyanhydride, containing a larger number of thinner crystals. In general, as CPH content increases, the degree of crystallinity decreases but the lamellar thickness increases.

Drug/polymer interactions:

To examine these interactions, DSC studies were also performed on several copolymer-drug systems. Changes in the crystallinity and melting temperature were monitored. We examine the resultant interactions of two model compounds, brilliant blue (a hydrophilic dye) and p-nitroaniline (a hydrophobic drug) when added to our least hydrophobic polymer, 0:100 CPH:SA. Upon the addition of hydrophilic brilliant blue to 0:100 CPH:SA, T_{ml} and ΔH are essentially unchanged. The brilliant blue does not interact with the crystalline structure of the compatible polymer. To ensure that the compatible drug does not effect the structure of the polymer, the lamellar thickness of drug-incorporated samples (15% w/w) were determined. The $T_{m_i\hat{U}}$ values for 0:100 CPH:SA with and without the addition of brilliant blue were 93.1°C and 92.5 °C, respectively. The lamellar thickness of the drug-incorporated samples was found to be 16.4 nm while that of the 0:100 CPH:SA alone was found to be 17.1 nm. This provides evidence that the hydrophilic drug does not interact with the hydrophobic polymer. We examined the effects of drug loading to characterize the interactions between 0:100 CPH:SA and hydrophobic p-nitroaniline. DSC analyses of 0:100 CPH:SA with 5, 10, and 15 wt.% p-nitroaniline (Figure 3) was performed. Increasing p-nitroaniline content enhances melting point depression, demonstrating that the drug acts as a diluent.

Conclusions and Future Work

We have synthesized and characterized the morphology of bioerodible polyanhydrides based on CPH and SA. DSC was used to characterize the degree of crystallinity, the lamellar thickness, and polymer/drug interactions. Our results are of immense significance to designing drug delivery systems based on copolymers, where the interesting phase behavior observed in copolymers could be used a tuning parameter to modulate the drug release. Ongoing work in our group is focused on characterizing the phase behavior (using techniques such as atomic force microscopy and small angle X-ray scattering) in the CPH:SA systems that we have studied.

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Table 1. Molecular weights (M_n and M_w) and polydispersities (PD) from gelpermeation chromatography of various polymer compositions. Compositions are given as molar ratios of 1,6-bis-(p-carboxyphenoxy) hexane (CPH) to cosebacic anhydride (SA).

Composition	M_n	M_w	PD
0:100	18619	38038	2.04
20:80	8841	26529	3.00
50:50	5396	20608	3.82
80:20	5515	20696	3.75

Table 2. Degree of crystallinity and crystal lamellar thickness from DSC.

Composition	T_{ml}	T_{m}	ΔH (J/g)	lamellar thickness (nm)	X_{DSC}%
0:100	79.0	92.5	221.3	17.2	60.8
20:80	66.5	78.8	153.3	26.3	59.2
50:50	50.2	51.0	92.1	80.9	29.1
80:20	114.9	117.5	55.3	288	25.8

Figure 1

From DSC, a plot of heat flows versus temperature for a ramp of 10°C/min. The area above the melting point is the latent heat of fusion.

