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Synthesis, characterization and slow release properties of O-naphthylacetyl chitosan

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ABSTRACT

O-naphthylacetyl chitosan (NA-chitosan) was first prepared via protecting the amino groups with phthalic anhydride, followed by reaction with 1-naphthylacetyl chloride. The intermediates were hydrolyzed with anhydrous hydrazine to obtain final product. The derivatives of each step were characterized with Fourier transform infrared spectroscopy (FT-IR) and ^{13}C solid state nuclear magnetic resonance (NMR). Results showed NA-chitosan had both naphthylacetyl and amino groups in the main chain of the polysaccharide. Elemental analysis showed that the substitution degree of hydroxyl was 0.4. Thermogravimetric analysis (TGA, DTG) of NA-chitosan was observed with much lower decomposition peak at 283 °C than that of chitosan at 300 °C. The release of 1-naphthylacetic acid was dependent on both pH values and the medium temperature, and at pH 12.0, 60 °C the release period could last for 55 days.

1. Introduction

Slow/controlled release polymers have been widely investigated in the industry, agriculture and daily life productions for the release of active substances such as nutrients, pesticides, drugs and aromatics (Fernández-Pérez, Villafranca-Sánchez, Flores-Céspedes, & Daza-Fernández, 2011; Herrmann, 2007; Shaviv, 2000). Slow/controlled release formulations regulate the supply of active ingredients, allowing a slower and continuous delivery to the environment. Therefore, they reduce the loss caused by leaching and evaporation, maintaining the concentration between the limit of toxicity and the effectiveness (Johnston, Such, & Caruso, 2009; Treeudom, Wanichwecharungruang, Seemork, & Arayachukeat, 2011).

1-Naphthylacetic acid (NAA), one of the well known plant growth regulators (PGRs) which belongs to the auxin family, is a rooting agent and used for the vegetative propagation from stem and leaf cutting of plants. Literatures shows various kinds of slow or controlled release polymers containing NAA were synthesized which were based on both synthetic and natural polymers (Arranz & Sánchez-Chaves, 1995; Jantas & Delczyk, 2005; Jantas, 2007; Manolova, Ignatova, Rashkov, Sepulchre, & Spassky, 1997). Natural polymers such as starch, cellulose, chitosan, sodium alginate, lignin and there derivatives are more promising than synthetic polymers on food and biomedical applications due to their better biodegradability and biocompatibility (Fernández-Pérez, Villafranca-Sánchez, Flores-Céspedes, Pérez-García, & Daza-Fernández, 2010; Thérien-Aubin, Baille, Zhu, & Marchessault, 2005; Muzzarelli, 2009a; Zhang, Jin, Liu, & Du, 2001). Unfortunately, natural polymers often have low reactivity with the bioactive compound due to the poor solubility in common solvents. Many attempts have tried to improve the reactivity between the carrier and the bioactive compound which mainly include creating new, highly reactive functional groups both in the carrier and in the bioactive agent, or finding specific activators to get a direct reaction (Jantas & Delczyk, 2005; Martin, Sánchez-Chaves, & Arranz, 1999; Sánchez-Chaves, Rodríguez, & Arranz, 1997).

Among the natural polymers, chitosan is an amino polysaccharide possessing unique properties, multidimensional structures, highly sophisticated functions and wide applications in biomedical, agricultural, and other industrial areas (Muzzarelli et al., 2012; Sogias, Williams, & Khutoryanskiy, 2008). Due to the abundant hydroxyl groups and highly reactive amino groups, it offers great opportunity for chemical modification, such as acylation, N-phthaloylation, alkylation, graft copolymerization and so on, which affords a wide range of derivatives used in food and nutrition products, drugs and pharmaceuticals industry, materials science and agricultural practice (Kumar, Muzzarelli, Muzzarelli, Sashiwa, & Domb, 2004; Muzzarelli, 2009b; Pillai, Paul, & Sharma, 2009; Sashiwa & Aiba, 2004).

