# The Effect of Substitution Levels on the Luminescent and Degradation Properties of Fluorescent Poly(ester-anhydride)s

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**ABSTRACT:** In this work, two kinds of diacid monomers were synthesized by a convenient scheme, where 4-hydroxy-3-methoxybenzoic acid (vanillic acid) or 4-hydroxy-3,5-dimethoxybenzoic acid (syringic acid) directly condensated with succinic chloride. Corresponding polyanhydrides were obtained by melt polycondensation. Copolyanhydrides composed of the new monomers and sebacic acid (SA) were further prepared and characterized by NMR, DSC, and fluorometer. The two new kinds of polyanhydride emit strong fluorescence and have similar fluorescent spectra to poly(di(*p*-carboxyphenyl) succinate anhydride) (P(dCPS)). The emission wavelength ($\lambda_{em}$) of the copolymers could be tuned by the excitation wavelength ($\lambda_{ex}$). Degradation rate of the copolyanhydrides decreased as dMOCPS or ddMOCPS fraction increased, and the degradation duration could be modulated from several days to more than 3 months. It addition, the copolyanhydrides displayed typical surface-degradation characteristics. © 2006 Wiley Periodicals, Inc. J Appl Polym Sci 100: 1214–1221, 2006

**Key words:** poly(ester-anhydride); polycondensation; copolymerization; fluorescence; degradation

## INTRODUCTION

Within the last two decades, wide attention has been paid to biodegradable polymers for a variety of biomedical applications, such as surgical sutures, orthopedic implants, scaffolds and drug depots for controlled release.[1] Compared with other biomaterials, polyanhydrides are a class of biodegradable polymers, which have hydrophobic backbone with hydrolytically labile anhydride linkages.[2] In 1980, Langer was the first to take an advantage of the hydrolytically unstable nature of polyanhydride for sustained release of drugs and utilized these polymers for constructing various medical devices.[3] The structure of polyanhydride can be conveniently tailored to get different properties for various applications. For example, the mechanical strength of polyanhydride was greatly improved by introduction of imide groups into polymer backbone or photo-crossing of double-bond existing in the backbone.[4–7] Mathiowitz et al. found a novel class of hydrophobic microspheres with strong bioadhesivity, which were based on rapidly-degradable poly(fumaric-*co*-sebacic anhydride) (P(FA:SA)) and could enhance oral bioavailability of bioactive agents such as proteins and DNA.[8–11]

In our previous work, we initially found a class of polyanhydrides and copolyanhydrides displaying strong fluorescent properties.[12–15] Recently, our group synthesized new polyanhydrides, poly(di(*p*-carboxyphenyl)succinate anhydride) (P(dCPS)) using *p*-hydroxy benzoic acid as an initial substance. Similar fluorescent properties were observed compared to previous systems. The maximum emission wavelength varies with the excitation wavelength, 480 and 520 nm with the excitation wavelength at 470 and 430 nm at 356 nm.[16] But, the copolyanhydrides with dCPS content more than 50% could not be dissolved in common organic solvents, which limited their applications. To circumvent the shortcoming and find fluorescent polyanhydrides with new properties, we synthesized two diacids by the same method using 4-hydroxy-3-methoxybenzoic acid (vanillic acid) and 4-hydroxy-3,5-dimethoxybenzoic acid (syringic acid) as initial substances. Vanillic acid and syringic acid exit in natural plants and show no toxicity to humans.[17–21] They also show antimicrobial activity.[22,23] The corresponding polyanhydrides, (poly(di(3-methoxyl-*p*-carboxyphenyl) succinate anhydride) (PdMOCPS), and poly(di(3,5-dimethoxyl-*p*-carboxyphenyl) succinate anhydride) (PddMOCPS)), as well as their copolymers with sebacic acid (SA), were obtained by melt polymerization. We evaluated the influence of polymer structure on solubility, fluores-

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cence, and degradation with introduction of methoxy in repeat units. Those new polyanhydrides showed similar fluorescent spectra to PdCPS. The copolymers with less than 70% PdMOCPS can be dissolved in common organic solvents, such as chloroform. In this article, the synthesis, characterization, fluorescence properties, and in vitro degradation of the two fluorescent poly(anhydride-ester)s are reported.

## EXPERIMENTAL

### Materials

Sebacic acid was obtained from Shanghai Chemical (Shanghai, China). Succinic chloride, 3-methoxyl-*p*-hydroxy benzoic acid, and 3,5-dimethoxyl-*p*-hydroxy benzoic acid were purchased from Aldrich (Milwaukee, WI). Tetrahydrofuran (THF), pyridine, dimethyl formamide (DMF), chloroform, and petroleum ether were dried over $CaH_2$. All other reagents were used as received.

