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Synthesis and Characterization of Novel Biodegradable Polyamides Containing α-amino Acid

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The polyamides were obtained from 1,6-hexanediamine and diacylchloride which incorporated α-amino acid residues through interfacial polycondensation. High molecular weight ($\eta_{inh} = 1.05$–1.18 dL/g) polymers were produced with high yields. The structure of polyamides was verified by FT-IR and ^{1}H NMR spectra. They showed a remarkable ability to develop high crystallinity with melting temperatures in the range 117–191°C and was stable up to 350°C under nitrogen. Two methods such as alkali hydrolysis (10% NaOH w/v, 80°C) and enzymatic hydrolysis were employed for assessing the susceptibility of these polyamides to degradation. A preliminary investigation of the 5-fluorouracil (5-FU) release characteristics of these polyamides showed that the release rate increased with increasing water absorption of the polymers.

Keywords: Drug release, interfacial polycondensation, polyamide, synthesis, thermal properties

1 Introduction

Synthetic polyamides, being structurally close to natural polypeptides, have often attracted the interest of several research groups, as they already contain nitrogen essential for life growth, and show excellent hydrophilic character, reasonably high melting points and good mechanical properties, even at relatively low molecular weights (1). In recent years, sustained efforts have been devoted to rendering polyamides more degradable, to extend their applications to new fields demanding materials with lower environmental impact or displaying biodegradable and biocompatible properties (2).

In particular, the use of monomers derived from carbohydrates and amino acid in the design of polyamides with enhanced hydrophilicity and biodegradability constitutes an interesting strategy that is being intensively explored (3–7). The introduction of short sequences of appropriate amino acid residues along the chain generates peptide bonds potentially susceptible to enzymatic degradation. Polyamides derived from naturally occurring amino acids can be employed for many different purposes, from medical, pharmaceutical and personal care applications to the domains of agriculture and environment (8). Therefore, they have been the subject of intensive studies and their synthesis is a topic of current interest.

Extensive work has been done to develop biodegradable polyamides containing amino acids and properties of the resultant materials have been found dependent on both the nature and the content of amino acid (9–14). Bailey and co-workers found that nylons containing amino acids linkages such as nylon 26 and nylon 266 were biodegradable (15). Arvanitoyannis et al. synthesized a series of copolyamides using commercially available precursors such as nylon-6,6 prepolymer and various α-amino acids by melt polymerization (16). When the α-amino acid content was higher 15%, the copolyamides turned from semicrystalline to amorphous. The degradation rates of these copolyamides were correlated with the α-amino acid structure and content. Polyamides from succinylsarcosine and ethylenediamine by polycondensation in water using 1-ethyl-3-(3-dimethyl-aminopropyl)-carbodiimide and 1-hydroxybenzotriazole were reported (17). It was found that polyamides could be digested by some enzymes and degraded *in vivo*. Recently, a chemoenzymatic synthesis of polyamides containing amino acids was investigated, leading to polyamides with low yields and low molecular weights due to substrate specificity of the enzyme (18).

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Puiggalí et al. prepared sequential copolymers of glycine and even-even nylons by active ester and interfacial polycondensation methods (19, 20). Higher molecular weight polyamides were obtained by interfacial polycondensation, but this led to two additional steps. Structural studies indicated that glycine residues always tended to adopt their characteristic polyglycine II conformation.

In the present work, we synthesize novel polyamides starting from α-amino acid, sebacoyl chloride and 1,6-hexanediamine through interfacial polycondensation. Because of the low solubilities of amino acids in suitable organic solvents, there are few examples of single phase polycondensation reactions. To overcome this problem, the amino acid can be converted to a more soluble derivative. Here, α-amino acids were amidated with sebacoyl chloride to give N, N′-bis(α-amino acid)sebacoylamide, which was subsequently chlorinated with thionyl chloride, following interfacial polycondensation with 1, 6-hexanediamine to yield polyamides. Synthetic procedures, polyamide characterization and properties, as well as evaluation of *in vitro* biodegradation were given in the following sections. Moreover, a preliminary investigation of 5-fluorouracil (5-FU) release from polyamides was performed.

2 Experimental

2.1 Materials

Glycine, L-alanine, and 2-amino-*n*-butyric acid were purchased from Aldrich, and were used without further purification. Sebacoyl chloride was obtained from Aldrich. It was distilled under vacuum before use. 1,6-Hexanediamine was purchased from Guangzhou Chem. Co. (China) and purified by vacuum sublimation. 5-Fluorouracil (5-FU) was recrystallized twice from deionized water. Other reagents were commercially available and used as received.