To our knowledge, no previous report is available on the slow release of 1-naphthylacetic acid (NAA) based on chitosan. In the present work, a novel O-naphthylacetyl chitosan (NA-chitosan) was prepared by reacting the amino groups with phthalic anhydride, followed by reaction with 1-naphthylacetyl chloride and hydrolysis under anhydrous hydrazine. The structure of

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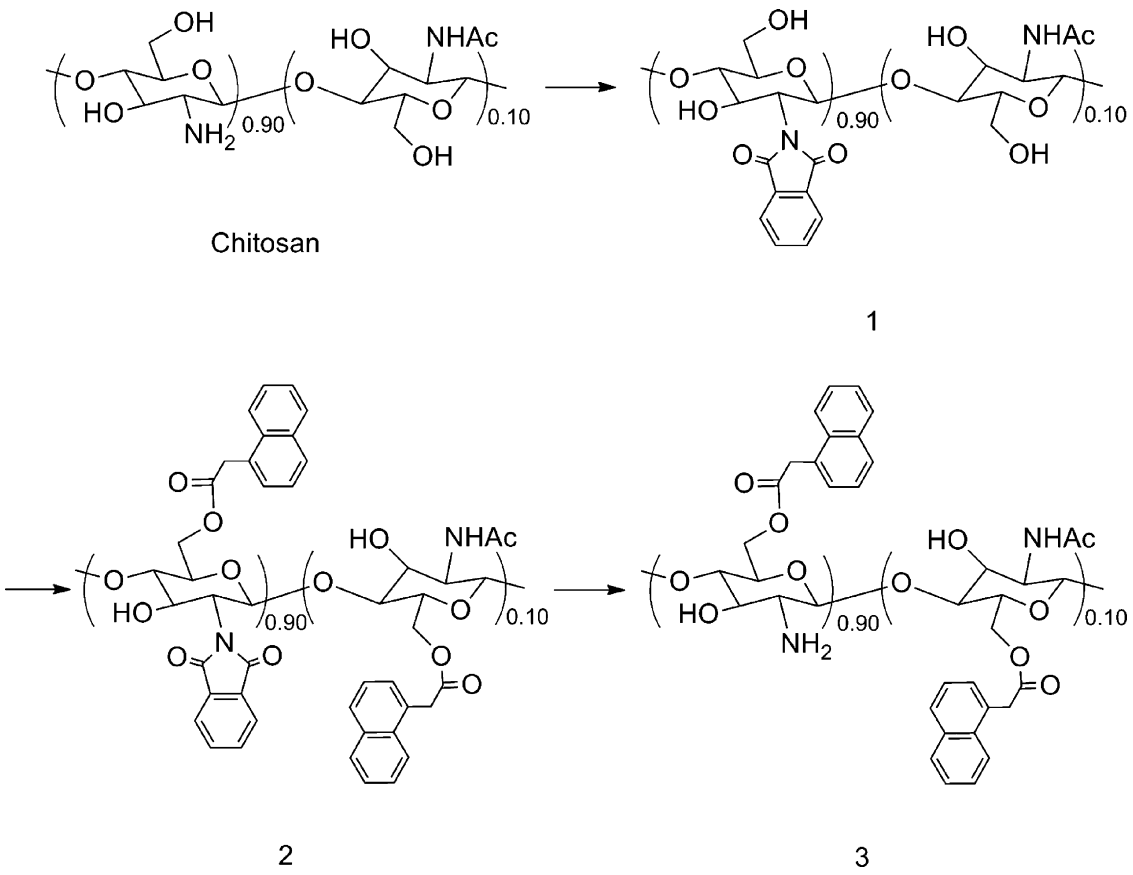

Scheme 1. Synthetic route of O-naphthylacetyl chitosan. Reagents and conditions: (1) phthalic anhydride, DMF/water, 120 °C, 8 h; (2) 1-naphthylacetyl chloride, DMF/LiCl, triethylamine, 24 h; (3) anhydrous hydrazine, absolute alcohol, 12 h.

NA-chitosan was characterized and its slow release property was also investigated.

2. Materials and methods

2.1. Materials

Chitosan was purchased from Golden-Shell Biochemical Co., Ltd. (Taizhou, China) with the deacetylation degree at 90% and was used without further purification. All other chemicals were purchased from Sinopharm Chemical Reagent Co., Ltd (Shanghai, China). N,N-dimethylformamide (DMF) was treated by stirring with CaH_2 (50 g/L) overnight, followed by vacuum distillation at 20 mmHg (2.7×10^3 Pa). Hydrazine was dried by refluxing it with an equal amount of KOH pellets for 3 h, and then distilled from fresh NaOH in a flow of dry N_2. Thionyl chloride was distilled at normal pressure prior to use. Phthalic anhydride and 1-naphthylacetic acid were of analytical grade and used without further treatments.