### Methods

IR spectra were recorded on a Bruker Vector 22 Spectrometer. Samples were either film cast in chloroform onto NaCl plates or pressed into KBr pellets. NMR spectra were obtained on a Bruker DMX-500 NMR spectrometer operating at 500 MHz. Photoluminescence spectra were recorded at room temperature on a fluorescence spectrophotometer (Hitachi F-4000). The bandpass of the monochromator was kept at 4 nm. The scan rate was 10 nm/s. Molecular weight of the polyanhydrides was estimated on a gel-permeation chromatography (Waters GPC Model 208), using THF as solvent (1.5 mL/min) and narrow molecular weight polystyrene (Polysciences, Dorval, Canada) as the standard in the molecular weight range of 3250–87,000. Styragel HR5, HR4, HR3, and HR1 columns in series were adopted. Thermal analysis was performed on a thermal analysis system (Perkin–Elmer, Pyris-1) at heating rate of 10°C/min. Glass-transition temperatures ($T_g$) were calculated as half $C_p$ extrapolated. Morphology of the polymers was observed with a Stereoscan 260 scanning electron microscopy. Samples for SEM were dried under vacuum, mounted on metal stubs, and sputter-coated with gold–palladium for 10 min.

### Di(3-methoxyl-*p*-carboxyphenyl) succinate (dMOCPS) synthesis

3-Methoxyl-*p*-hydroxy benzoic acid (13.4 g, 0.08 mol) was dissolved in a mixed solvent of THF (70 mL) and pyridine (36 mL). Succinic chloride (4.8 mL, 0.04 mol) was added dropwise to the above solution, with magnetic stirring under dry nitrogen atmosphere at room temperature. The mixture became violet red and a large amount of precipitates were generated. The addition of succinic chloride occurred over 40 min, and the reaction continued for further 2 h. The mixture was poured into ice water, and hydrochloric acid was used to acidify the mixture to pH <2; then, the precipitates were recovered by filtration and dried in vacuum. The crude product was purified by recrystallization from acetic acid. mp: 233°C.

IR (KBr, $cm^{-1}$): 1762 (ester C═O), 1690 (acid C═O), 1604 and 1507 (acid C═C). $^1$H-NMR (DMSO-$d_6$): $\delta$ = 7.57–7.62 (m, 4H, Ar), 7.19–7.21 (d, 2H, Ar), 3.81 (s, 6H, $CH_3$), 2.99 (s, 4H, $CH_2CH_2$). Analytically calculated for $C_{20}H_{18}O_{10}$:C, 57.42; H, 4.31. Found: C, 57.47; H, 4.33.

### Di(3,5-dimethoxyl-*p*-carboxyphenyl) succinate (ddMOCPS) synthesis

3,5-Methoxyl-*p*-hydroxy benzoic acid (15.9 g, 0.08 mol) was dissolved in a mixed solvent of THF (70 mL) and pyridine (36 mL). 4.8 mL Succinic chloride (4.8 mL, 0.04 mol) was added dropwise to the above mentioned solution, with magnetic stirring under dry nitrogen atmosphere at room temperature. The mixture became violet red and a large amount of precipitates were generated. Succinic chloride was added over 40 min, and the reaction continued for additional 2 h. The mixture was poured into ice water, and chlorhydric acid was used to acidify the mixture to pH <2; then, the precipitates were recovered by filtration and dried in vacuum. The crude product was purified by recrystallization from acetic acid. mp: 274°C.

IR (KBr, $cm^{-1}$): 1758 (ester C═O), 1689 (acid C═O), 1603, 1503 (aromatic C═C). $^1$H-NMR (DMSO-$d_6$): $\delta$ = 7.29 (s, 4H, Ar), 3.80 (s, 12H, $CH_3$), 2.97 (s, 4H, $CH_2CH_2$). Analytically calculated for $C_{22}H_{22}O_{12}$:C, 55.23; H, 4.60. Found: C, 55.29; H, 4.63.