2.2 Synthesis

2.2.1 Synthesis of N,N′-bis(α-amino acid)sebacoylamide (I)

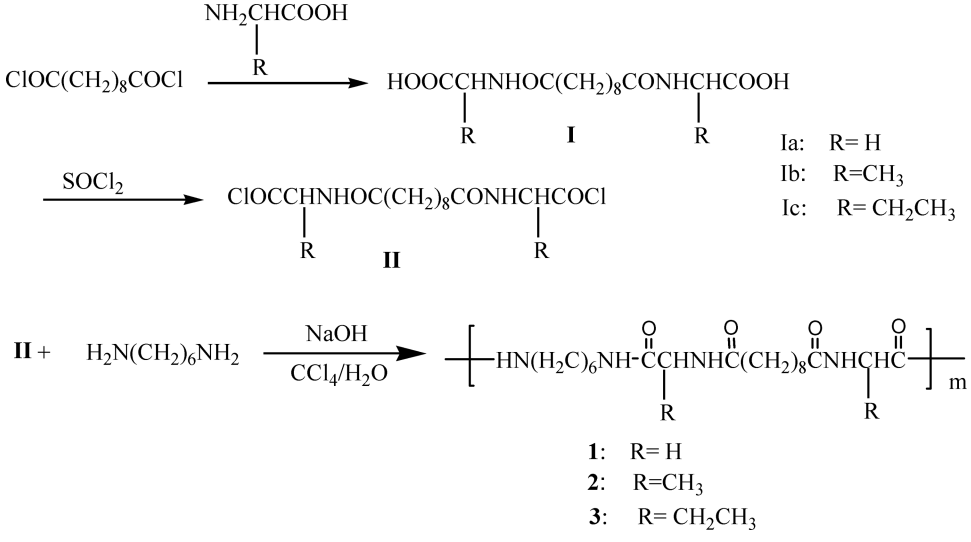
Monomers of N,N'-Bis(α-amino acid)sebacoylamide **I** were prepared as follows. Glycine (0.15 mol) was dissolved in 100 mL mixture solvent of water and acetone (v/v: 1/1), which was adjusted to pH = 9 with 6 mol/L NaOH aqueous solution. Then, a solution of sebacoyl chloride (17.73 g, 0.074 mol) in 150 mL dichloromethane was added at 0–5°C. During the reaction, the reaction solution was maintained at pH 8–9 with a 6 mol/L NaOH aqueous solution. After 6 h, the solution was acidified by HCl to yield after isolation and dry under vacuum. The white precipitate **Ia** was obtained. Monomers of **Ib** and **Ic** were synthesized with the same procedure except glycine was replaced with L-alanine, and 2-amino-*n*-butyric acid, respectively.

2.2.2 Preparation of diacylchloride (II)

Diacylchloride was prepared by refluxing N,N'-bis(α-amino acid)sebacoylamide **I** (0.25 mol) in thionyl chloride (1.60 mol) for 6 h. The excess thionyl chloride was removed, and diacylchloride (**II**) was distilled under vacuum.

2.3 Polymerization

A typical procedure for preparing polyamides is described as follows (shown in Scheme 1). Diacylchloride (15 mmol) was dissolved in 150 mL of carbon tetrachloride. Under vigorous stirring, the solution was rapidly poured into a 150 mL blender containing a aqueous solution of 1,6-hexanediamine 1.74 g (15 mmol), and sodium hydroxide,



Sch. 1. Synthesis of copolyamides.

1.2 g (30 mmol). The precipitated polymer was washed with water, carbon tetrachloride, acetone and diethyl ether, respectively, and finally dried at 80°C in vacuum overnight.

2.4 Instruments

The intrinsic viscosity of the polymer was determined with a Cannon-Ubbelohde microviscometer at a temperature of 25°C; *m*-cresol was used as a solvent. Infra-red spectra were obtained on KBr pellets using a Perkin-Elmer 783 spectrophotometer in the 4000–500 cm^{-1} range.^{1}H-NMR spectra were obtained in deuterated dimethyl sulfoxide using a Bruker AMX-300 spectrometer. Chemical shifts are reported in parts per million (δ) downfield from internal tetramethylsilane (TMS). The thermal behavior of the polymer was investigated by differential scanning calorimetry (DSC) using a Perkin-Elmer DSC-4 machine at a heating rate of 10°C/min from −80 to 300°C in a nitrogen atmosphere. The temperature was calibrated with an indium standard. Thermogravimetric analysis (TGA) was carried out with Perkin-Elmer TGA-6 under nitrogen atmosphere at a heating rate of 10°C/min. The determination of the molecular-weight distribution of the polyamides was carried out with Gel permeation chromatography (GPC) measurements. A Waters (USA) GPC system, supplied with a Styragel column, was used and *m*-cresol as an eluent at a rate of 0.6 $mL.min^{-1}$. The calibration of the GPC was conducted with a series of polystyrene samples of determined molecular weight.

2.5 Biodegradability Experiments

2.5.1 Alkali hydrolysis

200 mg of powdered sample was kept in bottles filled with a100 mL of 10% NaOH w/v aqueous solution for all the samples at 80°C. After the immersion time, the retrieved samples were thoroughly rinsed with water, dried to constant weight in vacumm at 80°C for 24 h, and stored over $CaCl_2$ before analysis.

2.5.2 Enzymatic hydrolysis

Enzymatic degradation studies were conducted at 37°C by using papain (Merck). Polymer powder sample (initial weight, 200 mg) were placed in small bottles containing 10 mL of the enzymatic medium. The enzymatic media consist of a sodium phosphate buffer (pH 7.2) containing sodium azide (0.03% wt%) and 1 mg of the appropriate papain. All enzymatic solutions were renewed every 72 h because of enzymatic activity loss. After the immersion time, the enzyme was inactivated by adding 1 mL of 1 mol/L HCl and the polymer weight loss was measured after centrifugation and drying to constant weight *in vacuo*.