2.2. Synthesis of O-naphthylacetyl chitosan (Scheme 1)

The three-step synthetic route is illustrated in Scheme 1. Chitosan was converted into N-phthaloyl chitosan based on previously reported method (Kurita, Ikeda, Yoshida, Shimojoh, & Harata, 2002). A total 7.0 g (42.4 mmol) chitosan was stirred with 19.0 g (128.27 mmol) phthalic anhydride in 140 mL DMF containing 5% (vol%) distilled water. The mixture was heated at 120 °C under nitrogen for 8 h. After the reaction, the resulting pale tan mixture was cooled to room temperature and poured into ice water. The precipitate was collected by filtration, then the precipitate was stirred with 200 mL methanol at room temperature for 1 h followed by another filtration. This process was repeated for 3 times to remove all of excess phthalic anhydride. The resulting precipitate was dried under vacuum at 80 °C overnight yields a total 10.5 g product as of pale tan powder (Scheme 1, product 1).

Thionyl chloride (15 mL) was added to 11.52 g 1-naphthylacetic acid in a 100 mL two-necked round bottom flask with a magnetic stirrer. The reaction proceeded at 50 °C for 12 h, and then evaporated with a rotary evaporator to remove excess thionyl chloride. The resulting orange oil was vacuum distilled (b.p. 152 °C at 0.54×10^3 Pa) and pure 1-naphthylacetyl chloride was obtained as a yellowish oil (Ignatova, Manolova, & Rashkov, 1998).

0.5 g N-phthaloyl chitosan was dissolved in 100 mL DMF containing 10% (wt%) LiCl, 2 g 1-naphthylacetyl chloride was added dropwise over 30 min. The mixture was intensively stirred using a magnetic stirrer for 24 h at room temperature. After the reaction, the mixture was filtrated by 100 mesh nylon net to remove insoluble substances, and then the bronzy liquid was transferred into a beaker with 100 mL methanol. The reddish brown precipitate was collected by filtration, washed three times with 100 mL methanol and 200 mL distilled water respectively and dried under vacuum to get 1.5 g product as N-phthaloyl-O-naphthylacetyl chitosan (PNA-chitosan) (Scheme 1, product 2).

40 mL absolute alcohol was blended with 0.5 g PNA-chitosan powder in a 100 mL two-necked round bottom flask with a condenser and a magnetic stirrer, and then added with 1.25 mL anhydrous hydrazine. After reflux for 12 h and filtration of the formed O-naphthylacetyl chitosan (NA-chitosan), the product was washed with 30 mL methanol for 3 times and dried under vacuum to get a yellowish powder (Scheme 1, product 3).

2.3. Analytical methods

FT-IR spectra were recorded on a Nicolet NEXUS-470 Spectrometer (Thermo Fisher Scientific, USA) from KBr pellets at room temperature. About 2 mg of the samples was ground thoroughly with KBr and pellets were prepared using a hydraulic press under a pressure of 600 kg/cm^2. All spectra were recorded with an accumulation number of 32 scans and a resolution of 8 cm^{-1}.

Solid-state ^{13}C cross-polarization magic angle spinning (CP/MAS) NMR spectra were taken by a BRUKER DMX 300 (Bruker, Germany) at 25 °C using a 7 mm probe with ^{13}C frequency of 100.40 MHz at total suppression of sidebands (TOSS) and TOSS dipolar-dephased for non-quaternary carbon suppression (TOSDL-NQS) mode.

C, H, N elemental composition of chitosan and its derivatives was determined using a Vario EL III instrument (Elementar, Germany).

The solubility of chitosan and its derivates was evaluated in organic solvent such as dimethyl sulfoxide (DMSO), N,N-dimethylformamide (DMF), chloroform, toluene, and 1% aqueous acetic acid solution at the concentration of 10 mg/mL at 25 °C.

Thermogravimetric analysis (TGA, DTG) was carried out with a TGA Q50 (TA Instruments, USA). All analysis was performed with a 5 mg sample in an open aluminum pans under nitrogen atmosphere, and the gas flow rate was 40 mL/min. Then the sample was heated at constant rates of 10 °C/min during the analysis and the final temperature was up to 600 °C.

The NAA release from NA-chitosan tests was carried out in fresh buffer solutions at pH 4.0 (0.05 M NaOH, 0.288 M CH_3COOH), pH 9.2 (0.147 M $NaHCO_3$, 0.0178 M Na_2CO_3), pH 12.0 (0.01 M NaOH). A 10 cm long dialysis bag with 10 mg NA-chitosan was placed in conical bottle containing 100 mL buffer solution and incubated at 20 °C, 40 °C, and 60 °C. Periodically, 2.5 mL sample was withdrawn and analyzed by UV at 281 nm. The residue was checked by FT-IR to confirm the structure.

