Carbohydrate Polymers 74 (2008) 862–867

Contents lists available at ScienceDirect

Carbohydrate Polymers

journal homepage: www.elsevier.com/locate/carbpol

Preparation, characterization, and in vitro drug release behavior of biodegradable chitosan-graft-poly(1, 4-dioxan-2-one) copolymer

Gui-Ying Liu [a], Yan-Li Zhai [a], Xiu-Li Wang [a,*], Wen-Tao Wang [a], Yan-Bo Pan [a], Xue-Ting Dong [a], Yu-Zhong Wang [a,b,*]

[a] Center for Degradable and Flame-Retardant Polymeric Materials, Key Laboratory of Green Chemistry and Technology(MoE), College of Chemistry, Sichuan University, 29 Wangjiang Road, Chengdu 610064, China
[b] State Key Laboratory of Polymer Materials Engineering, Chengdu 610065, China

ARTICLE INFO

Article history:
Received 6 March 2008
Received in revised form 28 April 2008
Accepted 6 May 2008
Available online 13 May 2008

Keywords:
Chitosan
p-Dioxanone
Graft copolymer
Drug controlled release

ABSTRACT

A novel copolymer of chitosan-g-poly(*p*-dioxanone) (CGP) was synthesized in bulk by ring-opening polymerization of *p*-dioxanone (PDO) initiated by the hydroxyl group or amino group of chitosan using $SnOct_2$ as catalyst. The chemical structure was determined by ^1H NMR. It was found that the feed ratio of chitosan to PDO had a great effect on the degree of polymerization (DP) and the substitution (DS) of PDO. The thermal stability and crystallization behavior of graft copolymer CGP were closely related to the values of DP and DS. When the resulting copolymer was used as Ibuprofen carrier, the release rate of Ibuprofen decreased compared with that of pure chitosan carrier. The drug release behavior was also influenced by the structure of graft copolymers.

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 unit of β-(1-4)-2-amino-deoxy-β-D-glucan. Due to its biodegradability, biocompatibility, and non-toxicity, CS has been widely applied in biomedical fields as a carrier for drug delivery, wound dressing, etc. (Azab et al.2007; Muzzarelli et al., 2007; Sarmento, Ribeiro, Veiga, Ferreira, & Neufeld, 2007). However, its insolubility in common solvents and its poor thermoplasticity restrict its wider researches and application. Apart from its biodegradability in physiological conditions, CS has reactive amino and hydroxyl groups, which provide the possibility to solve those problems by using chemical modifications such as graft reactions (Gaffar, Rafie, & Tahlawy, 2004; Gorochovceva & Makuska, 2004; Jayakumar, Prabaharan, Reis, & Mano, 2005) and ionic interactions (Dutta, Ravikumar, & Dutta, 2002; Li, Shi, Du, & Tang, 2007; Mao et al., 2001).

Synthetic aliphatic polyester, such as poly(lactic acid) (PLA), poly(ε-caprolactone) (PCL), poly(lactic-*co*-glycolic acid) (PLGA), and poly(3-hydroxybutyrate) (PHB) have attracted much attention in recent years due to their excellent biocompatibility and biodegradability, and have been frequently used as surgery repair materials, or drug delivery systems (Albertsson & Varma, 2002; Gupta, Revagadea, & Hilborn, 2007; Ikada & Tsuji, 2000; Vert, Schwach, & Coudance, 1998; Wang, Rodriguez-Perez, Reis, & Mano, 2005). It is promising to prepare amphiphilic copolymers (Feng & Dong, 2006; Fujioka et al., 2004; Liu, Li, Liu, & Fang, 2004; Wu et al., 2005; Yu, Wang, Deng, & Jing, 2006) or the blends based on chitosan and these aliphatic polyesters for various purposes (Sarasam, Krishnaswamy, & Madihally, 2006; Sebastien, Stephane, Copinet, & Coma, 2006).

As one of the biodegradable and biocompatible aliphatic polyesters, PPDO has high flexibility and good tensile strength, which can be utilized not only in medical materials but also in films, molded products, laminates, foams, non-woven material, adhesives, and coatings (Nishida, Yamashita, Hattori, Endo, & Tokiwa, 2000; Yang, Wang, & Wang, 2002a). However, the discontinuous degradation rate in human body is one of main factors to limit its wide application in medical fields. Graft copolymerization is a versatile method for providing functionality and regulating polymer properties for the resulting polymers (Chen, Zhou, Wang, Wang, & Yang, 2006a). However, there are a few reports on the graft copolymerization of PPDO with other polymers such as starch, PVA, etc. (Chen, Wang, Yang, Wu, & Wang, 2006b; He et al., 2006; Wang, Yang, & Wang, 2004a). Combining chitosan with PPDO would provide a new amphiphilic copolymer and could be applied in a drug delivery system.

* Corresponding authors. Address: Center for Degradable and Flame-Retardant Polymeric Materials, Key Laboratory of Green Chemistry and Technology (MoE), College of Chemistry, Sichuan University, 29 Wangjiang Road, Chengdu 610064, China. Tel./fax: +86 28 85410259.
E-mail addresses: xiuliwang1@163.com (X.-L. Wang), yzwang@email.scu.edu.cn (Y.-Z. Wang).

