Synthesis, Degradation, and Drug Delivery of Cycloaliphatic Poly(ester anhydride)s

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ABSTRACT: The high melting point of poly(1,4-cyclohexanedicarboxylic anhydride) [poly(CHDA)] is a disadvantage, in that it is intractable in the melting process of a drug delivery system. This report relates to diols introduced into the polyanhydride main chain to decrease its melting point. Various poly(ester anhydride)s containing ethylene glycol, 1,3-propanediol, 1,4-butanediol, or 1,6-hexandiol [poly-(CHDA–XDO)] were synthesized by the esterification reaction and melt polycondensation. FTIR, DSC, WAXD, and intrinsic viscosity of polymers were recorded and hydrolytic degradation, as well as *in vitro* drug delivery, was conducted. The results show that the samples are stable in an anhydrous environment at room temperature and degrade in water following a surface erosion mechanism. The degradation period of poly(CHDA–XDO) ranged from 130 to 320 h as a result of the different diols and amounts of XDO introduced. The *in vitro* drug delivery gave 130–350 h of stable delivery along with the typical surface erosion mechanism. © 2002 Wiley Periodicals, Inc. J Appl Polym Sci 86: 2509–2514, 2002

Key words: 1,4-cyclohexanedicarboxylic acid; poly(ester anhydride); synthesis; degradation; drug delivery

INTRODUCTION

The first polyanhydride was synthesized by Brucher and Slade[1] in 1909. During the following 60 years, various polyanhydrides were synthesized in attempts to use them as chemical fibers by many scientists. Unfortunately, compared with fibers of polyester, polyamide, polypropylene, polyacrylonitrile, and so forth, the hydrolysis resistance of these polyanhydrides was always unsatisfactory for the requirement of commercial products. Therefore, research on polyanhydrides almost stopped after the 1960s.

However, noticing the ease of hydrolysis of polyanhydrides, Langer et al. began to study polyanhydrides for use in drug-controlled release in the 1970s. Since then, polyanhydrides have been intensively studied as matrices of drug controlled release systems because of their excellent biocompatibility and surface eroding properties.[2–5] Over the past 15 years, various polyanhydrides with different main-chain structures have been synthesized for drug delivery systems, such as the poly[bis(*p*-carboxyphenoxy) alkyl-*co*-sebacic acid] anhydride series,[6] poly[ω-(*p*-carboxyphenoxy)alkanoic] anhydride series and its copolymers,[7] poly(fatty acid dimer–sebacic acid) [P(FAD-SA)] series,[8–10] poly(amide–anhydride), poly(ester–anhydride), and polyanhydrides containing urethane linkage[11] and poly(imide–anhydride) series.[12,13]

Recently, a type of crosslinked polyanhydride with a tensile modulus nearly an order of magnitude larger than that of linear poly(sebacic acid) was synthesized from methacrylated anhydride monomers of sebacic acid and 1,6-bis(carboxyphenoxy) hexane.[14] Some modifications have also been conducted on the other polyanhydrides mentioned above.[15,16]

The hydrolysis properties of polyanhydride are greatly affected by the chemical structure of the backbone. Studies on the aliphatic polyanhydrides,[17–20] aromatic polyanhydrides,[21] and aliphatic-aromatic copolyanhydrides[22] showed that the aliphatic polyanhydrides degrade in a few hours, whereas some aromatic polyanhydrides degrade over a few years.[23] Many researchers are thus looking for new polyanhydrides to satisfy the different requirements of drug delivery systems. In our previous study, a novel cycloaliphatic polyanhydride, poly(1,4-cyclohexanedicarboxylic anhydride) [poly(CHDA)] was introduced,[24,25] although the high melting point of poly(CHDA) was an obvious disadvantage in the drug delivery system process. For this study, a new series of cycloaliphatic polyanhydride and poly(ester anhydride)s was prepared, and their degradation and drug delivery properties were studied.