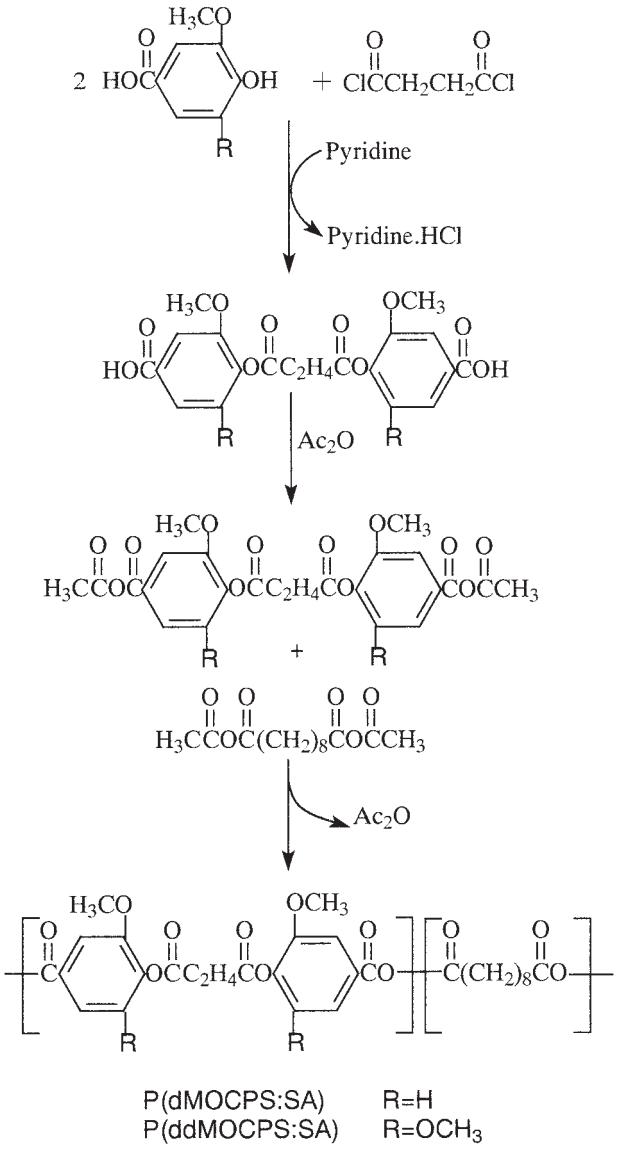
### Prepolymer synthesis

dMOCPS prepolymer was prepared by refluxing 10 g of the monomer in 100 mL of acetic anhydride under dried nitrogen atmosphere over 2 h. The reaction mixtures were then evaporated to dryness at 50°C. Anhydrous ether was added to the solid to extract acetic anhydride residue, and the resulting mixture was swirled overnight; the prepolymer was filtrated and dried to yield prepolymer. mp: 89°C. Chemical structure of the prepolymer was confirmed by IR analysis.

IR (KBr, $cm^{-1}$): 1805, 1728 (anhydride C═O), 1768 (ester C═O), 1605 and 1502 (aromatic C═C).

ddMOCPS prepolymer was prepared by the same method as dMOCPS. mp: 146°C. Chemical structure of the prepolymer was confirmed by IR analysis.

IR (KBr, $cm^{-1}$): 1809, 1730 (anhydride C═O), 1770 (ester C═O), 1604 and 1503 (aromatic C═C).




**Scheme 1** Synthetic route to the copolyanhydrides.

SA prepolymer was synthesized according to the literature.[2,13]

## Polyanhydride synthesis

All the polyanhydrides were prepared by melt copolycondensation.[2,15,24] For example, different molar ration of dMOCPS and SA prepolymers were added to glass tubes with a side arm equipped with a capillary