0144-8617/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carbpol.2008.05.002

In this research, we synthesized chitosan-g-PPDO copolymer (CGP) in bulk by ring-opening polymerization of *p*-dioxanone initiated by the hydroxyl group or amino group of chitosan in the presence of stannous octoate ($SnOct_2$). The incorporation of PPDO into CS through graft polymerization would lead to the controllability of physical properties by controlling the chemical structure of the graft copolymer. The copolymer was characterized by ^{1}H NMR, DSC, TG, and WAXD. Its *in vitro* release of Ibuprofen was studied in a phosphate buffered solution.

2. Experimental section

2.1. Materials

CS (Mn = 8×10^5 Da, 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. *p*-Dioxanone (PDO), which was provided by the Pilot Plant of the Center for Degradable and Flame-Retardant Polymeric Materials (Chengdu, China), was dried over CaH_2 for 48 h, and distilled twice under reduced pressure immediately before use. Stannous octoate ($SnOct_2$) was purchased from Sigma (USA) and used as received. Ibuprofen (IBU) was purchased from Hubei Baike Hengdi Medicine. All the other commercially available chemicals were used as received without further purification.

2.2. Synthesis of CGP

A typical synthetic procedure was as follows: CS was placed in a dried flask quickly and then the reactor was vacuumed and purged with nitrogen gas three times. After that, PDO was slowly added into the reactor through an injector while agitating. It was placed in an oil bath at 60 °C for 2–3 h with stirring. Then the toluene solution of $SnOct_2$ was injected in the flask under nitrogen, and the molar ratio of PDO to $SnOct_2$ was 1000:1. The reaction was allowed to proceed for 48 h at 100 °C. After quick cooled in ice water, the crude products were extracted with acetone in a Soxhlet apparatus for 48 h to remove the homopolymer. The final product, CGP, was dried at 40 °C in vacuum until constant weight was reached. The yields of copolymers with different molar ratios of PDO to CS are summarized in Table 1.

2.3. ^{1}H NMR spectroscopy

The ^{1}H NMR spectra of graft copolymer were recorded with Bruker AV400 spectrometers (Bruker, Germany) at 400 MHz in DMSO-*d*6.

2.4. Differential scanning calorimetry (DSC)

DSC datum was recorded with TA DSC Q100 (TA instruments, USA) under a nitrogen atmosphere 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 fusing (ΔH_m) were determined from DSC curves.

2.5. Thermal gravimetry (TG)

TG analysis was recorded with TA TGA Q500 (TA instruments, USA) under a nitrogen atmosphere at 10 °C/min.

2.6. Wide-angle X-ray diffraction (WAXD)

Wide-angle X-ray diffraction (WAXD) was recorded by using an X-ray diffractometer (Philips X'Pert X-ray diffractometer) with CuKα radiation in the range of 10–50° at 40 kV and 30 mA.

2.7. In vitro release behavior of IBU

Ibuprofen (IBU)-loaded powders were simply prepared by dissolving a certain amount of IBU in 5 mL DMF solutions of CGP (C = 60 mg/mL) with stirring for 24 h. Then, the drug-loaded powders were obtained after the evaporation of DMF under vacuum. Finally, the dried powders were compressed into flakes at room temperature. For a comparison, ibuproben-loaded chitosan powders were prepared in a similar procedure except that chitosan was directly mixed with the DMF solution of IBU.

About 100 mg of CGP-IBU flakes were re-suspended in 5 mL of 0.2 M (pH 7.4) phosphate buffered solution (PBS) and were put into a tied dialytic bag (3500 Da cutoff), which then was immersed into 100 mL PBS. The entire system was kept at 37 °C. After a predetermined period, 1 mL of PBS medium was drawn out from release system for analysis, and 1 mL of fresh medium was added into the release system. The amount of released IBU was determined by UV analysis on a UV-240 spectrophotometer (Shimadzu, Japan). The absorbance had been analyzed at a fixed wavelength of 221 nm, a strong absorption band of IBU.

3. Results and discussion

3.1. Structure parameters of CGP

The grafting copolymers were prepared by ROP of 1, 4-dioxan-2-one initiated by the hydroxyl group or amino group of chitosan

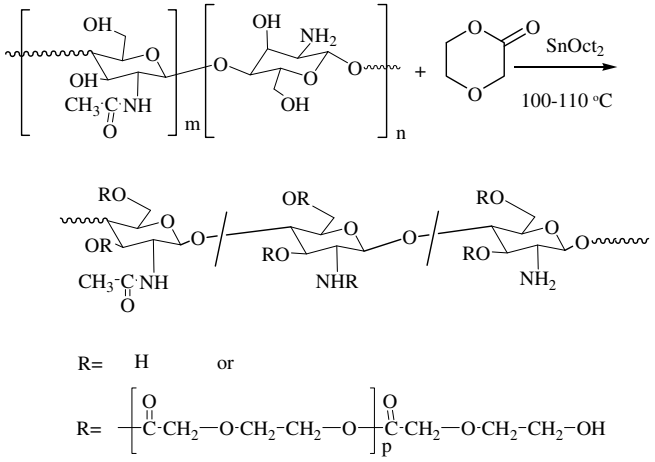
Table 1
Structure parameters and thermal decomposition temperature of CGPs

