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Chitosan-graft poly(*p*-dioxanone) copolymers: preparation, characterization, and properties

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ABSTRACT

A new biodegradable copolymer of chitosan and poly(*p*-dioxanone) (PPDO) was prepared through a protection-graft-deprotection procedure using *N*-phthaloyl-chitosan as an intermediate. PPDO terminated with the isocyanate group was allowed to react with hydroxyl groups of the *N*-phthaloyl-protected chitosan, and then the phthaloyl group was cleaved to give the free amino groups. The length of PPDO graft chains can be controlled easily by using the prepolymers of PPDO with different molecular weights. The resulting products were thoroughly characterized with FT-IR, ^{1}H NMR, TG, DSC, SEM, and WAXD. The copolymers were used as drug carriers for sinomenine (7,8-didehydro-4-hydroxy-3,7-dimethoxy-17-methyl-9α,13α,14α-morphinan-6-one) and these exhibited a significant controlled drug-releasing behavior whether in artificial gastric juice or in neutral phosphate buffer solution.

1. Introduction

Chitosan (CS) is a fully or partially deacetylated product of chitin, the second most abundant natural resource next to cellulose, and has a repeating structure of β-(1→4)-linked 2-amino-2-deoxy-D-glucan. Due to its biodegradability, biocompatibility, and nontoxicity, CS has been widely applied in biomedical fields as carrier for drug delivery, wound dressing, etc.[1–3]

Chemical modification can introduce desired properties and functionality into chitosan and enlarge its potential application fields.[4] Usually, chitosan derivatives show excellent solubility, processability, and low polarity compared to chitosan. Graft copolymerization is among the widely used chemical modification methods for chitosan in order to improve its properties.[5] Many reports have focused on the preparation of amphiphilic copolymers via graft copolymerization of chitosan and aliphatic polyesters or polyethers, such as poly(lactic acid) (PLA),[6–10] poly(ε-caprolactone) (PCL),[11–18] and poly(ethylene glycol) (PEG).[19,20]

Poly(1,4-dioxan-2-one) (PPDO), an aliphatic polyester with the following structure: $+O-(CH_2)_2-O-CH_2-CO+_n$, has been widely used as biodegradable suture material due to its good strength and knotting properties.[21] However, its slow degradation rate in the human body is one of main factors that limit its wide application in medical fields. Chen et al.[22] found that when PPDO was grafted onto poly(vinyl alcohol), the copolymer showed an improved degradation rate. Liu et al.[23] prepared chitosan-graft-PPDO (CGP) via reaction between hydroxyl groups of chitosan and 1,4-dioxan-2-one (PDO) in the presence of $Sn(Oct)_2$. However, it took 48 h to complete the copolymerization due to the heterogenous reaction medium. Therefore, in the present work, we have developed a method to connect the PPDO macromonomer with *N*-phthaloyl-chitosan via the residual hydroxyl groups. In order to overcome the effect of the length of the PPDO side chains on the properties of the graft copolymer, PPDO with two different intrinsic viscosities was introduced into the chitosan backbone. The resulting products were characterized using FT-IR, ^{1}H NMR, TG, DSC, and WXRD. It was found that combining PPDO with chitosan not only provides a new amphiphilic copolymer but also leads to an improved controlled releasing behavior for the analgesic drug sinomenine (7,8-didehydro-4-hydroxy-3,7-dimethoxy-17-methyl-9α,13α,14α-morphinan-6-one).

2. Results and discussion

2.1. Synthesis of the chitosan-graft copolymer

The chitosan graft poly(*p*-dioxanone) copolymer (CGP) was prepared according to the procedure given in Scheme 1 starting from *N*-phthaloyl-chitosan (PHCS).[30] PHCS is soluble in organic solvents,

Abbreviations: PDO, 1,4-dioxan-2-one or *p*-dioxanone; PPDO, poly(1,4-dioxan-2-one) or poly(*p*-dioxanone); CGP, chitosan graft poly(*p*-dioxanone) copolymer; PHCS, *N*-phthaloyl-chitosan; PPDO-NCO, tolylene-isocyanate-terminated poly(*p*-dioxanone); *G*, grafting percent; GE, grafting efficiency.