The weight losses (D) of all the samples after their alkali and enzyme treatment were calculated by the following equation:

$$D(\%) = (W_0 - W_d)/W_0 \times 100 \quad (1)$$

Where W_0 is the weight of the dried specimen before hydrolysis and W_d is the weight of the dried specimen after hydrolysis. Each determination was obtained by averaging the results of three measurements.

2.6 Water Absorption

Water absorption was used to evaluate the hydrophilicity of polyamides obtained. A polyamides thin pellet was prepared by compression molding, and was dried *in vacuo* to constant weight (W_d), following by placed in deionized water at 37°C for 3 h. After that, the thin pellet was withdrawn and dried by rapidly dipping in ethanol (95%), and then the wet weight was recorded (W_w). Equilibrium water absorption (q) was calculated according to the following formula:

$$q = (W_w - W_d)/W_d \quad (2)$$

2.7 Controlled Release of 5-FU

A mixture of polyamides containing 5-FU (10 wt%) was pressed into a disc (15 mm in diameter with 0.6 mm thickness) under a pressure of 21.0 kPa. The disc was immersed in a vial with 0.1 M PBS (pH 7.4). The vial was sealed with a rubber septa and placed in a shaking apparatus at constant temperature 37°C. The immersion PBS was refreshed regularly, and the UV absorbency of 5-FU at $\lambda = 266$ nm was recorded.

3 Results and discussion

3.1 Monomer synthesis

The outline of polyamide synthesis is illustrated in Scheme 1. The general procedure includes three steps: the preparation of carboxyl-terminated compound containing α−amino acid residues − N,N′−bis(α−amino acid)sebacoylamide (**I**), then preparation of the corresponding diacylchloride (**II**), and the polycondensation of monomers **II** and 1,6-hexanediamine.

Monomers (**I**) were prepared by the reaction of sebacoyl chloride with glycine, L-alanine and 2-amino-*n*-butyric acid, respectively. They are confirmed by both FTIR and ^{1}H-NMR spectra, as detailed in Table 1. The representative FTIR and ^{1}H-NMR spectra of monomer **Ib** are shown in Figure 1(a) and Figure 2(a), respectively. In Figure 1(a), the N-H stretching band and the carbonyl stretching band could be observed at 3327 cm^1 and at 1697 cm^1, respectively.

Table 1. Yield and spectroscopic data for monomer **Ia–Ic**

Monomer	*Yield (%)*	*IR data (cm^{-1})*	*^{1}H-NMR data (ppm)*
Ia	72.1	3329 (amide A)	12.15 (2H,—COO*H*)
		1698 (carboxyl CO stretching)	7.93 (2H, —N*H*—C(O)—)
		1646 (amide I)	4.28 (4H, —CH_2COOH)
		1531(amide II)	2.31 (4H, —C(O)CH_2)
		1465 (amide III)	1.56, 1.25 (12H, CH_2(CH_2)$_6$—)
Ib	67.2	3327 (amide A)	12.10 (2H,—COO*H*)
		1697 (carboxyl CO stretching)	7.87 (2H, —N*H*—C(O)—)
		1647 (amide I)	4.21 (2H, —C*H*(CH_3)—COOH)
		1528 (amide II)	2.28 (4H, —C(O)CH_2)
		1460 (amide III)	1.54, 1.21 (12H, CH_2(CH_2)$_6$—)
			1.43 (6H, —CH_3)
Ic	64.3	3321 (amide A)	12.05 (2H,—COO*H*)
		1689 (carboxyl CO stretching)	7.81 (2H, —N*H*—C(O)—)
		1649 (amide I)	4.25 (2H, —C*H*(CH_2CH_3)—COOH)
		1518 (amide II)	2.23 (4H, —C(O)CH_2)
		1467 (amide III)	1.54, 1.24 (16H, CH_2(CH_2)$_6$—, —CH_2CH_3)
			1.34 (6H, —CH_3)

The broad band at 3446 cm^1 was assigned to O-H stretching band of carboxyl groups. The characteristic amide stretching bands at 1647, 1528 and 1460 cm^1 could be observed as well. From Figure 2(a), the single peak at 12.10 ppm is assigned to a proton of the carboxyl group. The peak at 7.87 ppm, attributing to proton of –N*H*C(O)- groups, can be observed. The resonances at 2.28 ppm belong to methylene protons of –CH_2C(O)- unit, while the peaks between 1.54 and 1.21 ppm are assigned to remaining methylene protons of sebacoyl chloride units. The peaks at 4.21 and 1.43 ppm attribute to protons of –C*H*- and -CH_3 groups of alanine units.