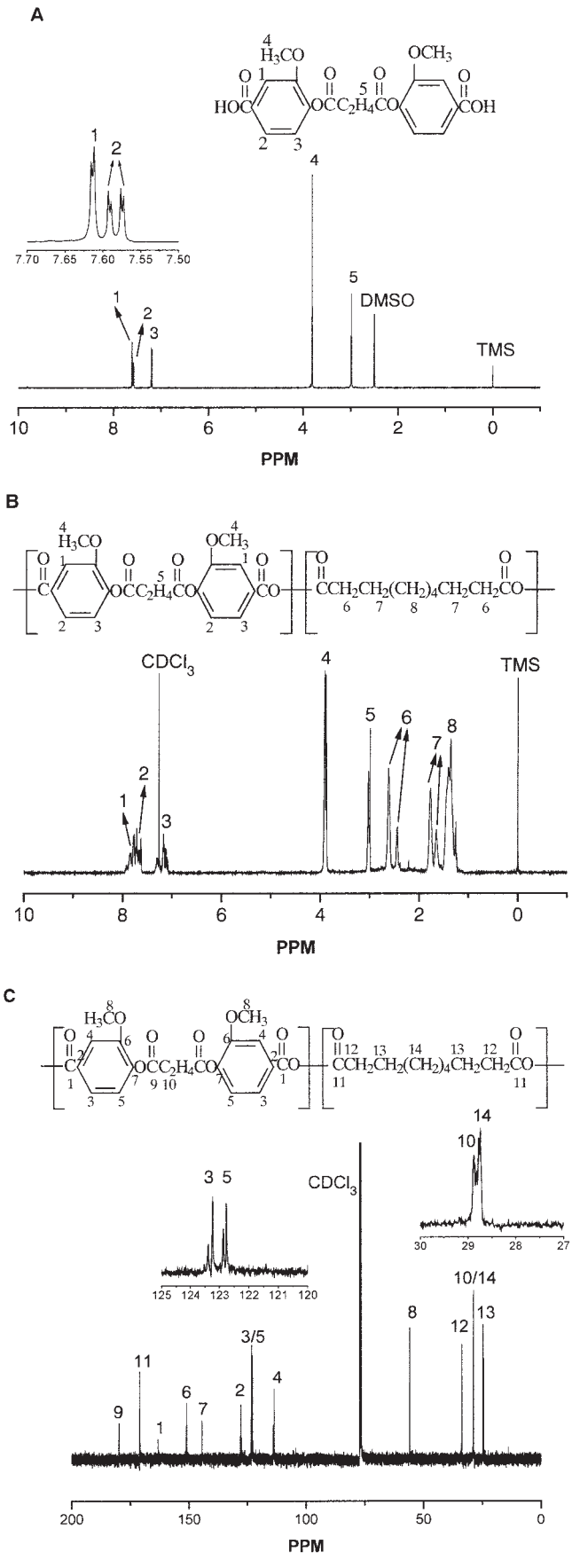



**Figure 1** NMR spectra of dMOCPS and PdMOCPS measured at room temperature, using DMSO-$d_6$ as a solvent of dMOCPS and $CDCl_3$ as a solvent of PdMOCPS. $Me_4Si$ was used as internal reference. A: $^1$H-NMR spectra of dMOCPS; B: $^1$H-NMR spectra of P(dMOCPS:SA); C: $^{13}$C-NMR spectra of P(dMOCPS:SA).

**TABLE I**
**Characteristics of P(dMOCPS:SA) and P(ddMOCPS:SA)**

| Polymer | Yield (%) | $M_w$[a] | $M_n$ | $T_g$[b] (°C) | $T_m$ (°C) | dMOCPS% (mole) | Contact angle (degree) |
|---|---|---|---|---|---|---|---|
| PSA | 72 | 42,300 | 28,900 | 52 | 81 | / | 71 |
| P(dMOCPS:SA) 20:80[d] | 85 | 19,600 | 15,100 | 28 | 66.2 | 19 | 74 |
| P(dMOCPS:SA) 30:70 | 86 | 17,500 | 11,300 | 22 | 61.6 | 28 | 77 |
| P(dMOCPS:SA) 50:50 | 76 | 11,600 | 7,200 | 9 | 58.2 | 47 | 81 |
| P(dMOCPS:SA) 70:30 | 64 | 8,500 | 6,000 | 36 | 56.7 | 68 | 84 |
| P(dMOCPS:SA) 80:20 | 23 | 7,100 | 5,300 | 64 | NF[e] | 75 | 86 |
| P(ddMOCPS:SA) 20:80 | 85 | 18,600 | 11,400 | 34 | 69.7 | 17 | 72 |
| P(ddMOCPS:SA) 30:70 | 83 | 17,100 | 10,900 | 30 | 65.2 | 27 | 76 |
| P(ddMOCPS:SA) 50:50 | 72 | 11,200 | 7,100 | 38 | 77.8 | 45 | 79 |

[a] Determined by GPC; THF as solvent and polystyrene as standard.
[b] Measured by DSC.
[c] Calculated by $^1$H-NMR.
[d] Molar ratio.
[e] Not found.

nitrogen inlet, which were immersed in an oil bath at 180°C. After the prepolymers were melted, high vacuum was applied (<0.1 mmHg) for 2 h. The copolymers dissolved in chloroform were precipitated in anhydrous petroleum ether or anhydrous diethyl ether. Then, the P(dMOCPS:SA) copolymers were obtained. The P(ddMOCPS:SA) copolymers can be produced from ddMOCPS and SA prepolymers with the same method.

### Contact angle measurement

Static contact angle of distilled water on the copolyanhydride surface was used to evaluate the hydrophobicity of P(dMOCPS:SA) and P(ddMOCPS:SA) by a contact angle meter (JY-82). The copolymer films were prepared by casting polymer/chloroform solution (40 mg/mL) onto silanized glass microscopy slides, then evaporating at room temperature. The film thickness was about 2 $\mu$m. Static contact angles were measured at 25°C on profiles of sessile drops using a microscope with a fixed goniometer eyepiece, magnification 20×. Readings were taken within 10–15 s; average drop size was 0.05 mL. Angles were measured on six different regions of each polymer surface and an average was taken with no more than 8% deviation from the mean (~5°).

### Polymer degradation

Cylinder-shaped samples of about 60 mg of the polymers were prepared by compression molding with a homemade apparatus at 100 kg/cm$^2$ and 37°C for 5 min. Hydrolysis of the copolymer in vitro was performed in 5 mL of 0.1*M*, pH 7.4, phosphate buffer solution (PBS) at 37°C. The buffer was changed daily and fresh buffer was added to approximate the perfect sink condition. Weight loss of the matrix was determined gravimetrically. The morphologies of the degrading samples were observed by SEM.

### Microsphere preparation

Copolyanhydride microspheres were prepared by the oil-in-oil (O/O) emulsion solvent evaporation technique.[8] About 0.2 g of the copolymers dissolved in 0.5 mL of chloroform was used as the inner oil phase, which was emulsified into 10 mL of silicon oil containing 5% Span 85 under mechanical stirring to form O/O emulsion. The O/O emulsion was stirred with magnetic stirrer for 1 h. Then, 50 mL of petroleum ether was introduced and stirring was continued for another hour. The resulting microspheres were collected by centrifugation, washed three times with petroleum ether, freeze-dried, and stored in refrigerator.