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EXPERIMENTAL

Materials

1,4-Cyclohexanedicarboxylic acid (CHDA) was kindly provided by Dr. S. Liang of Eastman Chemical Company as high-purity grade (the assay as total CHDA was 99.97% and the *cis*-isomer assay was 74%). 1,3-Propanediol was purchased from Fluka Chemie (Buchs, Switzerland); analytical-grade ethylene glycol, 1,4-butanediol, and 1,6-hexandiol were purchased from Beijing Chemical Regents Works (China) and used without further purification. All the organic solvents, such as chloroform, *N*,*N*′-dimethylformamide (DMF), and ethyl ether, were dried by a 4-Å molecular sieve and distilled before used. The model drug ibuprofen [α-(4-isobutylphenyl) propionic acid] was obtained from The Chinese Pharmaceutics University. Ibuprofen was used because it loses less than 1 wt % at the melt temperature of the polymers used in the drug delivery systems (145°C).

Instrumentation

The intrinsic viscosity values ([η]) were determined in DMF at 30 ± 0.1°C using a Ubbelohde viscometer.[26] The differential scanning calorimetry (DSC) thermograms were recorded with a 10°C/min heating rate using a second scan in a N_2 atmosphere and ranged from room temperature to 250°C, with a TA Instruments 2910 DSC analyzer (TA Instruments, New Castle, DE). FTIR spectra were measured with a Nicolet 170SX FT-IR spectrometer (Nicolet Analytical Instruments, Madison, WI) in KBr pellets. Wide-angle X-ray diffractions (WAXD) of the polymers were recorded in a Rigaku D/Max-RA rotating anode X-ray diffractometer (Rigaku, Tokyo, Japan) using a Cu–K_α source. UV detection was recorded on a Shimadzu UV240 analyzer at room temperature (Shimadzu, Kyoto, Japan).

Prepolymer synthesis

Poly(1,4-cyclohexanedicarboxylic anhydride) [poly(CHDA)] and poly(CHDA-*co*-diols) [poly(CHDA–XDO)] were synthesized by melt-polycondensation.[27] A typical reaction procedure was carried out in two stages: the synthesis of prepolymer and the postpolycondensation. XDO includes ethylene glycol (EDO), 1,3-propanediol (PDO), 1,4-butanediol (BDO), and 1,6-hexandiol (HDO).

CHDA anhydride prepolymer was prepared by refluxing the CHDA monomer (10 g) in acetic anhydride (100 mL) for 1 h. The excess acetic anhydride was removed under vacuum at 100°C and the residue dissolved in $CHCl_3$ (20 mL). The solution was then added to anhydrous ethyl ether with stirring to precipitate the prepolymer. The crude prepolymer was then extracted in a Soxhlet apparatus using ethyl ether for 24 h to remove any trace of the acetic anhydride.

The FTIR spectrum of prepolymer showed that there was no hydroxyl group in the prepolymer and typical anhydride peaks appeared at 1799, 1737, and 1060 cm^{-1}. The melting point of prepolymer was about 160°C.

Polymer synthesis

The melt-polycondensation of poly(CHDA) was carried out as follows: CHDA prepolymer was mixed with 2 mol % cadmium acetate (catalyst) in a Kimax tube and, after it was filled with dried nitrogen three times under vacuum, the tube was immersed into a salt bath at 280°C. After the prepolymers were melted, high vacuum (<5 Pa) was applied through the side arm for about 1.5 h and the condensate (acetic anhydride) was collected in a liquid nitrogen trap. After the polymerization finished, $CHCl_3$ was used to extract the crude polymer in a Soxhlet apparatus for 24 h. The refined polymer was then sucked dry and ground to powder for later experiments.

Using poly(CHDA–EDO) as an example, poly(CHDA–XDO) were synthesized as follows: CHDA prepolymer with 2 mol % cadmium acetate (catalyst) was mixed with different amounts of EDO in a Kimax tube and, after it was filled with dried nitrogen three times under vacuum, the tube was immersed into a salt bath at 170°C. The esterification reaction between the prepolymer and EDO was continued for about 30 min at this temperature. Then a vacuum was applied through the side arm and increased slowly in about 1 h to reach 5 Pa or lower. The postpolymerization was then conducted with the high vacuum for about 1.5–2 h and the condensate was collected in a liquid nitrogen trap. For some samples, the polymerization temperature was increased and they were polymerized for about 1.5–2 h. The exact postpolymerization temperatures of different polymers are listed in Table I. After the polymerizations were finished, the samples were cooled to room temperature with continued vacuum and then ground to powder for later experiments.