To improve the reactivity of **I**, the resulting dicarboxylic acid compound is reacted with excess thionyl chloride to convert all the carboxyl ends into acyl chloride ends, which is confirmed by FTIR and ^{1}H-NMR analysis. The representative FTIR and ^{1}H-NMR spectra of diacylchloride of **IIb** are shown in Figure 1(b) and Figure 2(b), respectively. The broad band at 3446 cm^1 assigned to O-H stretching band disappears, showing all the carboxyl ends have been converted into acylchloride ends. Moreover, the carbonyl stretching band is observed at 1725 cm^1 due to the presence of electron-withdrawing acylchloride groups. In Figure 2(b), resonances of protons of –C*H*- group shift to lower

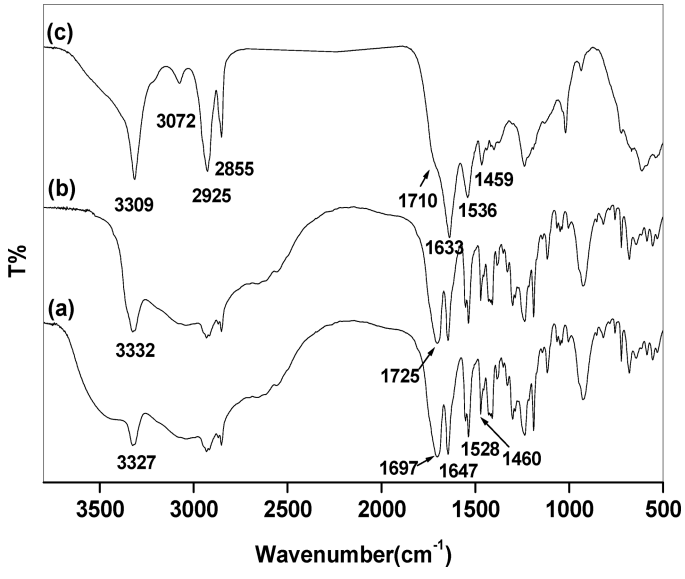


Fig. 1. FTIR spectra of (a) monomer **Ib**, (b) diacylchloride **IIb**, and (c) Sample **2**.

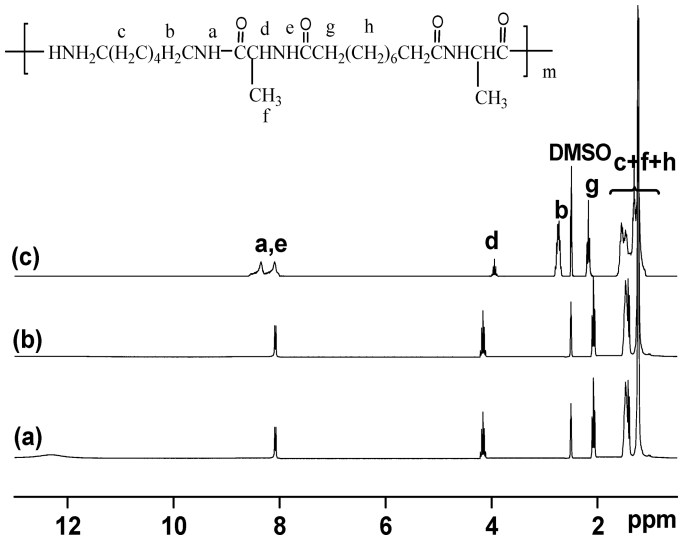


Fig. 2. ^{1}H-NMR spectra of (a) monomer **Ib**, (b) diacylchloride **IIb**, and (c) Sample **2**.

Table 2. Synthesis of polyamides

Sample	*α—amino acid*	*Yield (%)*	η_{inh} *(dL/g)*	M_n *(g/mol)*	T_m^a *(°C)*	X_c^b *(%)*	$T_{d,5}^c$*(°C)*	*q*
1	glycine	83	1.05	17420	191,183	39.2	383	3.51 ± 0.04
2	L-alanine	79	1.12	19100	182, 151	31.5	374	2.45 ± 0.03
3	2-amino-*n*-butyric acid	82	1.18	22490	171, 117	28.7	357	1.97 ± 0.04

[a]When multiple peaks are observed, the less intense peaks are indicated by italics.
[b]Percentage crystallinity (X_c) is determined from DSC.
[c]Temperature corresponds to decomposition lower than 5%.

field (4.36 ppm). The same trend is observed for resonances of CH_3 groups (1.48 ppm) of alanine residues.

3.2 Syntheses and Characterization of Polyamides

The polyamides were prepared by interfacial polycondensation between 1,6-hexanediamine and diacylchloride (**II**) which incorporated α-amino acid residues. Table 2 summarizes the characteristics of the polymers. In fact, high yields in the range of 79–83% are achieved in all cases, which is similar with results reported by Puiggali et al. (19–20). Moreover, high intrinsic viscosity ranging from 1.05 to 1.18 dL/g is obtained and the values of intrinsic viscosity are found to depend, as reported elsewhere (21, 22), on the molecular weights of the introduced α-amino acid. That is, the higher molecular weight of the α-amino acid, the higher intrinsic viscosity values are observed. As compared with data reported previously (19, 20), our results reported here conveniently gave higher molecular weight polyamides including three steps under a mild condition. The reason may be that in interfacial polycondensation process the irreversible polymerization of two fast-reacting intermediates occurs near the interface of the two phases of a heterogeneous liquid system. And the reaction of 1,6-hexanediamine and diacid chlorides monomers **II** is believed to be rapid enough to minimize the side reaction. As shown in Table 2, number-average molecular weights (M_n) of all samples measured by GPC ranged from 22490 to 17420 g/mol.