## RESULTS AND DISCUSSION

### Synthesis and characterization of the copolyanhydrides

Previously, we synthesized di(*p*-carboxyphenyl) succinate (dCPS) by a very convenient scheme in which *p*-hydroxy benzoic acid condensed with succinic chloride. PdCPS and copolymers with sebacic acid were obtained by melt polymerization. The monomer can be purified by recrystallization from acetic acid, but less than 0.5 g dCPS can be dissolved in 100 mL of hot acetic acid. In addition, the copolymers with dCPS content above 50% cannot be dissolved in common organic solvents. In this work, we synthesized dMOCPS and ddMOCPS. Such introduction of methoxyl groups will improve the solubility while maintaining the fluorescent properties. dMOCPS and ddMOCPS were obtained by the same method as dCPS, the chemical structure as shown in Scheme 1.

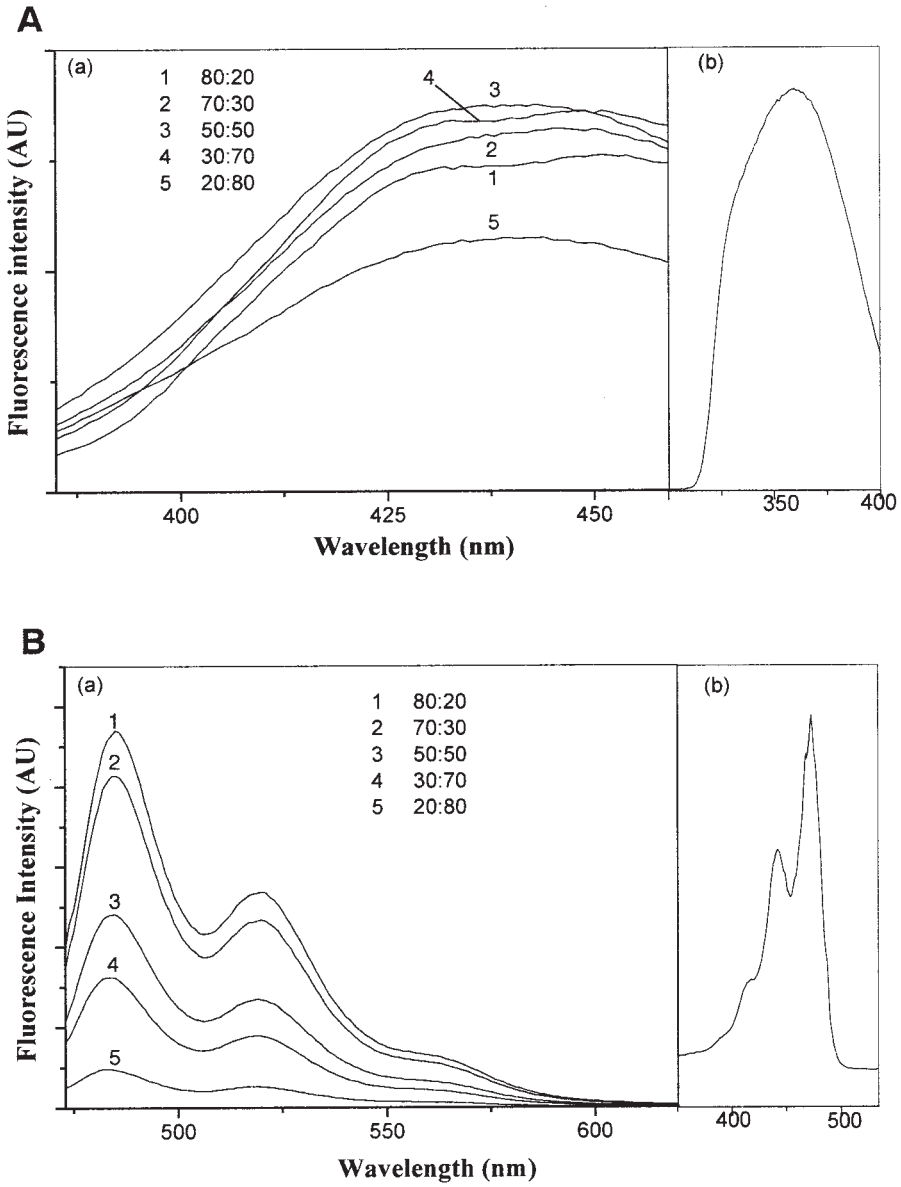



**Figure 2** Fluorescence spectra of the P(dMOCPS:SA) solution in chloroform (1 mg/mL). A: excited at 360 nm; B: fluorescence spectra excited at 473.5 nm; (a): emission spectra and (b): excitation spectra.