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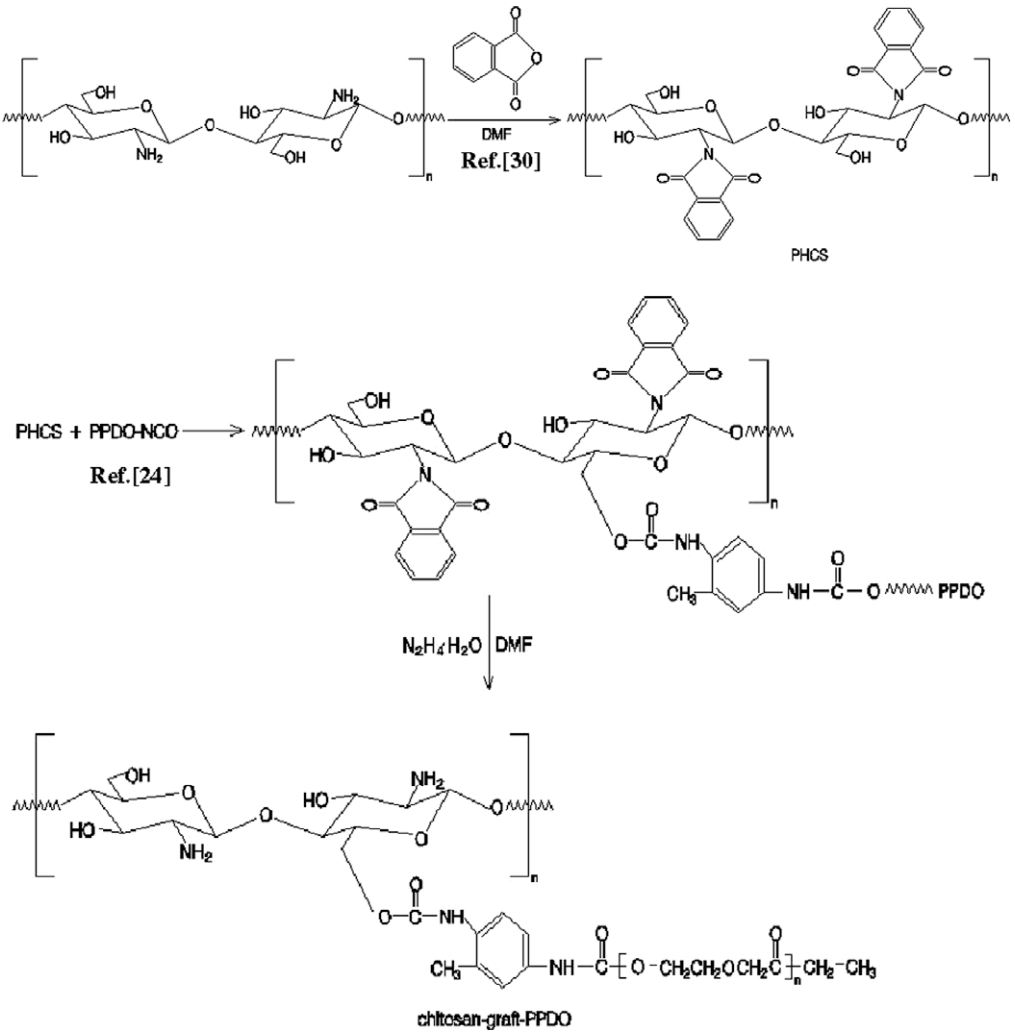

Scheme 1. Synthesis route for chitosan-grafted PPDO.

such as DMF and Me_2SO, due to the presence of the phthaloyl protecting group which prevents formation of inter- and intramolecular hydrogen bonds as present in chitosan. It could then be reacted with the previously prepared reactive poly(1,4-dioxane-2-one) tolylene-isocyanate (PPDO-NCO),[24] in DMF homogeneous solution, allowing grafting of PPDO onto the chitosan backbone, in a similar manner as described for the grafting of PPDO onto starch.[24] Finally, deprotection of the *N*-phthaloyl protecting group was carried out in the presence of hydrazine in order to regenerate the free amino group.

The FT-IR spectrum of CGP is shown in Figure 1. The broad peak around 3500 cm^{-1} was assigned to the hydroxyl groups of chitosan. Moreover, a sharp peak at 1735 cm^{-1} ascribed to the ester carbonyl of PPDO was observed. Besides this, a peak at 721 cm^{-1} ascribable to the tolyl group could be found, together with a N–H stretching vibration band at 1536 cm^{-1}.

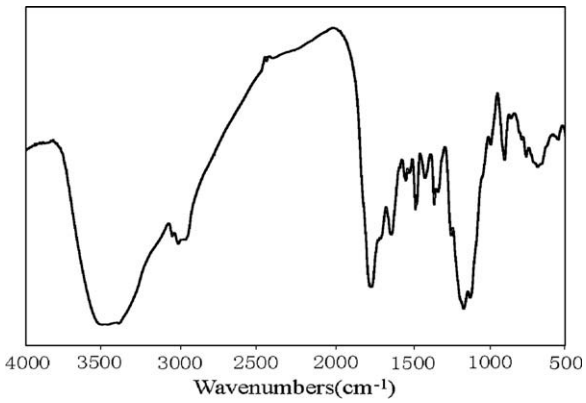

Figure 1. IR spectrum of CGP.

The ^1H NMR spectrum also confirmed the coupling reaction between chitosan and PPDO. In Figure 2, the strong signals at 4.21, 3.70, and 4.17 were assigned to a, b, and c methylene protons of the PPDO chain, respectively, and signals at 4.43 and 1.24 were the terminal methylene (Hd) and methyl (He) protons of PPDO. Protons of the chitosan backbone appeared between 3.3 and 4.7 ppm.[10,11] Signals at 2.15 and 7.05 were ascribed to the methyl and benzene protons of the tolyl group. All evidence validated that the PPDO side chain had been grafted onto the backbone of chitosan. The grafting percent (G) can be estimated by the following equation:

$$G = W_{PPDO}/W_{chitosan} = \frac{102 \times I_{HC}}{161 \times 2 \times I_{H1}} \times 100$$

where I_{H1} is the integral peak area for H-1 of chitosan, 102 (g/mol) is the molecular weight of the PDO monomer, and 161 (g/mol) is the molecular weight of an anhydrous glucosamine unit. The data are listed in Table 1.