Sample	PDO/CS molar ratio	Yields (%)	F_{PDO}/F_{CS}[a]	DS[b]	DP[c]	$T_{5\%}$[d] (°C)	T_{max1}[d] (°C)	T_{max2}[d] (°C)
Chitosan	–	–	–	–	–	275	311	–
CGP1	6	66	5.97	0.92	10.7	147	211	301
CGP2	10	72	9.21	0.62	15.7	159	243	300
CGP3	20	73	10.44	0.59	17.7	–	–	–
CGP4	30	86	25.03	0.55	29.0	184	257	296
CGP5	40	77	10.83	0.61	17.9	–	–	–

$T_{5\%}$ represents the temperature of 5% weight decomposition.
T_{max} represents the temperature at which the decomposition rate is maximal.
[a] Molar composition in graft copolymer, calculated by ^{1}H NMR: $F_{PDO}/F_{CS} = (Ia + Ia')/2(I_1 + I_{1'})$.
[b] The degree of substitution of copolymer, calculated by ^{1}H NMR: $DS = Ia'/2(I_1 + I_{1'})$.
[c] The degree of polymerization of PPDO, calculated by ^{1}H NMR: $DP = (Ia + Ia')/Ia'$.
[d] Data determined by TG and DTG.

in the presence of $SnOct_2$. The structure of CGP is shown in Scheme 1. To obtain detailed information on the microstructure of CGP, including the degree of substitution (DS) and degree of polymerization (DP), ^1H NMR experiments were performed.

The ^1H NMR spectrum of CGP2 (CS:PDO = 1:10, mol/mol) is shown in Fig. 1. The multiples at 3.3–3.8 ppm and the singlet at 2.09 ppm were ascribed to the ring methine protons (H3, H4, H5, H6) of the chitosan and the methyl group of *N*-acetyl glucosamine units survived from the saponification of chitin, respectively (Wu et al., 2005). Compared with the ^1H NMR spectrum of CS (Detchprohm, Aoi, & Okada, 2001; Wu et al., 2005; Zong, Kimura, Takahashi, & Yamane, 2000), that of graft copolymer showed some new proton signals at 4.16, 3.70, and 4.22 ppm assigned to the a-, b-, and c-methylene of PPDO side chain (Fig. 1).

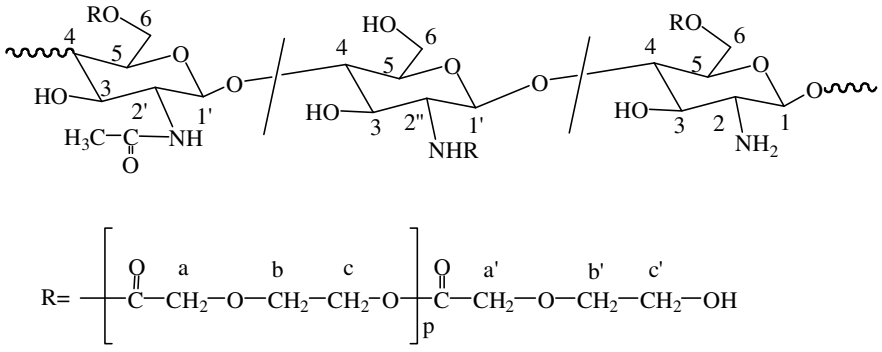


Scheme 1. The chemical structure of CGP.

At the same time, three different chemical shifts for H2 of CS marked by 2, 2′, 2″ could be found by magnifying the spectrum due to the electron withdrawing effect of NH_2, $NHCOCH_3$, and NHPPDO. The above evidence demonstrated that a small amount of PPDO was grafted onto CS via the initiation of the amino group of chitosan. A similar result was also observed by Feng et al when they prepared the chitoan-PLA hybrid amphiphilies (Feng & Dong, 2006). They also reported another new peak at 4.19 ppm ascribed to the methylene group of H6 connected to PLA chain. However, in our system this peak could not be found because of overlapping.

Substitution of PPDO for the 2-amino group of the pyranose ring was also suggested by the appearance of a signal (H1′) due to H1 of the N-substituted pyrannose unit, which was overlapped by the signal ascribed to H1 of *N*-acetyl glucosamine unit at 4.58–4.61 ppm (Detchprohm et al., 2001). On the contrary, the proton of H1 of the unreacted pyrannose unit was found at 4.33 ppm. The proton of NH_2 was detected at 8.13 ppm, meaning that the graft copolymer still had free amino groups.

On the basis of the above results, the degree of substitution (DS) and the degree of polymerization (DP) of PDO in the copolymers were determined from the signal intensities of both PDO unit and CS unit. The signals of H-1 proton of CS including H-1 and