The two diacids have better solubility than dCPS, and can be recrystallized from acetic acid with high yields. Figure 1 shows the $^{1}$H-NMR spectra of dMOCPS and P(dMOCPS:SA) and $^{13}$C-NMR spectra of P(dMOCPS:SA). In the $^{1}$H-NMR spectra of P(dMOCPS:SA), aromatic protons ortho to the anhydride and ester bond appear at 7.63–7.79 and 7.15–7.43 ppm, respectively; the methoxyl protons appear at 3.88–2.92 ppm. The methylenic protons in PdMOCPS units appear at 2.99 ppm. The peaks at 2.40–2.70, 1.60–1.82, and 1.20–1.50 ppm can be attributed to the methylenic protons in SA units. P(dMOCPS) cannot be dissolved in common solvents, while P(dMOCPS:SA) with less than 70% dMOCPS content had good solubility in solvents such as chloroform. ddMOCPS was synthesized like dMOCPS, but in the process of melt polymerization, mixture of ddMOCPS and SA prepolmers with ddMOCPS content above 50% solidified within 5–10 min. We believed that the high mp of ddMOCPS polymer led to this phenomenon; as a result, polyanhydrides with ddMOCPS content above 50% can only get oligomers using this polymerization means.

The characteristics of the copolymers are listed in Table I. $M_W$ of the copolyanhydrides decreases with an increase in dMOCPS fraction, which is similar to other copolyanhydrides containing SA residues.[3,4,25] Thermal properties of the copolyanhydrides were evaluated with DSC (Table I). It can be seen that glass-transition temperatures ($T_g$) of P(dMOCPS:SA) decreases from 52 to 9°C as dMOCPS content in-

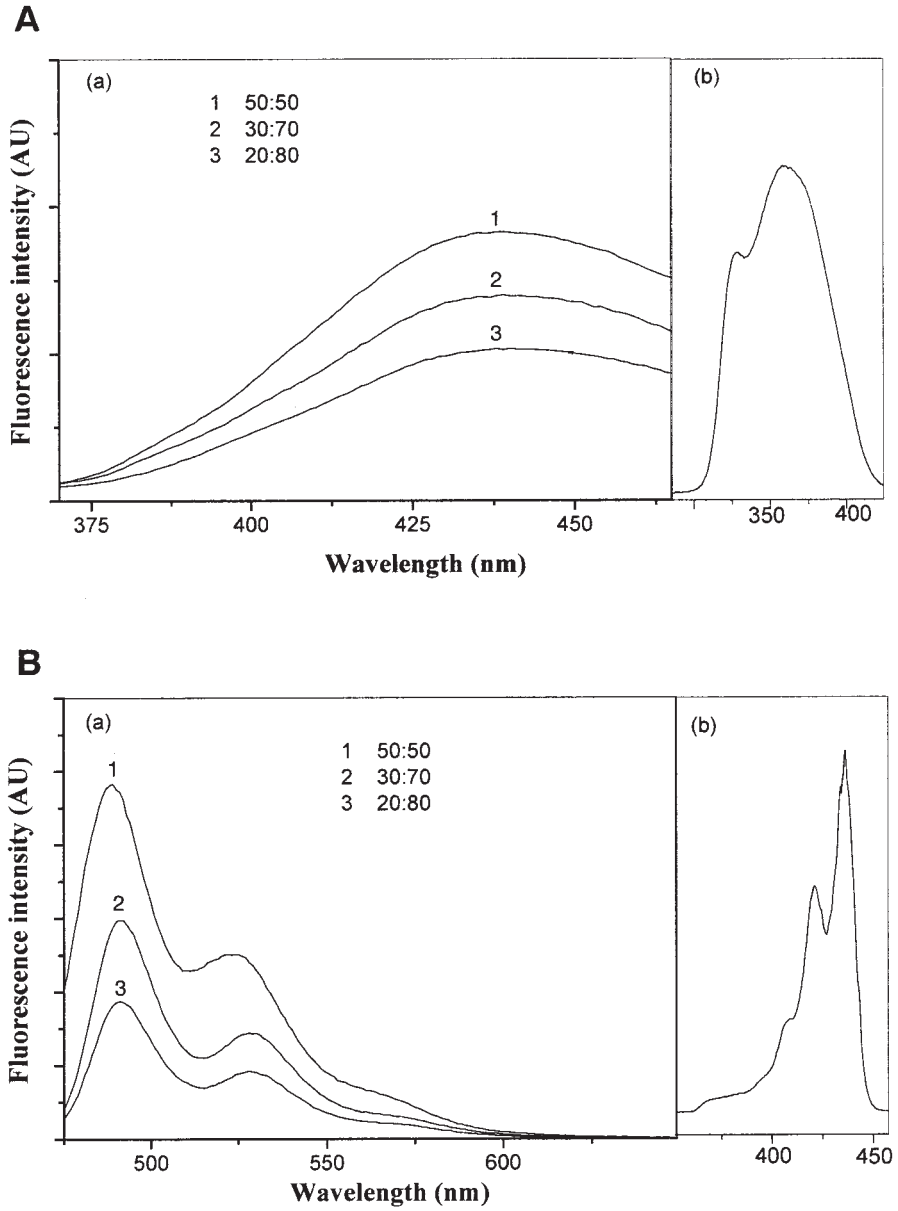



**Figure 3** Fluorescence spectra of the P(ddMOCPS:SA) solution in chloroform (1 mg/mL). A: excited at 360 nm; B: fluorescence spectra excited at 486 nm; (a): emission spectra and (b): excitation spectra.

creases to 50%, then increases to 116°C in the case of P(dMOCPS) homopolymer, revealing a negative linearity of $T_g$ as a function of monomer fraction. Similar results were also reported for other copolyanhydrides containing monomers differing in size and chemical nature,[3,25] which can be explained by the Couchman relation that describes the relationship between $T_g$ of copolymers and sequential distribution of the monomer units.