Hydrolytic degradation

For the degradation experiments, the polymer samples were prepared by melting the polymers in a small tube, and then cooled to room temperature under N_2 atmosphere, to cast a cylinder sample of about 25 mm in length and 8 mm in diameter. The processing of samples was at the melting temperature of the polymers with processing times not over 2 min. The samples were placed into 500 mL of 0.1 mol/L phosphate buffer (PB, pH 7.4) at 37°C for hydrolysis. The samples were taken at various time intervals from the buffer

TABLE I
Synthesis of Cycloaliphatic Polyanhydride and Poly(ester anhydrides)

Polymer	Polymerization temperature (°C)[a]	FTIR characteristic peaks (cm^{-1})	Melting point (T_m, °C)	Intrinsic viscosity ([η], mL/g)[b]
Poly(CHDA)	270	1799(s), 1730(s), 1083(s)	240–250[c]	—
Poly(CHDA–PDO)(70 : 30)	180	1799(m), 1732(s), 1697(s), 1172(s),	60–70[c]	—
Poly(CHDA–PDO)(80 : 20)	220	—	100–110[d]	—
Poly(CHDA–PDO)(90 : 10)	270	1799(m), 1732(s), 1698(s), 1172(s)	143[d]	4.42
Poly(CHDA–EDO)(90 : 10)	170	1802(m), 1736(s), 1697(s), 1201(m)	143[d]	4.05
Poly(CHDA–BDO)(90 : 10)	170	1801(m), 1730(s), 1705(s), 1203(m)	143[d]	4.12
Poly(CHDA–HDO)(90 : 10)	170	1800(m), 1728(s), 1700(s), 1202(m)	143[d]	4.03

[a] The temperature of salt bath.
[b] Determined in DMF at 30 ± 0.1°C.
[c] Determined by melting point tube.
[d] Determined by DSC with 10°C/min heating rate at 2nd scanning in N_2 atmosphere.

solution and weighed after drying in vacuum at room temperature for 2 h. The degradation of polyanhydride and poly(ester anhydride)s was estimated from the weight loss of the sample.