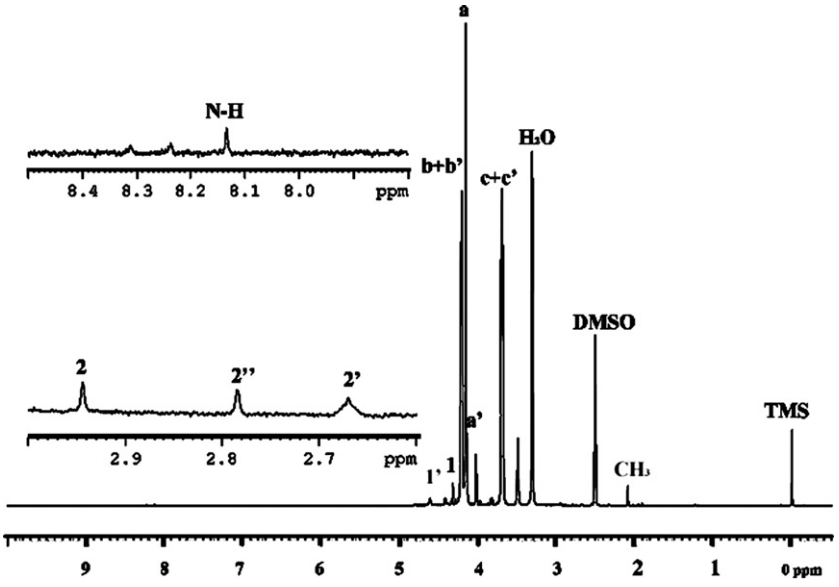


Fig. 1. ^1H NMR spectrum of CGP2.

H-1′ at 4.33 and 4.61 ppm, respectively, as well as H-a′ (the terminal methylene group of PPDO branches) at 4.14 ppm could be clearly differentiated from the other protons of chitosan and PPDO. Therefore, DS and DP values of PDO branches could be calculated as follows: DS = $Ia'/2(I_1 + I_{1'})$ DP = $(Ia + Ia')/Ia'$.

The structural parameters of CGP are summarized in Table 1. It was found that DP values increased with the increase of PDO content, and reached its maximum when the molar ratio of PDO to chitosan was 30. With the further increase of PDO content, however, DP value decreased. At the same time the yields of graft copolymers also decreased (from 86% to 77%), meaning that the homopolymerization of PDO was inevitable at high PDO content. Interestingly, DS value was almost invariable when the feed molar ratio of CS to PDO was higher than 10. According to our reasoning, the initiation ability of hydroxyl group or the amino group of chitosan was not high because of the heterogeneous reaction, which made DS value almost independent of the feed ratio of CS to PDO. A few initiated sites made more PDO to be coordinated into the tin alkoxide, lengthening PPDO chains.

3.2. Thermal stability of CGP

The thermal stability of copolymer was studied by TG in N_2 atmosphere at a heating rate of 10 °C/min, and the TG and DTG curves of CS and graft copolymers are shown in Fig. 2. The various decomposition temperatures determined from TG and DTG curves are given in Table 1. All of the copolymers had two decomposition stages and two maximum decomposition temperatures (T_{max}). T_{max1} was corresponding to the decomposition of PPDO and T_{max2} was ascribed to that of chitosan. However, T_{max2} of CGP was still lower than that of pure chitosan. It was because the hydrogen bond of chitosan was partially destroyed by the introduction of graft PPDO onto the backbone of chitosan (Wu et al., 2005).

It is clear that the thermal stability of chitosan was better than that of the copolymers as shown in Table 1. The 5%-weight-loss temperature ($T_{5\%}$) and the maximum decomposition temperature (T_{max}) of chitosan were 275 and 311 °C, respectively. However, both $T_{5\%}$ and T_{max} of CGP1, CGP2, CGP4 were decreased compared with chitosan. Beside this, it was found that the structure of copolymers had a significant influence on the stability of CGP. CGP1 with the shortest PPDO chains started to decompose at 147 °C, while CGP2 with longer PPDO chains had a higher initial decomposition temperature (159 °C). As far as CGP4 was concerned, its initial decomposition temperature increased to 184 °C. Besides the initial decomposition, the variation of T_{max1} of CGP with different structures had the same trend, that is, the longer the side chains, the better the thermal stability of graft copolymers. For example, the values of T_{max1} of CGP4, CGP2, and CGP1 were 257, 243, and 211 °C, respectively. This phenomenon also can be found in other systems (Yuan, Yuan, Zhang, & Xie, 2007).