FT-IR and NMR spectroscopic methods are used to confirm the polymers structure and the resulting data are shown in Table 3. FT-IR spectra of all polymers show characteristic methylene and amide absorption bands. As an example, the representative spectrum of Sample **2** derived from L-alanine has been reproduced in Figure 1(c). It shows the characteristic absorptions bands corresponding

Table 3. Spectroscopic data for synthesized polyamides

Polymer	*IR data (cm⁻1)*	*^{1}H NMR data (ppm)*
Sample **1**	3298(amide A)	8.39 (2H, —N*H*—$(CH_2)_6$—)
	3082 (amide B)	8.12 (2H, —N*H*C(O)—CH_2—)
	2945 and 2855 (CH_2 stretching)	4.12 (4H, —NHC(O)—C*H*$_2$—)
	1638 (amide I)	3.04 (4H, —NH—C*H*$_2$ $(CH_2)_4$—)
	1541 (amide II)	2.34 (4H, —C(O)C*H*$_2$)
	1453 (amide III)	1.41 (8H, —NH—CH_2 (C*H*$_2$)$_4$—)
		1.61–1.26 (12H, —C(O)CH_2(C*H*$_2$)$_6$—)
Sample **2**	3309 (amide A)	8.34 (2H, —N*H*—$(CH_2)_6$—)
	3072 (amide B)	8.01 (2H, —N*H*C(O)—CH(CH_3)—)
	2955 and 2855 (CH_2 stretching)	3.95 (2H, —NHC(O)—C*H*(CH_3)—)
	1633 (amide I)	2.75 (4H, —NH—C*H*$_2$ $(CH_2)_4$—)
	1536 (amide II)	2.19 (4H, —C(O)C*H*$_2$)
	1459 (amide III)	1.45 (6H, —NHC(O)—CH(C*H*$_3$)—)
		1.36 (8H, —NH—CH_2 (C*H*$_2$)$_4$—)
		1.55–1.24 (12H, —C(O)CH_2(C*H*$_2$)$_6$—)
Sample **3**	3312 (amide A)	8.30 (2H, —N*H*—$(CH_2)_6$—)
	3079 (amide B)	7.96 (2H, —N*H*C(O)—CH(CH_2CH_3)—)
	2959 and 2851 (CH_2 stretching)	3.95 (2H, —C*H*(CH_2CH_3)—)
	1632 (amide I)	2.64 (4H, —NH—C*H*$_2$ $(CH_2)_4$—)
	1545 (amide II)	2.19 (4H, —C(O)C*H*$_2$)
	1451 (amide III)	1.51 (4H, —C*H*$_2$$CH_3$)
		1.29 (6H, —CH_2C*H*$_3$)
		1.36 (8H, —NH—CH_2 (C*H*$_2$)$_4$—)
		1.55, 1.24 (12H, —C(O)CH_2(C*H*$_2$)$_6$—)

to the amide (3309, 3072, 1633,1536 and 1459 cm^1) and methylene (2925 and 2855 cm^{-1}) groups. The absorption band at 1710 cm^1 is due to the presence of the amino acid moiety. The peak at 1444 cm^{-1} attributed to δ_{CH3} is also observed.

More detailed elucidation of the structure of the polymers can be obtained from ^{1}H-NMR spectrum. Data from ^{1}H-NMR spectroscopy are fully consistent with the anticipated chemical composition. Figure 2(c) shows the ^{1}H-NMR spectrum of Sample **2**. As compared to Figure 2(a) and Figure 2(b), new peaks at 8.34, 2.75 and 1.36 ppm are detected. Peaks (a) (8.34 ppm), (b) (2.75 ppm) and, (c) (1.36 ppm) are assignable to–N*H*CH_2-, –NHC*H*$_2$- and remaining methylene protons of 1,6-hexanediamine units, respectively. Peaks (e) (8.01ppm), d (3.95 ppm) and f (1.45 ppm) belong to protons of -N*H*-C(O)-, -C*H*(CH_3)-, -CH(C*H*$_3$)- in L-alanine residues. Peaks (g) (2.19 ppm) and (h) (1.55, 1.24 ppm) are assigned to -C(O)C*H*$_2$- and remaining methylene protons of sebacoyl chloride unit. From FTIR and ^{1}H NMR spectra, it confirms that anticipated polyamides have been successfully obtained.