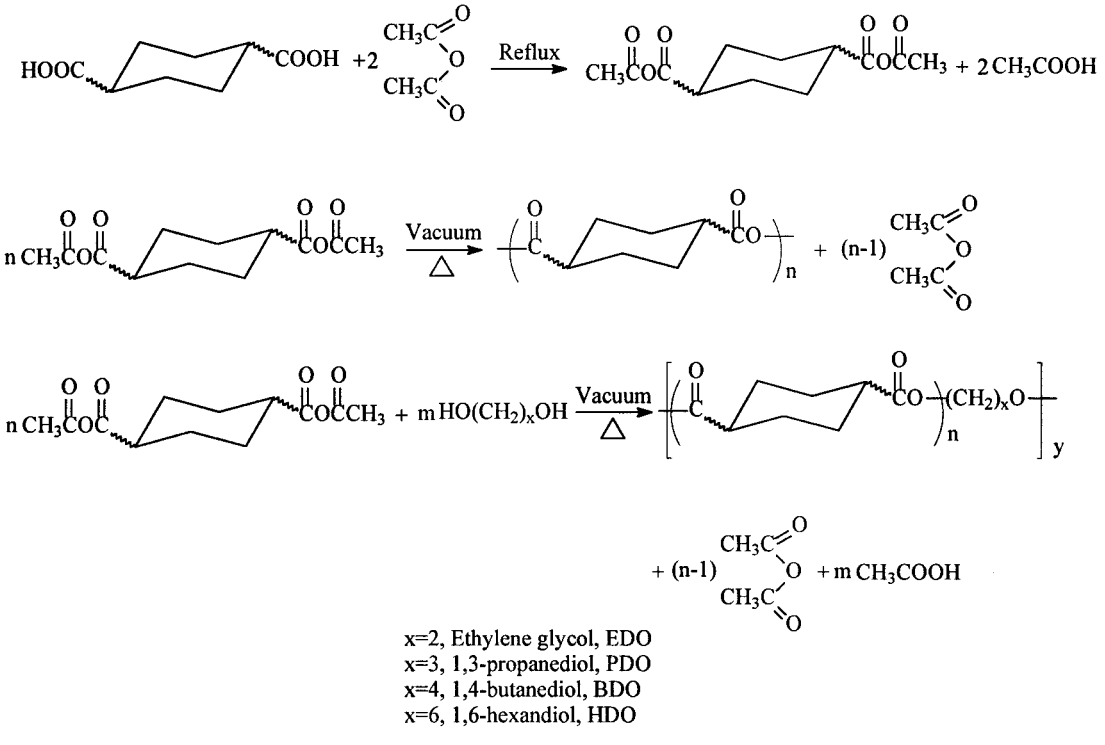
Drug delivery

Ibuprofen [α-(4-isobutylphenyl) propionic acid, 2 wt %] was blended with the polymer powder, which was then melted and cast into a Teflon disk mold to form a slablike drug-containing sample. Drug release studies were conducted by placing the disks into 10 mL PB at 37°C. The solution was replaced periodically with fresh buffer and the drug concentration in the buffer was determined by UV detection at 265 nm.

RESULTS AND DISCUSSION

Synthesis and analysis

The synthesis mechanism of cycloaliphatic polyanhydride and poly(ester anhydride) based on 1,4-cyclohexanedicarboxylic acid by melt polycondensation is shown in **Scheme 1**. Data on these polymers are summarized in Table I. Poly(CHDA) is a hard and brittle solid material at room temperature and the poly-



Scheme 1 Synthesis of polyanhydride and poly(ester anhydride).

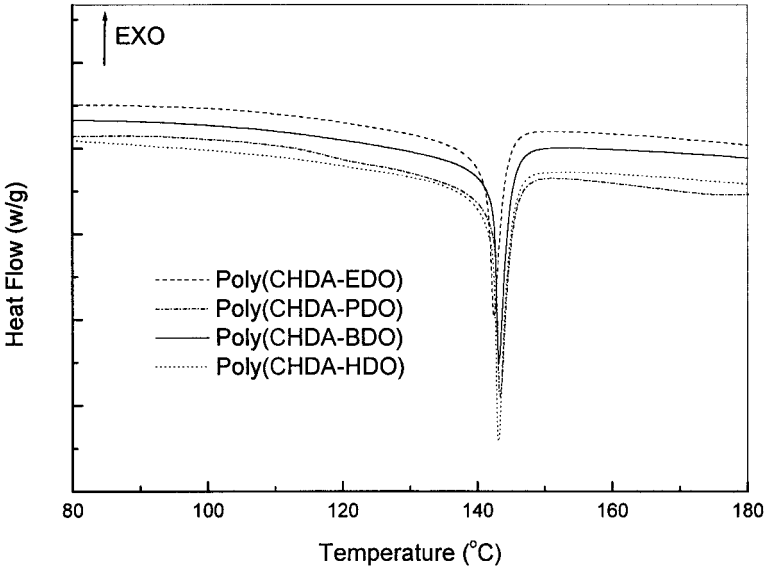


Figure 1 DSC second heating curve of poly(CHDA–XDO)(90 : 10).

(CHDA–XDO) looked tougher. All the polymers are opaque.

From Table I, the introduction of XDO into poly(ester anhydride) has a great influence on the properties of the polyanhydrides, especially on the melting points. Even when only 10% molar ratio of diols was introduced, the melting point of poly(ester anhydride) decreased about 100°C below that of poly(CHDA). When the amount of diols reached 50% molar ratio, the products turned into viscous liquids. Using poly(CHDA–PDO) as an example, we synthesized three different polymers containing different amounts of 1,3-propanediol (30, 20, and 10%). The melting points of these polymers were 60–70, 100–110, and 143°C, respectively. We think the melting point reduction is caused by destruction of the polymers' crystalline integrity by introducing diol segments into the polymer main chain.

When comparing the melting point of different poly(CHDA–XDO)s with the same XDO ratio, the change of the melting point is not so obvious. Figure 1 shows the second heating DSC curve of poly(CHDA–XDO) in N_2 atmosphere with the heating rate of 10°C/min. From the DSC curves, the differences of the melting point among the poly(CHDA–XDO)s do not exceed 1°C. Moreover, the melting points of polymers are not appreciably different for the odd and even carbon atoms in the diols. This can be explained by the random copolymerization in our experiments. The diol segment is randomly distributed in the polymer chain and the segment is not long enough to influence the melting point of polymers.

In addition, the WAXD spectra of the three samples shown in Figure 2 indicate that all the poly(ester anhydride)s are crystalline polymers and the crystallinities are about 50%. The high crystallinity explains why the endothermic peak in DSC is so sharp.