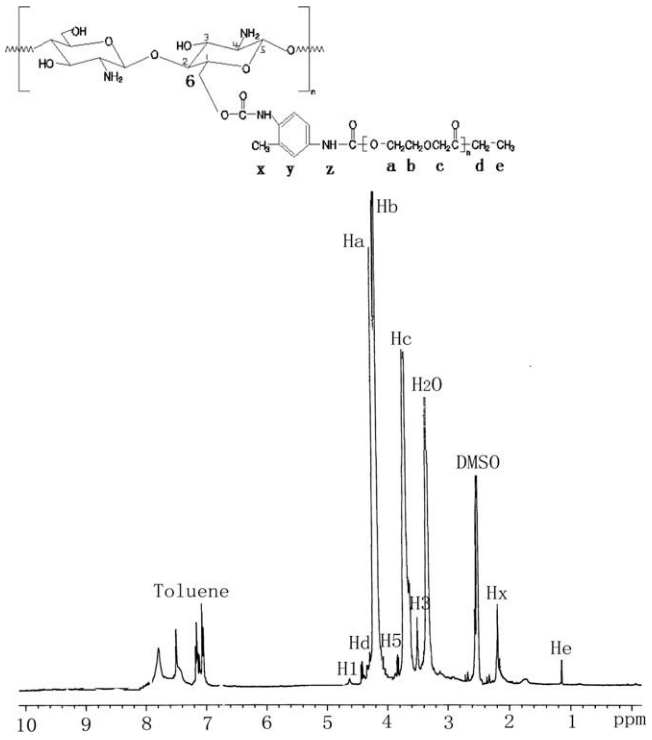

Figure 2. ^{1}H NMR spectrum of CGP.

Table 1
Effect of the deprotection time and temperature on the coupling reaction

	[η] of PPDO	Deprotection time (h)	Deprotection temperature (°C)	Y (%)	GE (%)	G[a] (%)
CGP1	0.12	1	80	71.3	33.2	62.5
		2	100	—	—	
CGP2	0.66	1	80	89.6	61.4	185.2
		1	100	73.5	43.6	99.6
		2	80	76.4	52.1	116.4
		2	100	70.1	12.5	42.1

[a] Weight of PPDO/weight of chitosan, determined by ^{1}H NMR.

It was found that the deprotection conditions of the *N*-phthaloyl group had an important effect on the yields (*Y*), grafting efficiency (GE), and grafting percent (*G*) of the obtained products (see Table 1). When the deprotection time was over 2 h, *Y*, GE, and *G* decreased, even for a reaction temperature of 80 °C. For example, the values for *Y*, GE, and *G* of CPG2 were 89.6, 61.4, and 185.2, respectively, at 80 °C in 1 h, and they decreased to 76.4, 52.1, and 116.4 within 2 h. It was found that the deprotection temperature also had a great influence on the coupling reaction. When the deprotection reaction was carried out at 100 °C for 1 h, the GE of CGP2 decreased to 43.6. This effect became even more considerable as far as CGP1 was concerned. This could be ascribed to the strong basicity of hydrazine which made the ester bonds of PPDO easily labile.

2.2. Morphology of CGP

Scanning electron microscopy (SEM) photographs of chitosan, PHCS, and CGP are shown in Figure 3. Pure chitosan is fibrous and layered, but upon derivatization by phthalic anhydride in DMF, spherical granules with a smooth surface are found (Fig. 3B). The morphology of the graft copolymer is clearly different: both CGP1 and CGP2 lost their original shapes and cannot be really differentiated.

2.3. Thermal stability of CGP

The TG and DTG curves of chitosan, CGP1, and CGP2 are shown in Figure 4. The various decomposition temperatures based on the TG and DTG curves are listed in Table 2. It can be seen that pure chitosan had a better thermal stability as compared to the graft copolymer. It showed only one decomposition range and the residue at 440 °C was as high as 44.8 (shown in Fig. 4B, curve a). In contrast with chitosan, the graft copolymers exhibited two decomposition ranges and the residues for CGP1 and CGP2 were 5.6 and 6.0, respectively. CGPs had two maximal decomposition temperatures (T_{max}), in which T_{max1} corresponded to the scission of the PPDO linkage in the chitosan backbone then the decomposition of the PPDO grafts, and T_{max2} was ascribed to the decomposition of glucosamine residues. Since T_{max2} of CGPs may relate to both the decomposition of PPDO residues and of phenyl groups introduced by TDI, T_{max2} of CGPs was higher than T_{max1} of pure chitosan. Above all, the thermal stability of the graft copolymer was lower than that of pure chitosan in agreement with the fact that hydrogen bonds of chitosan were partially destroyed by the introduction of PPDO into the backbone of chitosan.[10]

From Table 2, it can be seen that the thermal stability of CGP2 was better than that of CGP1. The 20%-weight-loss temperature ($T_{20\%}$) and 50%-weight-loss temperature ($T_{50\%}$) as well as the maximum decomposition temperature (T_{max}) of CGP2 were higher than those of CGP1. This observation could be correlated with the intrinsic viscosity of the prepolymer used to prepare CGP2 (0.62), which was higher than that of CGP1. It is then again concluded that for a graft copolymer, the longer the side chains are, the better the thermal stability is.[25]