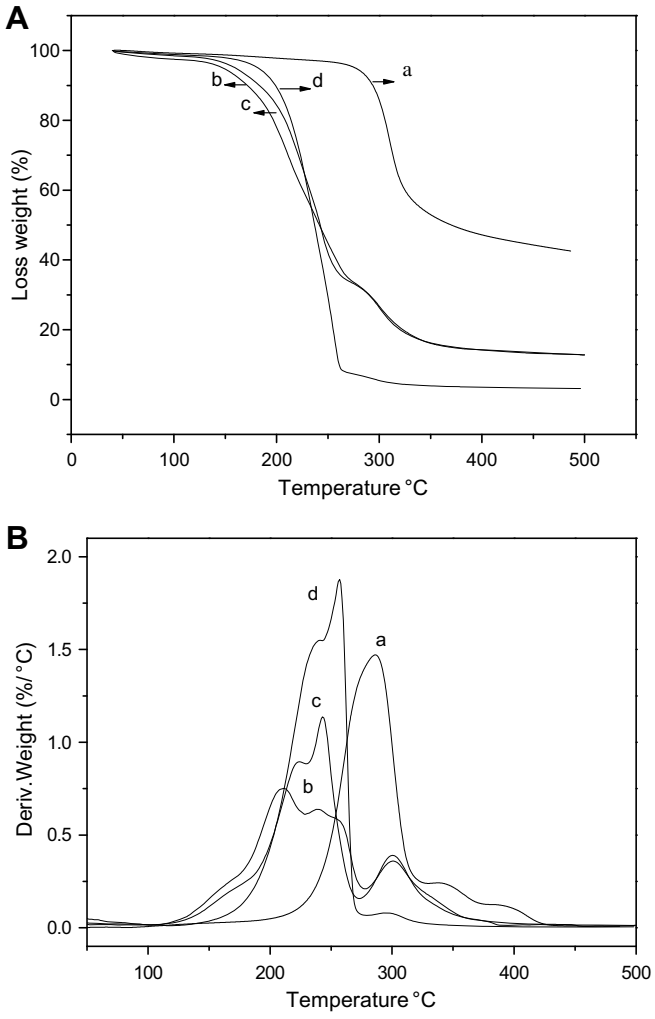


Fig. 2. TG and DTG curves of chitosan (a), CGP1 (b), CGP2 (c), CGP4 (d).

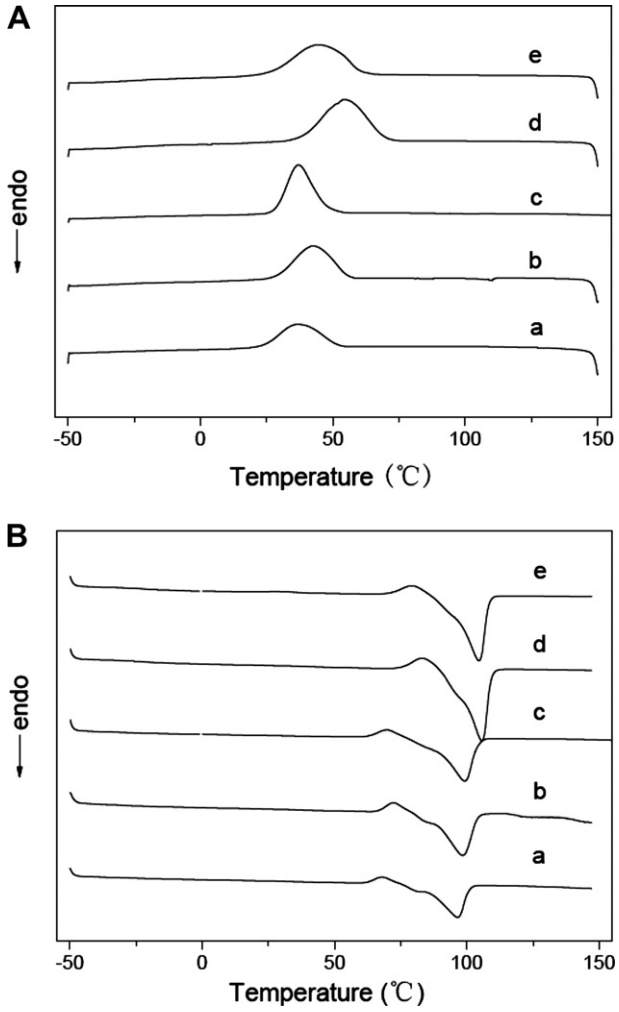


Fig. 3. DSC cooling (A) and heating curves (B) of CGP1 (a), CGP2 (b), CGP3 (c), CGP4 (d), CGP5 (e).

3.3. Thermal transition behavior of CGP

Fig. 3 shows the cooling and heating scans of CGP at 10 °C/min for different samples after keeping at 140 °C for 5 min in order to erase their thermal history. All of the relevant enthalpies (ΔH_m and ΔH_c), the glass transition as well as the melting temperatures (T_g and T_m) determined from Fig. 3, are listed in Table 2.

As shown in Table 2, the graft structure has a significant influence on the crystallization behavior of CGPs. The graft copolymers exhibited crystallization exothermal peaks around 36–54 °C, depending on their graft structures. CGP1 with the shortest PPDO grafts had the lowest crystallization enthalpy (ΔH_c), which was attributed to the weak driving forces of crystallization of the grafted PPDO. The crystallization enthalpy increased with the increase of the length of PPDO grafts. For all the samples studied in the paper, the number of PPDO chains did not have considerable effect on the crystallization behavior of copolymer, which might be due to too few grafts. CGP4, which had the longest grafts (DP = 29.0), had the highest crystallization enthalpy (−67.4 J/g) determined from the cooling scan curve. This can be ascribed to the side-chain crystallization of the comb-shaped macromolecule (Choi, Kim, & Park, 1999; Wang, Yang, Wang, Chen, & Chen, 2004b).

The heating scans (Fig. 3B) revealed that all of the samples exhibited a small re-crystallization exothermal peak before melting, which could be due to the fact that imperfect crystals form more perfect crystals at higher temperature. This phenomenon was similar to those of pure PPDO (Andjelic et al., 2001; Sabino, Feijoo, & Muller, 2000), PBS (Chae, Kim, & Kim, 2004) and chitosan-g-PLLA (Feng & Dong, 2006). It was reported by Andjelic et al. even at heating rate of 15 °C/min, an exothermal peak attributed to recrystallization could be found, followed by melting of the recrystallized crystallites. The length of PPDO grafts was low compared with pure PPDO, which made it easier to form perfect crystals. The melting point (T_m) of CGPs was closely related to the length of PPDO grafts. That is, the higher the degree of polymerization, the higher the melting temperature and melting enthalpy.