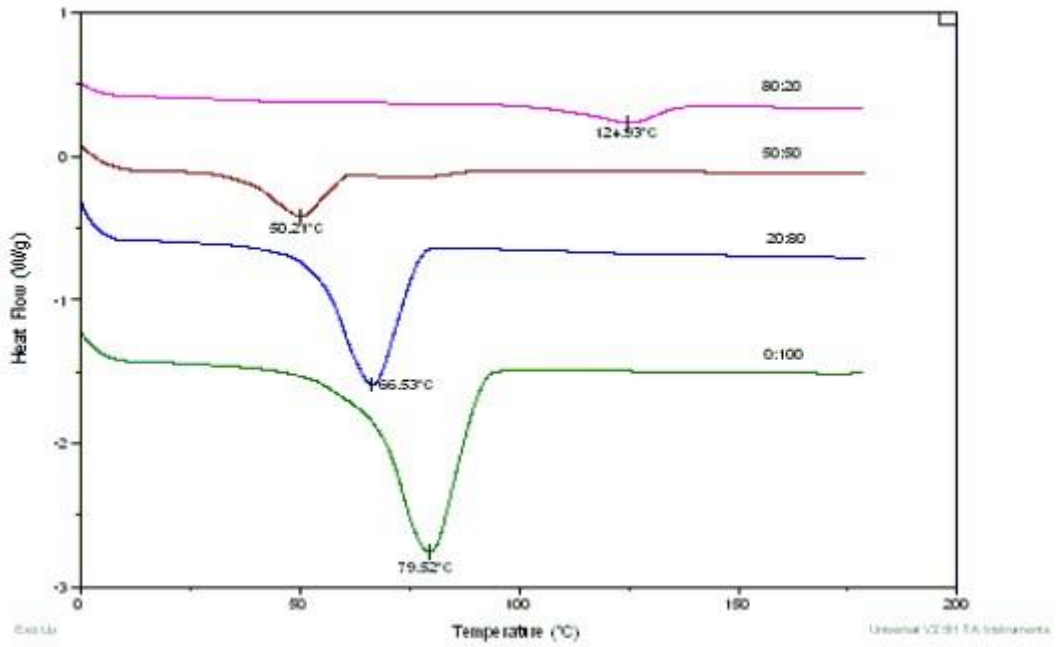

Figure 2

A graph of T_{ml} versus T_c for 0:100 CPH:SA. The lamellar thickness of the polymer was calculated using equation 4 and from $T_{m_i\hat{U}}$ which is the point where $T_{ml} = T_c$.

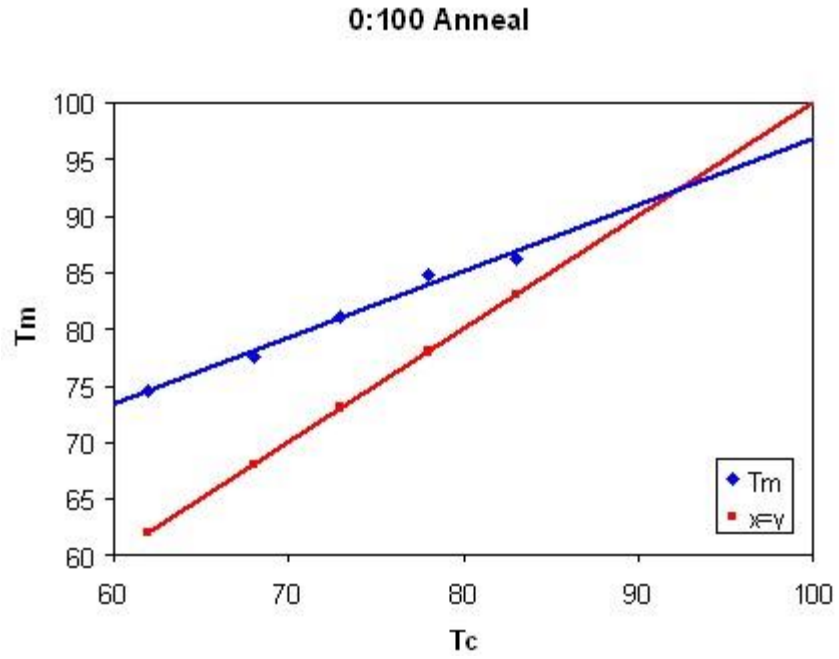

Figure 3

DSC thermogram of 0:100 CPH:SA (a) alone and with (b) 5%, (c) 10%, and (d) 15% w/w loading of p-nitroaniline. The melting peaks are observed to decrease with increase in p-nitroaniline content.