2.4. Thermal transition behavior of CGP

Cooling scans of CGP with different PPDO lengths after erasing the thermal history at 200 °C are shown in Figure 5A. The subsequent heating curves of CGP are shown in Figure 5B. From the cooling scans of CGP, we can see clearly that the side chain length of PPDO has a great influence on the crystallization of the copolymer. No crystallization peak was found for CGP1 at a heating rate of 10 °C/min; however, a clear crystallization peak was observed at 21.5 °C for CGP2. This fact indicates that the crystalline ability of the graft copolymer is affected greatly by its structure. CGP1 with very short PPDO side chains had a poor crystallization ability, which can be due to the destruction of the regularity of the chitosan backbone by introduction of PPDO graft and the shortness of the side chain length. Whereas as far as CGP2 is concerned, the length of the PPDO side chain is long enough to allow crystallization of the copolymer during the cooling scan. Both copolymers have a melting point around 95 °C and 99 °C in the heating curves, indicating that they are semi-crystalline. The thermal transition temperature and enthalpy determined from Figure 5 are listed in Table 3. One can see that the crystallization ability of CGP2 is better than that of CGP1, which is reflected in the higher fusing enthalpy and melting temperature. Because the crystallinity of CGP1 was low, its glass transition temperature can be seen clearly in the cooling scan, while the glass transition temperature of CGP2 is almost invisible. As we know, it is difficult to detect the glass transition temperature of highly crystalline polymers using DSC, owing to the fact that the molecular motion in amorphous region is restricted by the crystalline region.[26] The low T_g of CGP1 was also ascribed to the short PPDO side chain, compared with the reported value for PPDO.[27]

2.5. Crystallization structure of CGP

The wide-angle X-ray diffraction (WAXD) patterns of chitosan, PHCS, CGP1, and CGP2 are shown in Figure 6. The crystallization

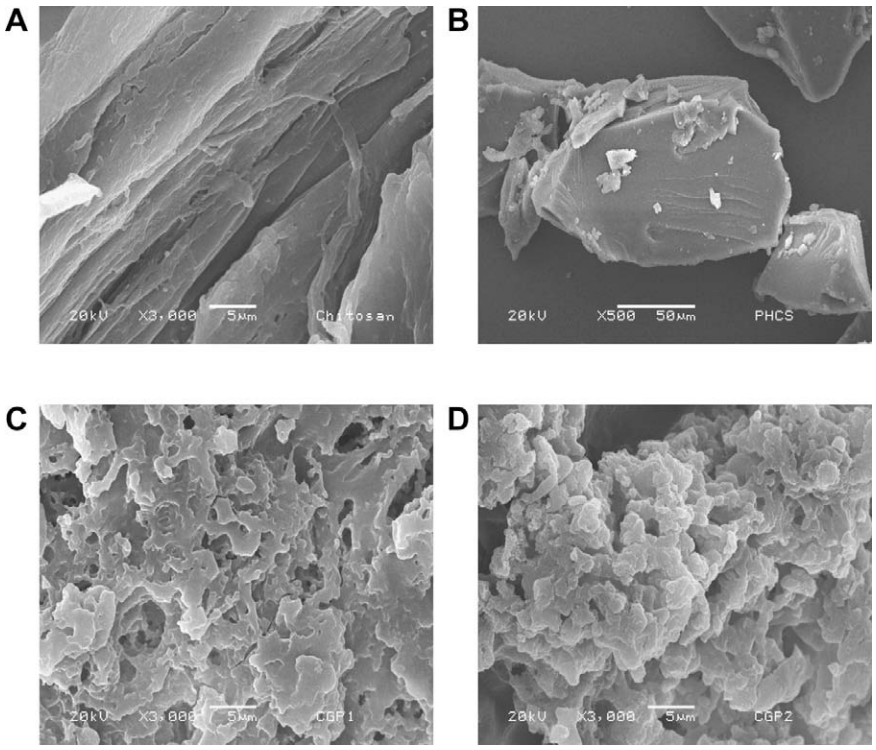

Figure 3. SEM photographs of (A) chitosan, (B) PHCS, (C) CGP1, and (D) CGP2.

structure of pure chitosan is rhombic, and the reflection peaks appear at $2\theta = 20°$, 11°, respectively.[28] For PHCS, the intensity of the reflection peak at 20° decreased greatly compared to that of pure chitosan, and 2θ at 11° disappeared. However, two new peaks were found at 7° and 26°, indicating that introduction of the phthaloyl groups into the chitosan backbone destroyed the original crystallization structure of chitosan. The WAXD patterns of CGP1 and CGP2 are different. For CGP1, some very weak peaks were found at $2\theta = 21.7°$, 22.9°, and 28.4° next to the broad peak around 15–20°, which agrees with that of the PPDO crystallization reflection peaks.[29] In contrast with CGP1, these peaks in CGP2 became very distinct, demonstrating that increase in PPDO side chains improves crystallization.