### Fluorescent property of the copolyanhydrides

The fluorescent properties of the copolyanhydrides were studied by fluorometry. Figure 2 shows the fluorescence spectra of the P(dMOCPS:SA) solution in chloroform (1 mg/mL). Figure 3 shows the fluorescence spectra of the P(ddMOCPS:SA) solution in chloroform (1 mg/mL). Both P(dMOCPS:SA) and P(ddMOCPS:SA) have two kinds of emission spectra. The maximum emission wavelength for the copolymer of P(dMOCPS:SA) is 438 nm, as the excitation wavelength is fixed at 360 nm (UV light), and 485 and 520 nm excited at 473.5 nm (Visual light). $\lambda_{em}$ of P(ddMOCPS:SA) was 438 nm with an excitation wavelength at 360 nm, and 490 and 527 nm excited at 486 nm. Compared with the copolyanhydrides containing dCPS, the maximum excitation/emission wavelength of the two kinds of copoyanhydrides shifts to higher wavelength. $\lambda_{em}$ of P(dCPS:SA) was 410 nm with an excitation wave-

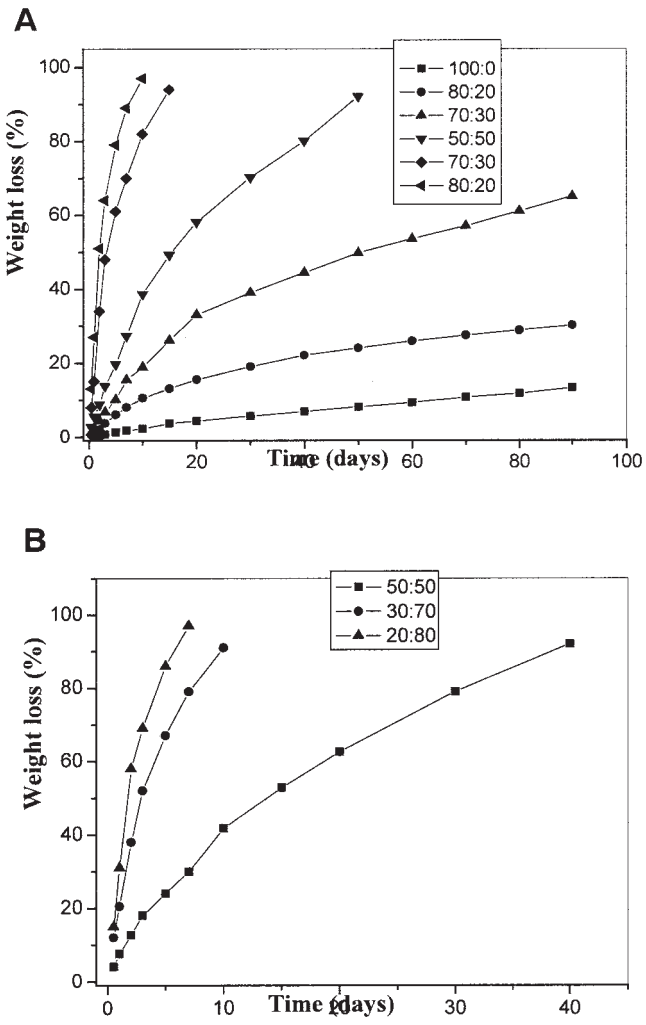
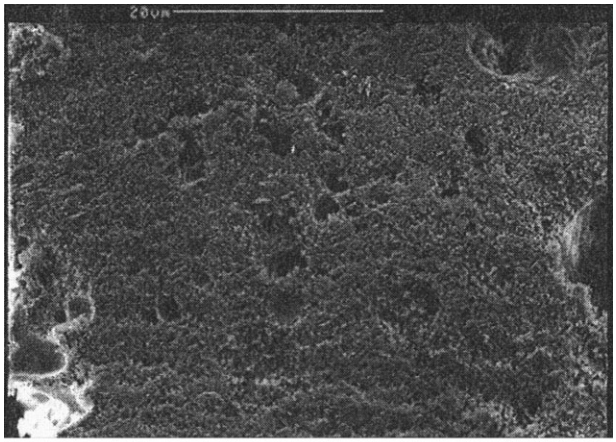



**Figure 4** Mass loss of the copolyanhydrides in 0.1*M* phosphate buffer (pH 7.4) at 37°C. A: dMOCPS/SA ratio in P(dMOCPS:SA), a: 100:0; b: 80:20; c: 70:30; d: 50:50; e: 30:70; and f: 20:80. B:ddMOCPS/SA ratio in P(ddMOCPS:SA), a: 50:50; b: 30:70; and c: 20:80.