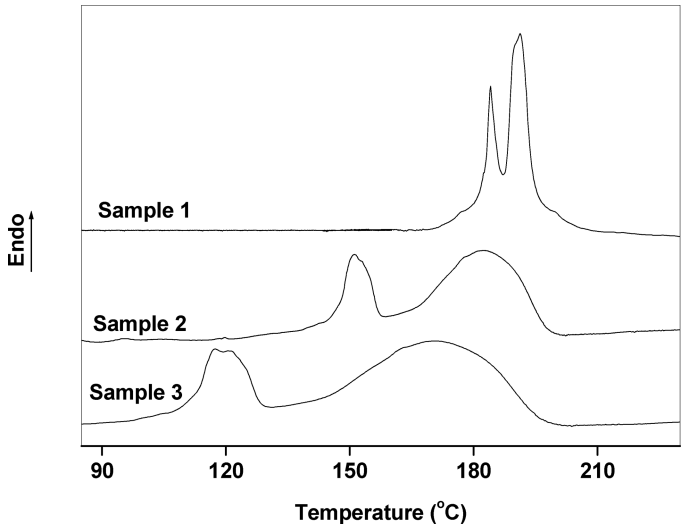


Fig. 3. DSC curves for polyamides.

3.3 Thermal Properties of Polyamides

As usual in polyamides (24), a double fusion peak associated with different crystalline forms or different crystallite size is observed for all the polyamides in the DSC heating runs, as shown in Figure 3. The melting point (T_m) data are summarized in Table 2. It can be clearly seen that the polyamides with bulky side groups have lower T_m's. Sample **3** derived 2-amino-*n*-butyric acid showes the lowest T_m's. The T_m's lie in the following order: Sample **1**> Sample **2**> Sample **3**. The same trend is observed in polyesteramides containing amino acid residue reported (25). As shown in Table 2, a crystallinity of ca. 39.2% could be calculated for Sample **1**, using as a first approximation the reported group contribution to the heat of fusion of the amide, methyl and methylene groups (26). However, Sample **2** and Sample **3** showed lower percentage crystallinity of 31.5% and 28.7%, respectively. The above effect may be attributed to the presence of bulky side groups, which interferes with the hydrogen bonding formation, thus preventing (at least in part) crystallization and increasing free volume of amorphous regions. No glass transition is detected in DSC thermograms for all the polyamides synthesized.

Thermogravimetric analysis (TGA) is employed for studying the thermal 'resistance' of these polyamides. Table 2 summarizes the TGA results in terms of temperature corresponding to a decomposition lower than 5% ($T_{d,5}$), which is higher than 350°C for all the polyamides. These values were clearly higher than the melting temperature, and consequently the polymer was stable through fusion and can be processed from the melt state.

3.4 Solubility of Polyamides

Table 4 indicates the relative solubility of polyamides. As can be seen, all these polyamides are soluble in 98%-H_2SO_4 and polar aprotic solvents such as NMP and DMF, while insoluble in common organic solvents like methanol, acetone, and chloroform. Moreover, *m*-cresol is found to be a good solvent for all polyamides. DMSO dissolves Sample **2** and Sample **3**, while Sample **1** just swells in this solvent. It is well known that the incorporation of bulky side groups produces a chain separation effect lowering the chain packing, which improves solubility. As compared to Sample **2** and Sample **3**, both the increase in melting point and the decrease in solubility for Sample **1** may be caused by its less bulky side groups and more compact structure.

Table 4. Solubility of polyamides[a]

Sample	*98%—H_2SO_4*	*m—cresol*	*NMP*	*DMF*	*DMSO*	*CH_3OH*	*Acetone*	*$CHCl_3$*
1	+	+	+	+	±	−	−	−
2	+	+	+	+	+	−	−	−
3	+	+	+	+	+	−	−	−

[a] +: soluble; ±: partially soluble or swelling; −: insoluble.

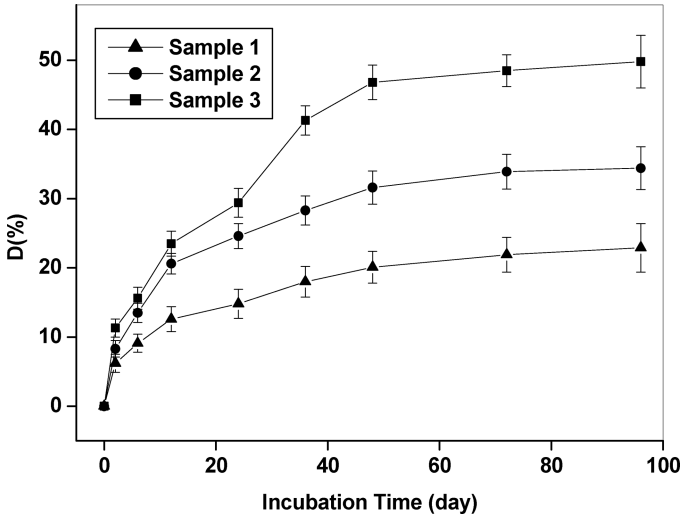


Fig. 4. Weight changes of polyamides amples during *in vitro* alkali hydrolysis (10% w/v NaOH, 80°C) (n = 3).