2.6. Drug delivery behavior

The comparative release profiles of sinomenine from pure chitosan and CGP2 in phosphate buffered saline (PBS) solution (A) or in an artificial gastric juice (B) are shown in Figure 7. It can be seen clearly that the graft copolymer had a better controlled releasing behavior compared to chitosan, since in PBS or the artificial gastric juice sinomenine was almost released completely in 4 h and 5 h, respectively, using chitosan as carrier, while the cumulative release percentages of sinomenine from CPG2 were 25.2% and 36.4% in PBS or the artificial gastric juice at the same time.

In order to investigate the influence of the chain length of PPDO on the releasing behavior, the cumulative release percentages of sinomenine from CGP1 and CGP2 were studied. Figure 8 shows the release profiles of sinomenine from CGP1 and CGP2 in neutral PBS (A) and the artificial gastric juice (B). From this figure, it can be seen that the cumulative release percentages of sinomenine from CGP1 are always higher than those of sinomenine from CGP2. Almost all the drug was released from CGP1 in 5 h in PBS, while the cumulative release percentage from CGP2 was 42.5% at the same time. The same result was also observed in the artificial gastric juice. For example, the cumulative release percentage of sinomenine from CGP1 was 85.2% in 5 h, and at the same time, it was only 36.4% for CGP2. These data indicate that the release of sinomenine in CGP is controlled by the diffusion and that the hydrophobicity of the carrier is crucial. The water uptake percentages of CGPs are listed in Table 3, in which the water uptake percentages of CGP2 and CGP1 are 19.6% and 23.6%, respectively. This demonstrated that the hydrophobicity of CGP2 is higher than that of CGP1, which makes the water penetration difficult, and the drug release slowed.

3. Experimental

3.1. Materials

Chitosan (viscosity-average molecular weight 8×10^5, degree of deacetylation >95%) was purchased from Yuhuan Ocean Biochemical Co. Ltd (Zhejiang, China), and dried in vacuum at 40 °C for 24 h prior to use. DMF was purchased from Kelong Chemical Reagent Factory (Chengdu, China), dried by refluxing over CaH_2, and purified three times by distillation. 1,4-Dioxan-2-one (PDO) was provided by the Pilot Plant of the Center for Degradable and Flame-Retardant Polymeric Materials (Chengdu, China). Triethyl-aluminum ($AlEt_3$) was provided by Nanjing Tonglian Chemical Corporation (Naning, China), and it was dissolved in anhydrous toluene with a concentration of 6.4%. Tolylene 2,4-diisocyanate (TDI) was purchased from the First Chemical Reagent Factory (Shanghai, China). Hydrazine monohydrate was purchased from Kelong Chemical Reagent Factory (Chengdu, China). Ethanol and 1,2-dichloroethane, which were used for the purification of the graft copolymers, were purchased from Changlian Chemical Reagent Factory and Kelong Chemical Reagent Factory (Chengdu, China), respectively. Both phenol and 1,1,2,2-tetrachloroethane were purchased from Kelong Chemical Reagent Factory (Chengdu, China). Sinomenine was purchased from Hubei Baike Hengdi Medicine. These materials were used as received without further purification.

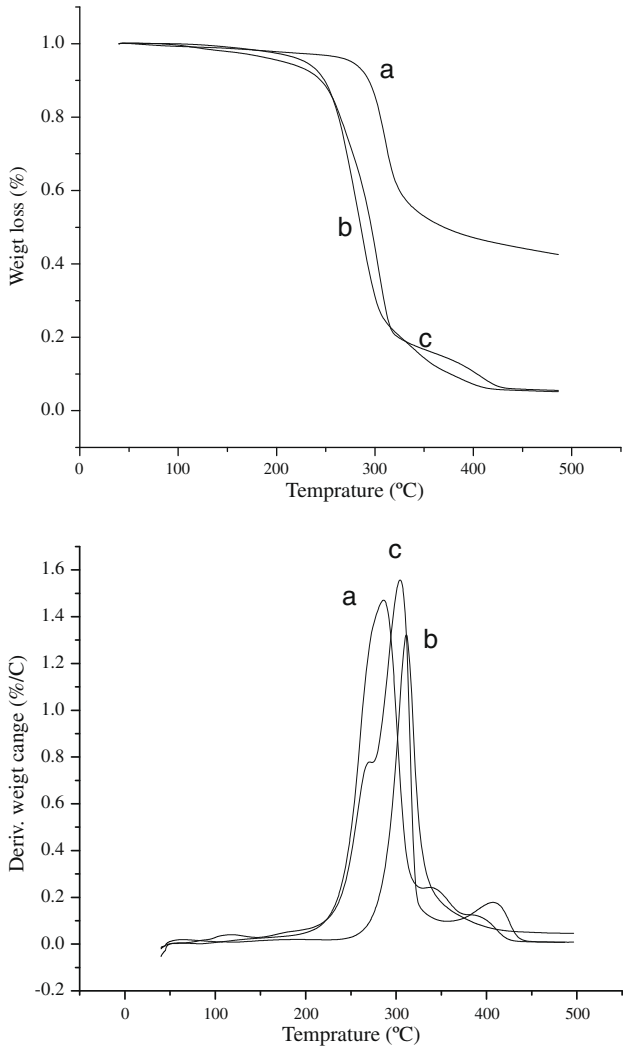

Figure 4. TG and DTG curves of chitosan (a), CGP1 (b), and CGP2 (c).