3. Results and discussion

Even chitosan is an attractive biomacromolecule, the poor solubility in common solvents restricts its further application. Chemoselective N-phthaloylation of chitosan not only provides protected functional groups but also improves its solubility. In our case (Scheme 1), dissolution of 0.5 g N-phthaloyl chitosan in 100 mL DMF containing 10% (wt%) LiCl enabled the acylation reactions occurred in homogeneous mixtures under mild conditions. Removal of the phthaloyl group from PNA-chitosan can be finished efficiently and conveniently by treating with anhydrous hydrazine.

FT-IR studies were carried out to confirm the structures as shown in Fig. 1. Compared the spectra of chitosan (curve a) with N-phthaloyl chitosan (curve b), the peaks at 1659 and 1599 cm^{-1} were attributed to carbonyl stretching vibration. N—H bending vibration in chitosan disappeared after the N-phthaloylation. The twin absorptions at 1778 and 1712 cm^{-1} were characteristic of imide C=O stretching vibration, and a relatively high intense peak at 721 cm^{-1} corresponded to —CH_2 bending vibration in phthalic ring demonstrated that the N-phthaloylation reaction was successful. In the case of PNA-chitosan (curve c), two new peaks at 1744 cm^{-1} and 781 cm^{-1} were assigned to the stretching vibration of ester groups in —$COOCH_2C_{10}H_9$ and —CH_2 bending vibration in the naphthyl ring (Hussein, Zainal, Yahaya, & Foo, 2002; Jantas, 2007). In the meantime, the broad band around 3443 cm^{-1} ascribed to stretching vibration of inter- and intra-molecular hydrogen bond from —NH_2 and —OH of chitosan molecules was either absented or decreased in the chitosan derivatives. After the deprotection of N-phthaloyl, the resulting NA-chitosan (curve d) revealed a characteristic absorption at 1592 cm^{-1} corresponding to N—H bending vibration in chitosan,

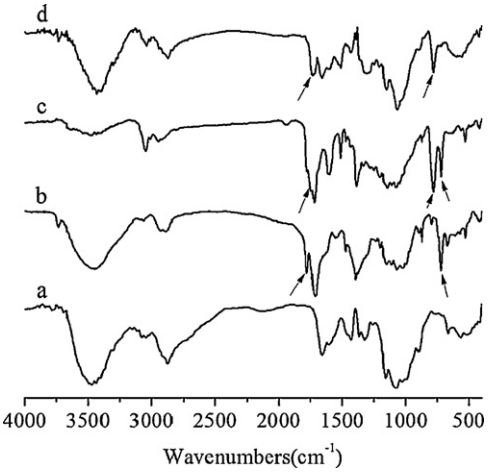

Fig. 1. FT-IR spectra of (a) chitosan; (b) N-phthaloyl chitosan; (c) N-phthaloyl-O-naphthylacetyl chitosan; (d) O-naphthylacetyl chitosan.

and absorptions at 1778, 1712 and 721 cm^{-1} due to phthalimido and aromatic groups in phthaloyl groups disappeared completely. Meanwhile, the peaks at 1738 and 781 cm^{-1} which represented O-naphthalene ester were still considerably sharp. The above data indicated that NA-chitosan had been successfully prepared.

To further validate the structure, the solid-state ^{13}C NMR spectra of the products were obtained. In the TOSS mode, chitosan showed typical chemical shift at 104.23 (C1), 86.00 (C4), 75.24 (C5, C3), 61.45 (C6), 58.47 (C2), 23.46 ppm (CH_3) (data not shown) (Gartner et al., 2011). Compared to chitosan, signals of phth, phenylene and phth C=O in N-phthaloyl chitosan were observed at 123.53, 131.42, 135.82 and 168.83 ppm (Fig. 2a$_1$) which were consistent with the previous literature (Kurita et al., 2002). Fig. 2b$_1$ shows much broad and strong peaks at 126 ppm, and the peak at 168 ppm is less sharp than Fig. 2a$_1$, and it can be explained by bonding of naphthylacetic acid, the ratio of aromatic in the main chain was increased, and the signal of phth C=O was overlapped by signals of C=O from —$COOCH_2C_{10}H_9$. After the deprotection of amino groups as shown in Fig. 2c$_1$, the signal of pyranose in NA-chitosan is significantly stronger due to the decrease of aromatic in the main chain.