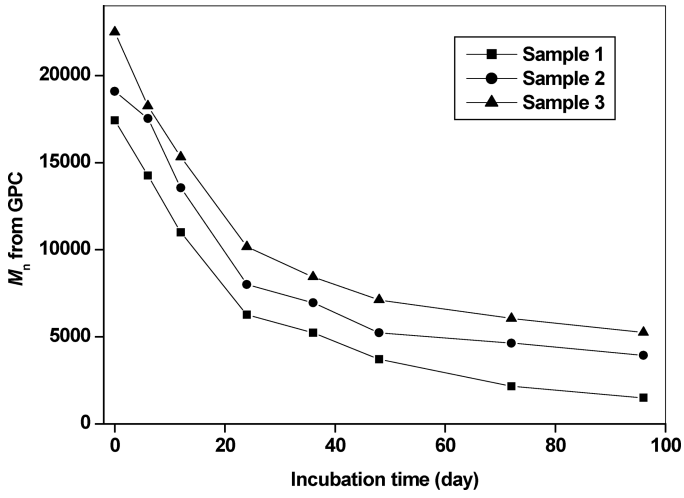


Fig. 5. Molecular weight decrease vs immersion time to NaOH (10% w/v NaOH, 80°C).

3.5 In Vitro Degradation of Polyamides

The degradability of the polyamides is investigated in an alkali and enzyme solution by using powdered samples. It is believed that *in vitro* degradation of polyamides in aqueous media proceeds via a random bulk hydrolysis of amide bonds in the polymer chain (11). The products of degradation and in particular the carboxylic acids catalyze the degradation process. The weight losses that occurred in polyamides during the tests of alkali hydrolysis (10% w/v NaOH, 80°C) are presented synoptically in Figure 4. The aqueous alkali solution is thought to initiate a 'homogeneous' degradation mechanism. The weight of all samples incubated in alkali solution starts to decrease continuously with time. It can be seen that the effect of alkali hydrolysis is stronger for the polyamides containing bulky side groups. Sample **3** shows the fastest and largest weight loss (49.8% weight loss at day 96), while weight loss (D) of 34.4 % and 22.9% were obtained for Sample **1** and Sample **2** after the same degradation time, respectively.

Degradation of these polyamides was also monitored by GPC analysis, to determine the changes in number-average molecular weights (M_n). The apparent molecular weights of all samples as a function of immersion time to NaOH (10% w/v NaOH, 80°C) are shown in Figure 5. The hydrolysis of all samples is characterized by a continuous and rapid decrease in molecular weight during the first period of degradation and a slow decrease giving low molecular weight fragments in the final stages. This result may be explained by the fact that, at the beginning of alkali hydrolysis experiment, hydroxyl ion will attack randomly the amide linkages of the initially large polyamides. This is likely to affect the molecular weight much more intensely than in the final steps of the degradation, when the hydroxyl ion attacks smaller fragments. A substantial decrease in the molecular weights of polyamides is due to cleavage of covalent bonds along polymer chain. The results of weight loss and molecular weights decrease indicated synthesized polyamides were degradable in alkali conditions.

The susceptibility of these polyamides to enzymatic attack is verified with papain. Due to the fact that enzymatic degradation is a surface process, the viscosity of samples is practically constant during exposure to the media (27). Hence, only the weight loss of the remaining samples is evaluated. The weight-change profiles of all polymers degradation are presented in Figure 6. All polymers are found to be enzymatically degraded by papain, and the weight loss after day 120 ranges from 35.9% to 62.8%. Note, that in Sample **3**, a significant change weight loss is found after only 15 days of exposure, probably due to the fact that the weight loss is an indication of degradation only when it has

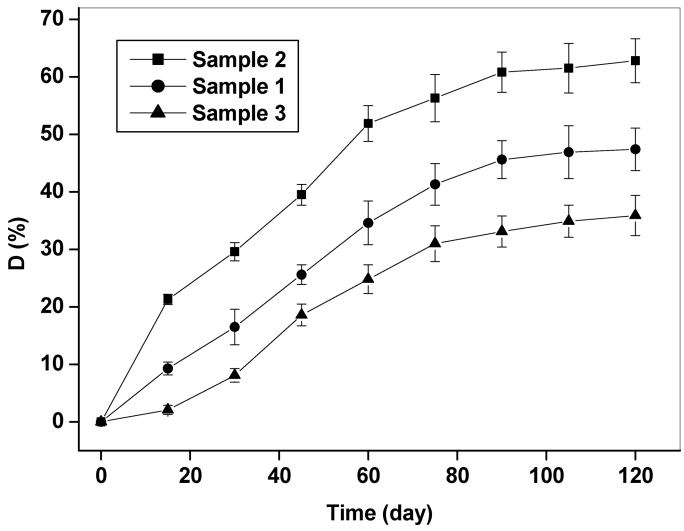


Fig. 6. Weight changes of polyamides samples during *in vitro* enzymatic degradation with papain (n = 3).

occurred in a sufficient extension to produce very small and soluble molecules. Over the 120 day study period, Sample **2** consistently has the highest enzymatically degradation rate and extent, and Sample **3** has the lowest rate and extent. It has been found that polymer containing alanine degrade faster than polymer based on glycine by using papain (27). In this study, the same trend is observed. A value of weight loss close to 62.8 % is determined after 120 d of exposure for Sample **2**, whereas only 47.7% of the Sample **1** is degraded after the same degradation time. It is obvious from the reported data that polyamides with a different susceptibility to enzymatic degradation can be obtained by varying their amino acid composition.