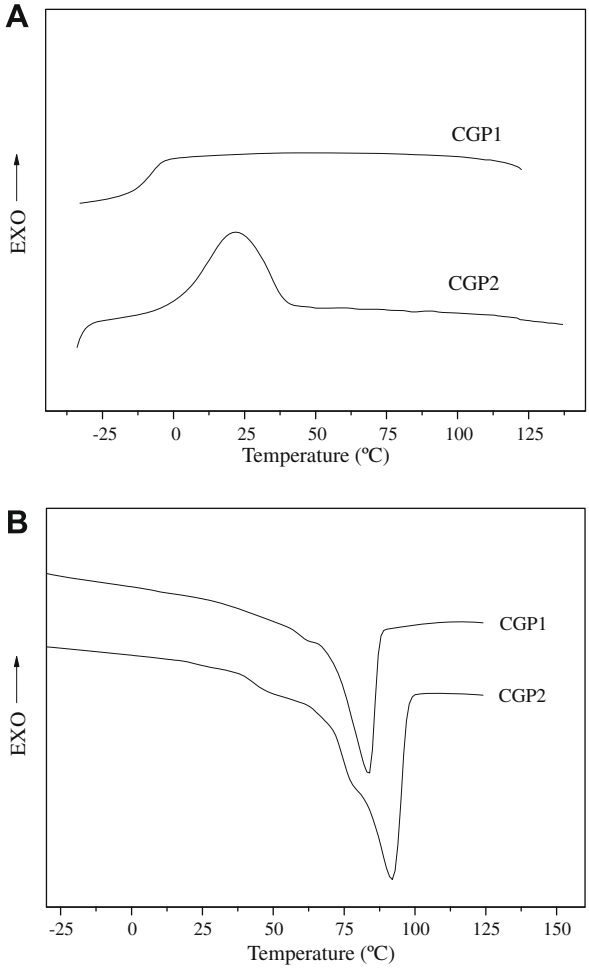

Figure 5. DSC cooling curves (A) of CGP after erasing thermal history and subsequent heating curves (B) of CGP.

Table 2
Data of thermal degradation of chitosan and graft copolymers

Sample	$T_{20\%}$ (°C)	$T_{50\%}$ (°C)	T_{max1} (°C)	T_{max2} (°C)	T_i (°C)	Residue at 440 °C (%)
Chitosan	305.5	370.0	311.4	—	295.2	44.8
CGP1	262.9	285.5	285.5	315.3	253.4	5.6
CGP2	264.7	296.1	304.1	409.1	269.1	6.0

3.2. Preparation of poly(*p*-dioxanone)

Poly(*p*-dioxanone) polymers with two different intrinsic viscosities were prepared according to the literature.[31] The detailed synthesis procedure was as follows: 5 g PDO was charged into oven-dried and silanized 20 mL vial, and a solution of $AlEt_3$ in dry toluene was injected into the vial through the butyl rubber stopper with a syringe at two different molar ratios of [PDO]/[$AlEt_3$]. As PPDO1 and PPDO2 were concerned, the molar ratios of [PDO]/[$AlEt_3$] were 250 and 2000, respectively. The vial was then heated in a silicone oil bath at 80 °C with a magnetic stirring under a dried argon atmosphere. The polymerization was stopped by immediately immersing into ice water when the reaction had run for 24 h. The product was purified by precipitation from the phenol/1,1,2,2-tetrachloroethane (2:3 w/w) solution with EtOH immediately and dried under vacuum. The intrinsic viscosities ([η]) of the resulting polymers were measured with concentration of 0.1 g/dL in phenol/1,1,2,2-tetrachloroethane (2:3 w/w) solution using an Ubbelohde viscosimeter thermostated at 25 °C. The intrinsic viscosities of the obtained PPDO1 and PPDO2 were 0.12 and 0.66 dL/g, respectively.

3.3. Preparation of chitosan-grafted PPDO

Vacuum-dried *N*-phthaloyl-chitosan (PHCS)[30] and anhydrous Me_2SO were added into a reactor at a ratio of 1:20 (g/mL), and they were placed in an oven at 60 °C until PHCS dissolved. The soln was slowly added into a reactor containing PPDO-NCO[24] with vigorous stirring at 80 °C. The feed ratio of PHCS/PPDO was 1:5 (g/g). After 3 h of reaction, the product was precipitated with EtOH and filtered. The unreacted PPDO and PPDO-NCO were removed by Soxhlet extraction with 1,2-dichloroethane until constant weight. The dried PHCS-graft-PPDO powder was obtained after further drying under vacuum for 24 h.

The obtained PHCS-g-PPDO (1 g) was stirred in DMF (10 mL) and heated to 100 °C under N_2. Hydrazine monohydrate was added and the mixture was heated at given temperature and time (see Table 1) to deprotect the phthaloyl group. The yellow solution was cooled to room temperature. Finally, the precipitate was collected and washed with EtOH and dried in vacuum. The yields (*Y*) and grafting efficiency (GE) were calculated by the following equations:

Table 3
DSC data and the water uptake percentage of pure PPDO and CGPs

Sample	Cooling				Heating			Water uptake (%)
	T_c (°C)	ΔH_c (J/g)	T_g (°C)	T_{c_1} (°C)	ΔH_{c_1} (J/g)	T_m (°C)	ΔH_m (J/g)	
PPDO[a]	43.8	−35.1	−9.0	45.0	−17.4	107.8	58.3	16.0
CGP1	—	—	−16.7	—	—	95.2	48.1	23.6
CGP2	21.5	−8.8	−11.2	45.3	−3.2	99.5	86.3	19.6

[a] Ref. 27.