From Table 2, we can find that the glass transition temperature (T_g) of CGPs is also influenced by the length of PPDO grafts, showing a nearly linear variation with the DP value. CGP4 with the longest PPDO chain had the highest T_g (−23.3 °C). The T_g of CGP1 could not be found as the PPDO chain was too short. Compared with the T_g of pure PPDO (about −10 °C), the glass transition temperature of CGPs was still rather low, which was ascribed to the low molecular weight of PPDO chain.

3.4. Crystallization structure of CGP

The WAXD patterns of CS and CGPs are shown in Fig. 4. Pure CS had two broad peaks at 10.5° and 20.1°, which were ascribed to crystal form I and II, respectively (Dung, Rinaudo, & Desbriers, 1994; Wu et al., 2005). Compared with original CS, CGP1 and CGP4 had new strongest reflection at $2\theta = 22.00°$, 23.91°, and 29.22°, which were attributed to the crystallization of PPDO chain (Yang, 2003b). This means that the DP value of PPDO graft was high enough to be able to form crystallization, which was consistent with DSC results. From Fig. 4, we could also see that the reflection of CS backbone disappeared, indicating that the original crystallinity of chitosan was destroyed when PPDO was grafted onto chitosan. A similar phenomenon can be found in chitosan-PLA graft copolymers (Wu et al., 2005).

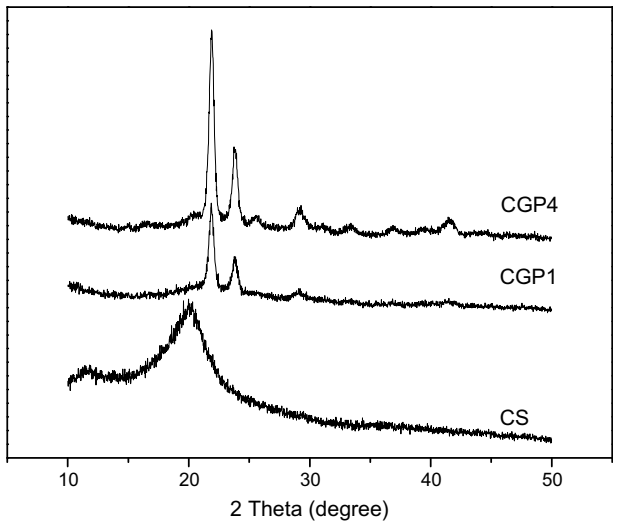


Fig. 4. WAXD pattern of CS, CGP1, and CGP4.

3.5. In vitro IBU release behavior

Fig. 5 shows the release profiles of IBU from chitosan, CGP3, CGP4, and CGP5 in 0.2 M PBS (pH 7.4) at 37 °C. The in vitro release behavior of IBU from CS and CGPs indicated that they had a same release trend. About 86.9% of IBU was released from CS in 4.5 h, in

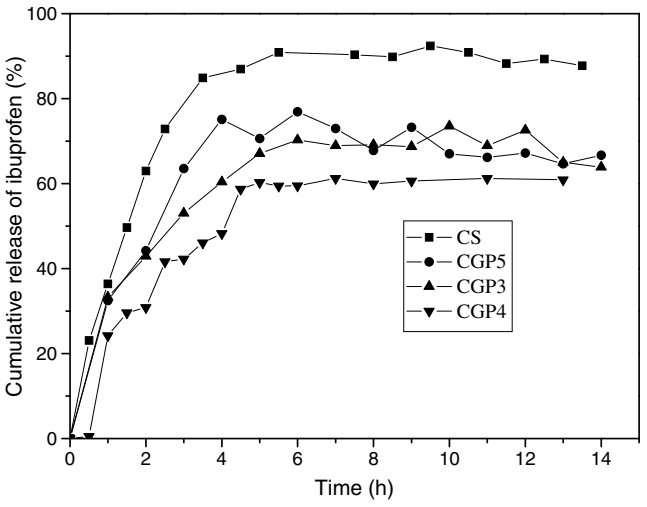


Fig. 5. In vitro release profiles of IBU from CS, CGP3, CGP4, and CGP5 in phosphate buffer solution (pH 7.4) at 37 °C.

Table 2
Relevant transitions and enthalpies determined by DSC

Sample	Cooling		Heating				
	T_c (°C)	ΔH_c (J/g)	T_g (°C)	T_{c1} (°C)	ΔH_{c1} (J/g)	T_m (°C)	ΔH_m (J/g)
CGP1	36.0	−37.6	–	68.5	−6.9	96.6	44.8
CGP2	42.0	−46.9	−31.2	72.8	−9.3	98.5	56.1
CGP3	37.0	−52.4	−28.9	70.3	−7.7	99.2	64.5
CGP4	54.1	−67.4	−23.3	83.6	−11.0	105.6	78.6
CGP5	43.9	−61.9	−26.9	79.8	−9.9	104.6	81.8

which, however, the cumulative release percentages of IBU from CGP3, CGP4, and CGP5 were 72.9%, 68.9%, and 58.7%, respectively. All of the CGP samples showed an initial burst release followed by a slowly sustained release phase. Moreover, the cumulative release percentage of CGP4 was much lower than those of CGP3 and CGP5, indicating that the cumulative release percentage was highly affected by the degree of polymerization (DP). The higher the DP value of PPDO grafts, the lower the cumulative release percentage. Those phenomena indicated that the release of IBU in CGPs was controlled by the diffusion and that the hydrophobicity of the carrier was crucial. The higher DP value made the copolymer more hydrophobic. The strong hydrophobicity of the carrier made water penetration difficult, and the drug release slowed.