In the TOSDL-NQS mode, peaks due to —CH and —CH_2 should disappear because of the short relaxation times. As expected, peaks between 20 and 100 ppm belonging to the pyranose were disappeared in TOSDL-NQS mode (Fig. 2a$_2$, b$_2$, c$_2$) compared with cures in TOSS mode (Fig. 2a$_1$, b$_1$, c$_1$). Only two peaks at 169.19 and 131.36 ppm ascribable to the carbonyl and C1, C2 of phthaloyl could be observed in N-phthaloyl chitosan (Fig. 2a$_2$). After the esterification between N-phthaloyl chitosan and 1-naphthylacetyl chloride (Fig. 2b$_2$), peaks at about 169 and 130 were much stronger than N-phthaloyl chitosan (Fig. 2a$_2$) mainly due to the bulk groups of naphthyl C5, C6 and the ester groups of —O—C=O. As discussed previously in the TOSS mode, these peaks were weak again after using anhydrous hydrazine to remove the protective groups as to NA-chitosan.

Carbon, hydrogen, nitrogen elements composition of chitosan and chitosan derivatives are given below: chitosan, Calc for $(C_6H_{11}NO_4)_{0.9}(C_8H_{13}NO_5)_{0.1}\cdot 0.56H_2O$, Found: C, 43.68; N, 7.97; H, 7.27. N-phthaloyl chitosan, Calc for $(C_{14}H_{13}NO_6)_{0.9}(C_8H_{13}NO_5)_{0.1}\cdot 0.65H_2O$, Found: C, 54.79; N, 4.82; H, 5.00. PNA-chitosan, Calc for $(C_{38}H_{29}NO_8)_{0.9}(C_{32}H_{29}NO_7)_{0.1}$, Found: C, 73.15; N, 2.15; H, 4.85. NA-chitosan, Calc for $(C_{18}H_{19}NO_5)_{0.4}(C_{20}H_{21}NO_6)_{0.1}$ $(C_6H_{11}NO_4)_{0.5}$, Found: C, 58.40; N, 6.12; H, 5.91. PNA-chitosan showed a high degree of substitution and the hydroxyl groups (1 primary hydroxyl at C6 and 1 secondary hydroxyl at C3) were fully substituted. It could be