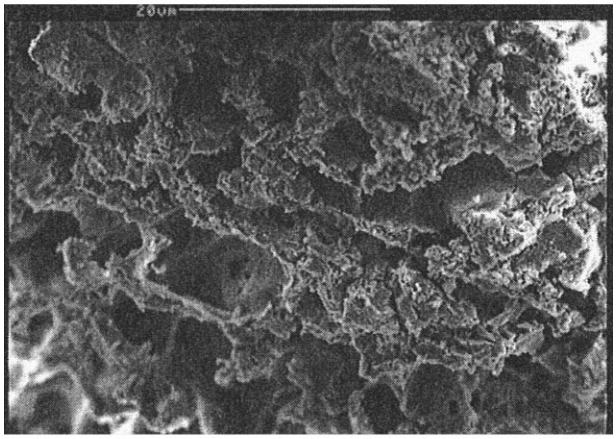
length at 327 nm, and 476 and 510 nm at 462 nm.[16] The phenomenon of shift may be due to conjugation between methoxyl group and benzene ring, which reduces the energy level of the excited state. P(dMOCPS:SA) and P(ddMOCPS:SA) have almost same wavelength of fluorescence with a UV excitation. When copolymers are excited by visual light, fluorescence wavelength of P(ddMOCPS:SA) is higher than P(dMOCPS:SA). So, the fluorescence excited by visual light is more sensitive to change of conjugation and structure of repetitive units. In Figure 2, when excited by visual light, fluorescence intensity of P(dMOCPS:SA) increase with addition of dMOCPS fraction. P(CEFB:SA) have the similar situation.[12] When the excitation source is UV light, intensity of fluorescence reaches a maximum with 70% SA fraction, rather than increasing with a decrease in the fraction of SA, which is commonly showed in P(dCPS:SA) and P(CEFB:SA). Similar phenomenon also appeared for poly(*o*-acetyl-*p*-(carboxyethylformamido)benzoic anhydride) (PACEFB) in which acetyl group was introduced to the benzene ring.[11] For the limited solubility of P(ddMOCPS:SA) in common organic solvents, we cannot estimate whether the similar maximum exit or not in P(ddMOCPS:SA).

## Degradation

Weight loss of P(dMOCPS:SA) during degradation is shown in Figure 4. It can be seen that the degradation rate of the copolymers decreases with an increase of dMOCPS content in the copolymers. For example, P(dMOCPS:SA) 20:80 degraded completely after 14 days, while P(dMOCPS:SA) 50:50 need 61 days. P(ddMOCPS:SA) degraded slightly more rapidly than P(dMOCPS:SA) with the same SA content. For in-



A



B

**Figure 5** SEM micrographs of the degrading P(dMOCPS:SA) 50:50 after 15 days. A: inner layer and B: outer layer.

stance, entire time of degradation of P(ddMOCPS:SA) 50:50 was 52 days. These results can be correlated with the hydrophilicity of the copolymers, which was showed as contact angle in Table I. Copolyanhydrides with smaller contact angle degraded more quickly; introduction of methoxyl group in repetitive units lead to better hydrophilicity and smaller contact angle. P(dMOCPS:SA) 70:30 degraded slowly, which is fit for long-term application as fluorescent tracers for monitoring *in vivo* translocation of the biomaterials.

The morphology of the degrading P(dMOCPS:SA) 50:50 microsphere sample after 15 days was observed by SEM (Fig. 5). The cross section through the copolyanhydride consists of two layers, the inner layer is compact, and the outer layer is porous. Figure 5(A) shows the morphology of inner layer while Figure 5(B) shows that of outer layer. It can be seen that the outer layer degraded more rapidly than the inner, which is typical phenomenon of surface degradation, and so the new copolyanhydrides are material of surface degradation as P(dCPS).

## CONCLUSIONS

P(dMOCPS:SA) and P(ddMOCPS:SA) were synthesized with a very convenient scheme. The polymers displayed inherent fluorescent properties. The emission wavelength is dependent of the excitation wavelength. Compared with P(dCPS:SA), the maximum excitation/emission wavelength shifts to higher wavelengths. Fluorescence intensity of P(dMOCPS:SA), which is excited by visual light, increases with decreasing SA content. However, when fluorescence is excited by UV light, the intensity reaches a maximum with 70% fraction of SA. The two new kinds of copolyanhydrides degraded more quickly than P(dCPS:SA) with same fraction of SA. In addition, the copolyanhydrides show surface-degradation characteristics. P(dMOCPS:SA) that show strong fluorescent properties and good solubility can find wide biomedical applications. In addition, P(dMOCPS:SA) and P(ddMOCPS:SA) were synthesized from vanillic acid and syringic acid, and the two diacids have antibacterial activity, so the medical usage of the polyanhydrides is possible.

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