4. Conclusions

A novel biodegradable copolymer, chitosan-g-PPDO, was synthesized in bulk via the ring-opening graft polymerization of *p*-dioxanone onto chitosan, which was initiated by the hydroxyl group or amino group of chitosan in the presence of stannous octoate. The feed ratio of CS to PDO had great influence on the DS and DP value of the copolymer. The thermal and crystallization behaviors of the copolymers were dependent on the structure of the copolymers. The in vitro release behavior of IBU indicated that the copolymers seem to be a promising vehicle for controlling delivery drugs.

Acknowledgements

This work was supported financially by the National Science Fund for Distinguished Young Scholars (50525309) and the Program for New Century Excellent Talents in University. The authors also acknowledge the Analytical & Testing Center of Sichuan University for the NMR measurements.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carbpol.2008.05.002.

References

Albertsson, A. C., & Varma, I. K. (2002). Aliphatic polyesters: Synthesis, properties and applications. *Advances in Polymer Science, 157*, 1–40.

Andjelic, S., Jamiolkowski, D., Mcdivitt, J., Fischer, J., Zhou, J., & Vetrecin, R. (2001). Crystallization study on absorbable poly(*p*-dioxanone) polymers by differential scanning calorimetry. *Journal of Applied of Polymer Science, 79*, 742–759.

Azab, A. K., Doviner, V., Orkin, B., Kleinstem, J., Srebnik, M., Nissan, A., et al. (2007). Biocompatibility evaluation of crosslinked chitosan hydrogels after subcutaneous and intraperitoneal implantation in the rat. *Journal of Biomedical Materials Research: Part A, 83A*, 414–422.

Chae, D. W., Kim, B. C., & Kim, D. K. (2004). Effects of shearing and comonomer content on the crystallization behavior of poly(butylenes succinate-co-butylene 2-ethyl-2-methyl succinate). *Polymer International, 53*, 1266–1273.

Chen, S. C., Zhou, Z. X., Wang, Y. Z., Wang, X. L., & Yang, K. K. (2006a). A novel biodegradable poly(*p*-dioxanone)-grafted poly(vinyl alcohol) copolymer with a controllable in vitro degradation. *Polymer, 47*, 32–36.

Chen, S. C., Wang, X. L., Yang, K. K., Wu, G., & Wang, Y. Z. (2006b). Copolymerization of poly(vinyl alcohol)-graft-poly(1,4-dioxan-2-one) with designed molecular structure by a solid-state polymerization method. *Journal of Polymer Science Part A: Polymer Chemistry, 44*, 3083–3091.

Choi, E. J., Kim, C. H., & Park, J. K. (1999). Structure–property relationship in PCL/starch blend compatibilized with starch-g-PCL copolymer. *Journal of Polymer Science: Part B. Polymer Physics, 37*, 2430–2438.

Detchprohm, S., Aoi, K., & Okada, M. (2001). Synthesis of a novel chitin derivative having oligo(ε-caprolactone) side chains in aqueous reaction media. *Macromolecular Chemistry and Physics, 202*, 3560–3570.

Dung, P. M., Rinaudo, M., & Desbriers, J. (1994). Water soluble derivatives obtained by controlled chemical modifications of chitosan. *Carbohydrate Polymers, 24*, 209–214.

Dutta, P. K., Ravikumar, M. N. V., & Dutta, J. (2002). Chitin and chitosan for versatile applications. *Journal of Macromolecular Science: Part C. Polymer Reviews, C42*, 307–354.

Feng, H., & Dong, C. M. (2006). Preparation, characterization, and self-assembled properties of biodegradable chitosan-poly(L-lactide) hybrid amphiphiles. *Biomacromolecules, 7*, 3069–3075.

Fujioka, M., Okada, H., Kusaka, Y., Nishiyama, S., Noguchi, H., Ishii, S., et al. (2004). Enzymatic synthesis of chitin- and chitosan-graft aliphatic polyesters. *Macromolecular Rapid Communication, 25*, 1776–1780.

Gaffar, M. A., Rafie, S. M. E., & Tahlawy, K. F. E. (2004). Preparation and utilization of ionic exchange resin via graft copolymerization of β-CD itaconate with chitosan. *Carbohydrate Polymers, 56*, 387–396.

Gorochovceva, N., & Makuska, R. (2004). Synthesis and study of water-soluble chitosan-*O*-poly(ethylene glycol) graft copolymers. *European Polymer Journal, 40*, 685–691.

Gupta, B., Revagadea, N., & Hilborn, J. (2007). Poly(lactic acid) fiber: An overview. *Progress in Polymer Science, 32*, 455–482.