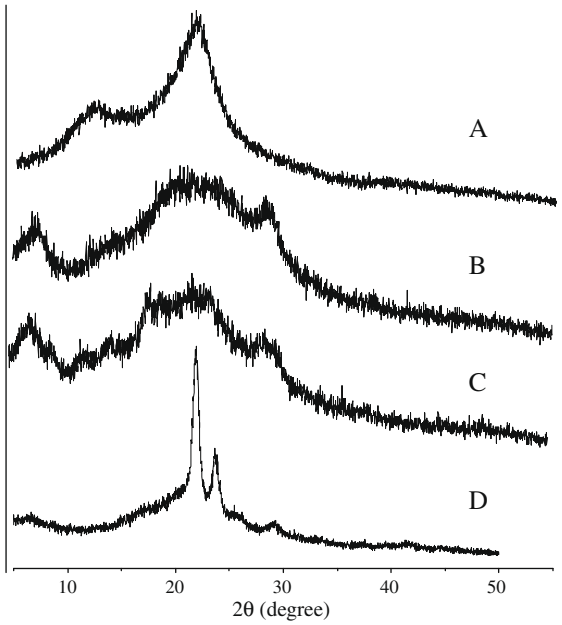

Figure 6. WAXD patterns of chitosan (A), PHCS (B), CGP1 (C), and CGP2 (D).

$$Y\ (\%) = \frac{W_1}{W} \times 100$$

$$\mathrm{GE}\ (\%) = \frac{(W_1 - W_2)}{(W - W_2)} \times 100$$

where W is the starting weight of both chitosan and PPDO, and W_1 and W_2 are the weights of the refined products and chitosan, respectively.

3.4. Characterization

The FTIR spectrum of CGP was measured with an FT-IR spectrometer (Nicolet 170SX), using KBr pellets of CGP. The ^{1}H NMR spectra of the graft copolymers were recorded with a Varian INOVA-400 spectrometer at 400 MHz using Me_2SO-d_6 as the solvent. DSC was recorded with a differential scanning calorimeter (SEIKO EXSTRA6000) (under N_2 at 10 C/min). Samples were heated to 140 °C for 5 min to erase all previous thermal history and then were cooled to −50 °C. The samples were heated again up to 140 °C. The melting temperature (T_m), glass transition temperature (T_g), crystallization temperature (T_c), and the heat of fusion (ΔH_m) were determined from the DSC curves. Thermal stability of the graft copolymers was measured with a thermal gravimetric analyzer (Perkin–Elmer TGA7) at a heating rate of a 10 °C /min under N_2. Wide-angle X-ray diffraction (WAXD) was recorded by using an X-ray diffractometer (Philips X'Pert X-ray diffractometer) with the Cu Kα radiation in the range of 10–50° at 40 kV and 30 mA. The morphology of the surface of CGP and PHCS powder was observed on gold sputter-coated samples, using a scanning electron microscope (JEOL JSM-5900LV) under an accelerating voltage of 10 kV.

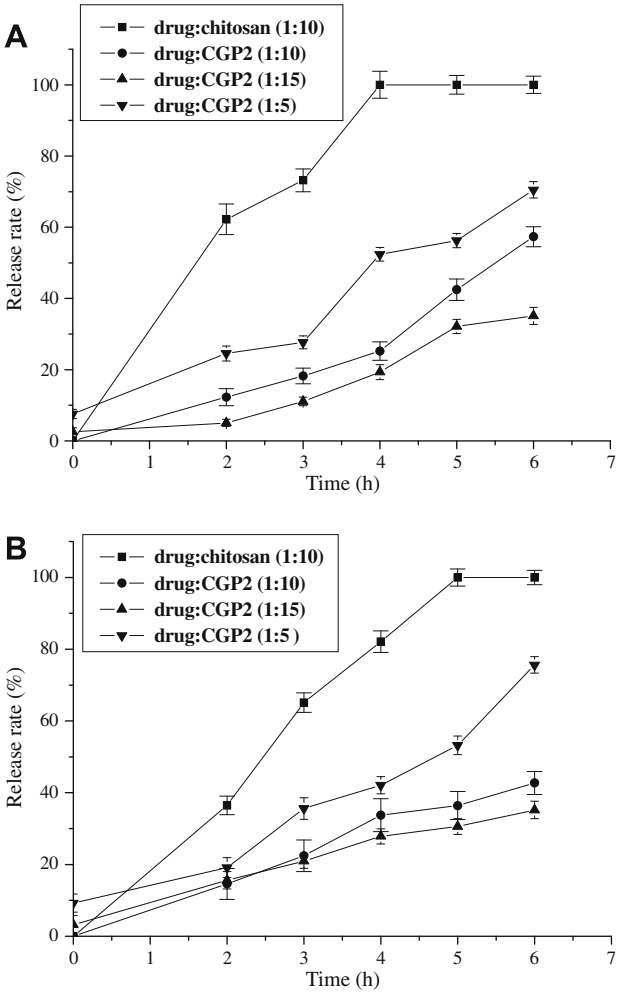

Figure 7. In vitro release profiles of sinomenine from pure chitosan and CGP2 in neutral PBS (A) and artificial gastric juice (B).