It is proposed that enzyme immobilization onto the polymer film surface may also be the factor that contributes to the different rate of enzyme catalyzed hydrolysis of polymers (28). Akashi et al. reported the amount of the absorbed enzyme toward surface effected enzymatic hydrolysis of a layer by layer assembly derived from chitosan and dextran sulfate (29). It has been found that spontaneous enzyme immobilization (surface aqueous solutions) onto the polymer film surface causes polymers to biodegrade at a relatively higher rate (28, 30). Moreover, the capability of surface immobilization of enzymes onto polymers is related to side groups of polymers. For example, it showed that poly(ester amide)s composed of α-amino acids with fatty lateral substituents had poor or none enzyme surface immobilization capability, whereas those poly(ester amide)s having the high hydrophobic benzyl side groups showed considerable enzyme surface immobilization (30). Furthermore, the rate and extent of the weight loss of the polymers by the enzymatic hydrolysis also depended on the solubility of the hydrolysis products because the polymer surface could be covered by unreactive biodegradation products that would retard the further biodegradation of the polymers if the biodegradation products were insoluble (25, 31). It is thought that there exists a critical length of polymer chain that is soluble according to the chemical structure of the polymer. Thus, these differences in enzymatic hydrolysis of polyamides could be attributed to combined factors discussed above, such as polymer molecular weight, different activity of papain toward different amino acids-based polyamides, enzyme immobilization onto the polymer surface and solubility of the hydrolysis products, et al.

3.6 5-FU Release from Polyamides

For controlled release devices, the equilibrium water absorption of polyamides is of primary interest. Equilibrium water absorption in PBS at 37°C is reached with 2 h due to the hydrophilic nature of the amide segments. As shown in Table 2, the equilibrium water absorption (q) increased with decreasing bulk of side group in polyamides. An increase in side groups of polyamides from H, CH_3 to CH_2CH_3 results in a decrease in q from 3.51±0.04, 2.45±0.03 to 1.97±0.04, respectively.

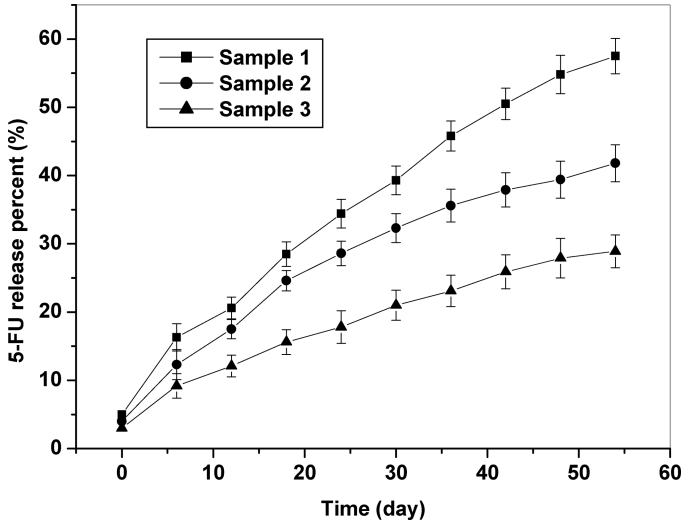


Fig. 7. Release of 5-FU in PBS at 37°C from polyamides (n = 3).

A preliminary investigation is performed on the suitability of the polyamides as a matrix for the controlled release of 5-FU. It is well known that 5-FU has a strong antitumor activity, however, it is accompanied by undesirable side effects. Release profiles of 5-FU from polyamides are presented in Figure 7. The amount of 5-FU released is determined on a UV spectrometer. The release of 5-FU from all the polyamides is well controlled and characterized by almost constant release. After 54 days, 57.5% of 5-FU is released from Sample **1,** whereas Sample **2** and Sample **3** release 41.8% and 23.9 %, respectively. This indicates that the decreased bulk in side groups in the polyamides enhances hydrophilicity and thus results in faster release rates of 5-FU. Another factor that might influence the release rate is the polymer molecular weight. It has been found that the diffusion rate increases with decreasing polymer molecular weight. Thus, the higher intrinsic viscosity of Sample **3** compared with Sample **1** and Sample **2** may contribute to the fact that 5-FU release through Sample **3** is lower than others. These results imply that the rates of drug release can be controlled by adjusting the component of the polyamides.

4 Conclusions

Three polyamides using sebacoyl chloride, 1,6-hexanedi amine and α-amino acids (glycine, L-alanine and 2-amino-*n*-butyric acid) were synthesized and characterized. The DSC and TGA measurements demonstrated the obtained polymers were crystalline and stable up to 350°C under nitrogen. The introduction of the bulky pendent groups into the polyamides backbone led to a decrease in melting point and improved solubility in organic solvents. The susceptibility of polyamides to degradation was confirmed by alkali hydrolysis and enzymatic hydrolysis. A preliminary investigation of 5-FU release from polyamides showed that the

5-FU release rate could be controlled by hydrophilicity of the polyamides.

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