Using a closed Ubbelohde viscometer, the intrinsic viscosities of poly(CHDA–HDO)(80 : 20) and poly(CHDA–EDO)(80 : 20) in DMF at 30°C were determined and the results showed that the intrinsic viscosity of the two samples did not change over 10 days. Another monitor of the intrinsic viscosity of a sample stored in a dehumidifier for 3 months also showed no change. It can be concluded that the poly(ester anhydride) based on cycloaliphatic and XDO is stable in an anhydrous environment at room temperature.

Hydrolytic degradation of polymers

The hydrolytic degradation of poly(CHDA) and poly(CHDA–XDO) is described in Figure 3. All experiments were conducted in 0.1 mol/L pH 7.4 PB at 37°C

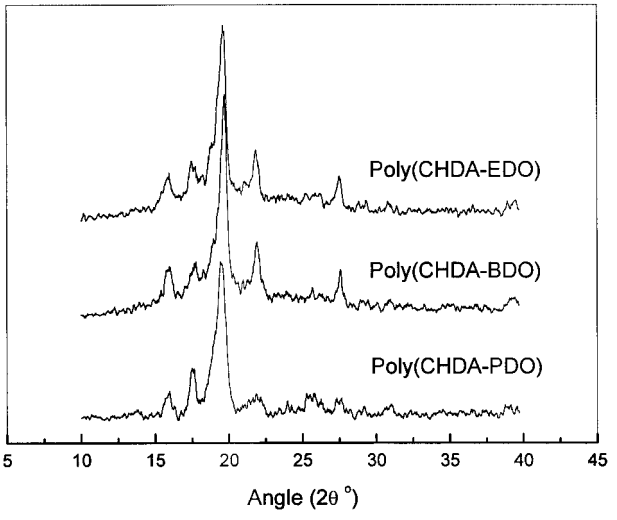


Figure 2 WAXD spectrum of poly(CHDA–XDO)(90 : 10).

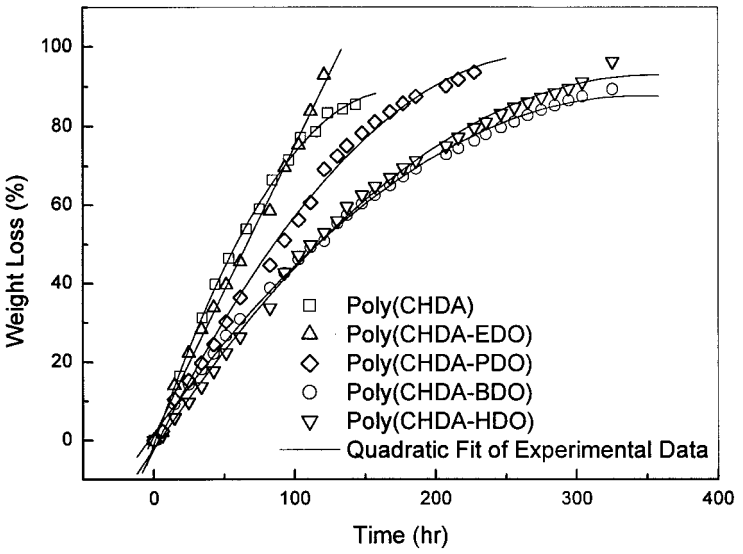


Figure 3 Hydrolytic degradation of poly(CHDA) and poly(CHDA–XDO)(90 : 10).

and the degradation was estimated by weight losses of the samples.

Figure 3 describes the degradation of both the homopolymer poly(CHDA) and the copolymer poly(CHDA–XDO)(90 : 10). Comparing their weight losses, poly(ester anhydride) shows slower degradation than that of poly(CHDA). This is caused by the difference of hydrolytic stability between the two kinds of bonds: it is well known that the ester bond is much more stable than the anhydride bond in water.

Among the various poly(CHDA–XDO)s, the degradation rate decreases in the order: EDO > PDO > BDO > HDO. This is caused by the relative decrease of anhydride bond content as the CH_2 segment lengthens in the polymer main chain.