3.5. Measurement of water uptake

The water uptake was measured after incubating the polymer films with a thickness of 0.3 mm in distilled water at 37 °C for 24 h. The water uptake was calculated as follows:

$$\text{Water uptake} = (W_{\text{wet}} - W_{\text{dry}})/W_{\text{dry}} \times 100\%$$

The weight of the wet polymer film, W_{wet}, was measured gravimetrically after incubating the film in distilled water at 37 °C for 24 h. The weight of the dried polymer film, W_{dry}, was measured gravimetrically after drying the wet film that was incubated in distilled water for 24 h in a vacuum oven for 24 h.

3.6. In vitro drug release study

Preparation of drug samples: sinomenine (10 mg) was mixed with various proportions of CGP (1:5, 1:10, 1:15, w/w), and pressed

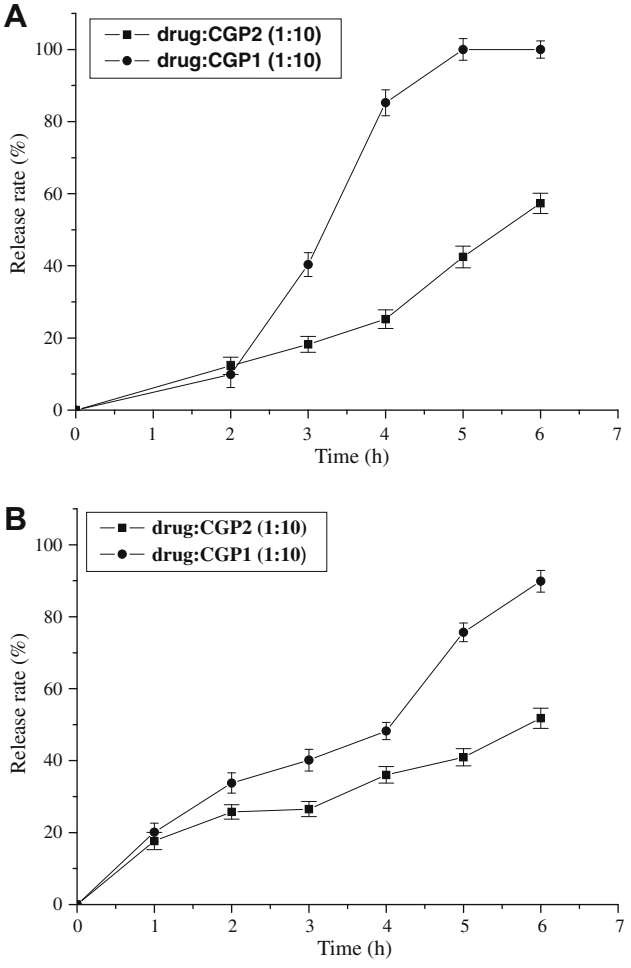

Figure 8. In vitro release profiles of sinomenine from CGP1 and CGP2 in neutral PBS (A) and artificial gastric juice (B).

into a pellet. Pure chitosan containing sinomenine (1:10, w/w) was prepared using the same procedure.

The standard curve of sinomenine was drawn as follows: 0.025 g sinomenine was weighed accurately, and put into a beaker containing 50 mL phosphate buffer solution (adjusted to pH 7.4 with NaOH) or artificial gastric juice (prepared from 1 N HCl, pH 1.2). Then, the beaker was placed in a shaking bed (at 37 ± 1 °C, 180 rpm) for 24 h to allow complete dissolution of sinomenine. The solution was transferred to a 100 mL volumetric flask to obtain a 0.05 g/L solution, and 10 mL of 0.005, 0.04, 0.02, 0.01, 0.005, 0.0025 g/L solution was prepared, respectively. Their absorbency was determined by UV spectrophotometry at 260 nm (for PBS solution) and 230 nm (for artificial gastric juice), respectively. The standard curve of sinomenine was plotted by the absorbency (A) evolution with concentration (C), that is, for PBS solution: $A = 13.89C + 0.09$ ($r^2 = 0.9996$); for artificial gastric juice: $A = 16.40C + 0.11$ ($r^2 = 0.9995$).

The drug load pellet was suspended in 5 mL PBS solution (0.1 M, pH 7.4) or artificial gastric juice (0.1 M, pH 1.2), and then transferred into a dialysis bag. The dialysis bag was sealed and immersed into 100 mL of PBS or artificial gastric juice. The system was shaken in a shaking water bath at 37 °C. At predetermined intervals, 1 mL of PBS solution or artificial gastric juice was taken out and replaced by fresh PBS or fresh artificial gastric juice. The drug concentration was determined by measuring the absorbance at 260 nm (for PBS) and 230 nm (for artificial gastric juice) in an ultraviolet–visible spectrophotometer (UV-1600 shimodzu). By comparing the amount of the released drug and the total drug loading, cumulative releases were obtained. Each sample batch was analyzed in triplicate.

Acknowledgments

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