He, R., Wang, X. L., Wang, Y. Z., Yang, K. K., Zeng, J. B., & Ding, S. D. (2006). A study on grafting poly(1,4-dioxan-2-one) onto starch via 2,4-tolylene diisocyanate. *Carbohydrate Polymer, 65*, 28–34.

Ikada, Y., & Tsuji, H. (2000). Biodegradable polyesters for medical and ecological applications. *Macromolecular Rapid Communication, 21*, 117–132.

Jayakumar, R., Prabaharan, M., Reis, R. L., & Mano, J. F. (2005). Graft copolymerized chitosan present status and applications. *Carbohydrate Polymers, 62*, 142–158.

Li, T., Shi, X. W., Du, Y. M., & Tang, Y. F. (2007). Quaternized chitosan/alginate nanoparticles for protein delivery. *Journal of Biomedical Materials Research: Part A, 83*, 383–390.

Liu, L., Li, Y., Liu, H., & Fang, Y. E. (2004). Synthesis and characterization of chitosan-graft-polycaprolactone copolymers. *European Polymer Journal, 40*, 2739–2744.

Mao, H. Q., Roy, K., Troung-Le, V. L., Janes, K. A., Lin, K. Y., Wang, Y., et al. (2001). Chitosan-DNA nanoparticles as gene carriers: Synthesis, characterization and transfection efficiency. *Journal of Controlled Release, 70*, 399–421.

Muzzarelli, R. A. A., Morganti, P., Morganti, G., Palombo, P., Palombo, M., Biagini, G., et al. (2007). Chitin nanofibrils/chitosan glycolate composites as wound medicaments. *Carbohydrate Polymers, 70*, 274–284.

Nishida, H., Yamashita, M., Hattori, N., Endo, T., & Tokiwa, Y. (2000). Thermal decomposition of poly(1,4-dioxan-2-one). *Polymer Degradation and Stability, 70*, 485–496.

Sabino, M. A., Feijoo, J. L., & Muller, A. J. (2000). Crystallisation and morphology of poly(*p*-dioxanone). *Macromolecular Chemistry and Physics, 201*, 2687–2698.

Sarasam, A. R., Krishnaswamy, R. K., & Madihally, S. V. (2006). Blending chitosan with polycaprolactone: Effects on physicochemical and antibacterial properties. *Biomacromolecules, 7*, 1131–1138.

Sarmento, B., Ribeiro, A., Veiga, F., Ferreira, D., & Neufeld, R. (2007). Oral bioavailability of insulin contained in polysaccharide nanoparticles. *Biomacromolecules, 8*, 3054–3060.

Sebastien, F., Stephane, G., Copinet, A., & Coma, V. (2006). Novel biodegradable films made from chitosan and poly(lactic acid) with antifungal properties against mycotoxinogen strains. *Carbohydrate Polymer, 65*, 185–193.

Vert, M., Schwach, G., & Coudance, J. (1998). Something new in the field of PLA/GA bioresorbable polymers. *Journal of Controlled Release, 53*, 85–92.

Wang, Y., Rodriguez-Perez, M. A., Reis, R. L., & Mano, J. F. (2005). Thermal and thermomechanical behaviour of polycaprolactone and starch/polycaprolactone blends for biomedical applications. *Macromolecular Materials and Engineering, 290*, 792–801.

Wang, X. L., Yang, K. K., & Wang, Y. Z. (2004a). Synthesis and nuclear magnetic resonance analysis of starch-g-poly(1,4-dioxan-2-one) copolymers. *Journal of Polymer Science: Part A. Polymer Chemistry, 42*, 3417–3422.

Wang, X. L., Yang, K. K., Wang, Y. Z., Chen, D. Q., & Chen, S. C. (2004b). Crystallization and morphology of starch-g-poly(1,4-dioxan-2-one) copolymers. *Polymer, 45*, 7961–7968.

Wu, Y., Zheng, Y. L., Yang, W. L., Wang, C. C., Hu, J. H., & Fu, S. K. (2005). Synthesis and characterization of a novel amphiphilic chitosan-polylactide graft copolymer. *Carbohydrate Polymer, 59*, 165–171.

Yang, K. K. (2003b). Synthesis of *p*-dioxanone-based aliphatic polyesters and their structures and properties (in Chinese). *PhD Thesis*, Sichuan University, Chengdu.

Yang, K. K., Wang, X. L., & Wang, Y. Z. (2002a). Poly(*p*-dioxanone) and its copolymers. *Journal of Macromolecular Science: Polymer Reviews, C42*, 373–398.

Yu, H. J., Wang, W. S., Deng, C., & Jing, X. B. (2006). Synthesis and characterization of the biodegradable polycaprolactone-graft-chitosan amphiphilic copolymers. *Biopolymer, 83*, 233–242.

Yuan, W. Z., Yuan, J. Y., Zhang, F. B., & Xie, X. M. (2007). Syntheses, characterization, and in vitro degradation of ethyl cellulose-*graft*-poly(ε-caprolactone)-*block*-poly(L-lactide) copolymers by sequential ring-opening polymerization. *Biomacromolecules, 8*, 1101–1108.

Zong, Z., Kimura, Y., Takahashi, M., & Yamane, H. (2000). Characterization of chemical and solid state structures of acylated chitosans. *Polymer, 41*, 899–906.