A quadratic equation fits the experimental data best, as shown in Figure 3. The fit equation can be written as

$$WL = At^2 + Bt + C \tag{1}$$

where WL is the weight loss of polymer, t is the degradation time, A and B are constants. For the initial time, the weight loss of samples is defined as zero, so $C \equiv 0$. WL is defined by

$$WL = \frac{w_0 - w_i}{w_0} \tag{2}$$

where w_i is the weight of polyanhydride at time t and w_0 is the initial weight of sample. Substituting eq. (2) into eq. (1) and rearranging yields

$$w_i/w_0 = 1 - Bt - At^2 \tag{3}$$

where the two coefficients A and B are functions of the degradation rate constant and sample shape parameter.

According to Langer,[28] for the surface erosion of polyanhydrides, the following relationship is applicable:

$$w_i/w_0 = 1 - [1 - k_0 t/r]^n \tag{4}$$

where w_i is the weight of polyanhydrides at time t, w_0 is the initial weight of sample, k_0 is the erosion rate constant, and r is the radius for a sphere or cylinder, or the half-thickness for a slab; $n = 3$ for a sphere, $n = 2$ for a cylinder, and $n = 1$ for a slab. For cylinder polyanhydride samples, $n = 2$; then the equation can be written as

$$w_i/w_0 = 1 - [1 - k_0 t/r]^2 \tag{5}$$

Equations (3) and (5) give the same curve shape in a figure, so we can say that the polyanhydrides show fine surface erosion according this similarity. This conclusion is also proved by observation of the experiments.

In vitro drug delivery

Besides the degradation of poly(ester anhydride), the drug delivery property of poly(ester anhydride) is another important problem to be considered. Thus drug controlled release experiments were carried out, the results of which are shown in Figure 4.

From the curves, all the poly(ester anhydride)s show excellent drug delivery properties and the delivery of ibuprofen from poly(CHDA–EDO)(90 : 10) is

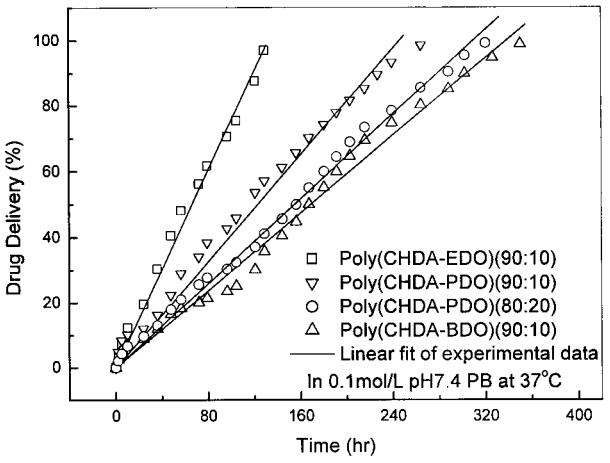


Figure 4 *In vitro* drug delivery of ibuprofen from poly(CHDA–XDO).

the fastest; it is the slowest from poly(CHDA–BDO)(90 : 10). Complete release ranged from 130 and 350 h. Compared to Figure 3, not only is the trend the same as the degradation of poly(ester anhydride) but the drug delivery time is also similar to the complete degradation time. It can be concluded that bulk degradation of polyester anhydride is the determinative factor in the drug delivery of polymers and both the drug delivery and the degradation are decided by the ratio of the number of anhydride bonds to the number of ester bonds in the polymer main chain.

Comparing the drug delivery rate of poly(CHDA–PDO)(90 : 10) and poly(CHDA–PDO)(80 : 20), as shown in Figure 4, the lower PDO content in polymer gives the faster delivery rate. This is further proof of the above-mentioned conclusion.

The experimental data best fit a linear equation. This result is in accord with the surface erosion model in the drug delivery of slab polyanhydride samples; in other words, the polyester anhydride shows excellent zero-order degradation and drug delivery properties. The drug delivery equation can be written as[28]:

$$M_i/M_\infty = \frac{k_0}{c_0 r}\, t$$

where M_i is the amount of drug released from the device at time t, M_∞ is the total amount of drug released when the device is exhausted, k_0 is the erosion rate constant, c_0 is the uniform initial concentration of drug in the matrix, and r is the half-thickness of the slab sample.

From the results, it can be concluded that these poly(ester anhydride)s can release drug at a rate ranging from a few days to more than 10 days. At the same time, the drug delivery range of poly(ester anhydride)s offers the possibility of adjusting drug delivery time by adjusting the ratio of the number of anhydride bonds to the number of ester bonds in the main chain of the poly(ester anhydride)s.

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