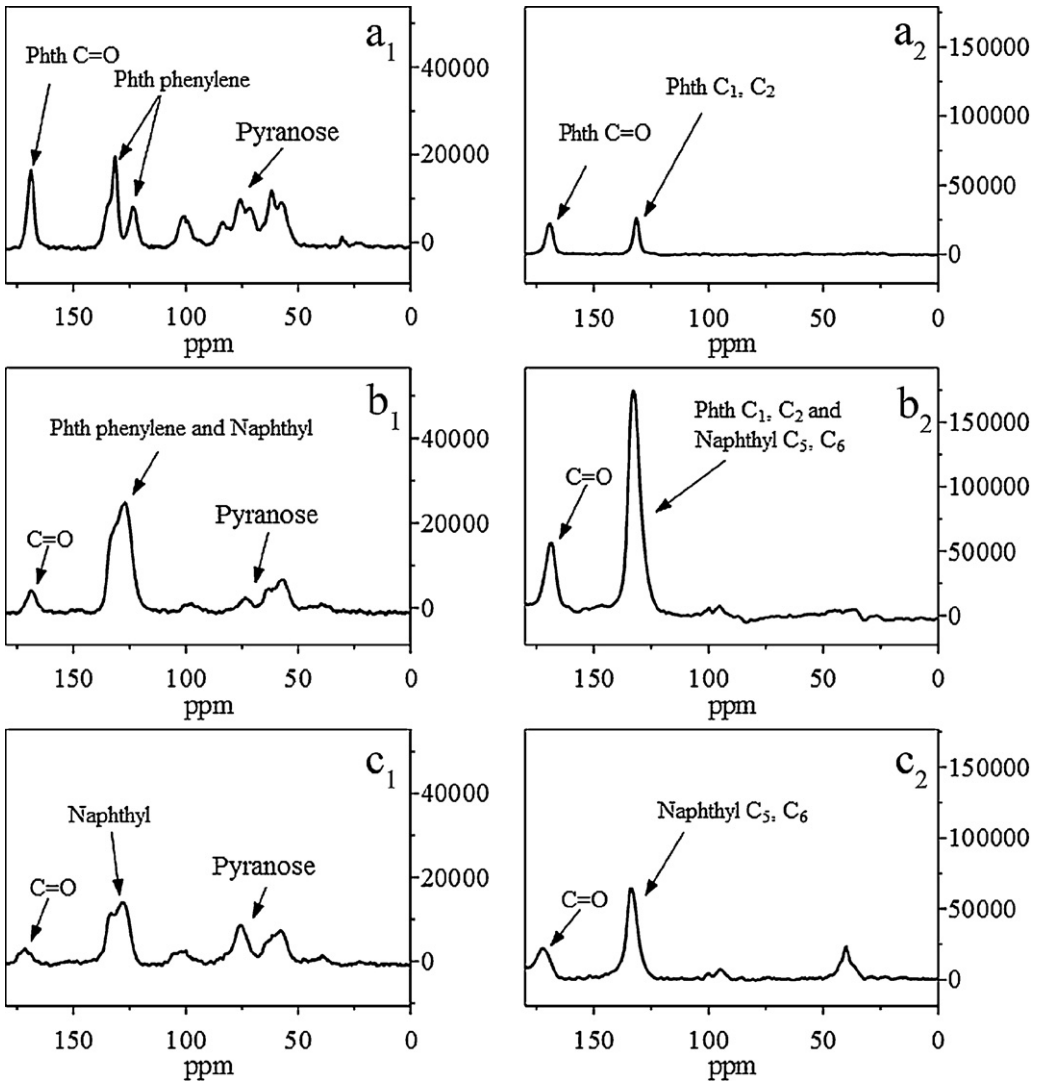

Fig. 2. Solid-state ^{13}C cross-polarization magic angle spinning NMR spectra in total suppression of sidebands mode (a_1) N-phthaloyl chitosan; (b_1) N-phthaloyl-O-naphthylacetyl chitosan; (c_1) O-naphthylacetyl chitosan; in total suppression of sidebands dipolar-dephased for non-quaternary carbon suppression mode (a_2) N-phthaloyl chitosan; (b_2) N-phthaloyl-O-naphthylacetyl chitosan; (c_2) O-naphthylacetyl chitosan.

validated from the FT-IR studies, in Fig. 1, curve c, there are no absorption around 3443 cm^{-1} ascribed to stretching vibration of inter- and intra-molecular hydrogen bond from —NH_2 and —OH of chitosan molecules. As to NA-chitosan, it could be calculated as $(C_{18}H_{19}NO_5)_{0.4}(C_{20}H_{21}NO_6)_{0.1}$ $(C_6H_{11}NO_4)_{0.5}$. The substitution degree of hydroxyl was about 0.4, which mainly causing naphthalene ester partly hydrolyzed in the alkaline environment when the deprotection of N-phthaloyl proceeded.

The solubility of chitosan derivatives is shown in Table 1. Original chitosan dissolved only in aqueous AcOH, and the resulting chitosan derivatives exhibited an enhanced affinity for organic solvents, thus the solubility of PNA-chitosan was significantly improved, which could be soluble in halogenated hydrocarbons, aromatic, and polar solvents such as chloroform, toluene, tetrahydrofuran, dimethyl sulfoxide and N,N-dimethylformamide. That was mainly because the hydroxyl and amino groups in the main chain of chitosan were mostly substituted by the bulk benzene and naphthalene groups. After the deprotection, the solubility of NA-chitosan was limited, but it was still highly swollen in dimethyl sulfoxide and N,N-dimethylformamide.

Table 1
Solubility of chitosan and chitosan derivatives.

Sample	Solvents				
	DMSO	DMF	$CHCl_3$	Toluene	1% HAc
Chitosan	–	–	–	–	+
N-phthaloyl chitosan	±	±	–	–	–
PNA-chitosan	+	+	+	+	–
NA-chitosan	±	±	–	–	–

+ Soluble; ± partially soluble or highly swelled; – insoluble.

TGA and DTG curves of chitosan and chitosan derivatives are shown in Fig. 3. It showed chitosan had a significant stage of weight losing started at about 280 °C and reached a maximum with weight loss of 52% due to the decomposition of chitosan, and at about 100 °C, a weight loss about 1.8% was corresponded to water evaporation in materials. The chitosan had a faster decomposition between 250 °C and 350 °C and reached the maximum at 300 °C which was consistent with the literature (Ma, Yang, Kennedy, & Nie, 2009). The N-phthaloyl chitosan showed higher initial decomposition temperature started at about 350 °C and decomposition peak at 409 °C than chitosan. It reached a maximum at 423 °C with weight loss of 88.0%. Compared to chitosan, PNA-chitosan showed a mild speed of decomposition during the temperature of 180 °C and 480 °C. It had a decomposition peak at 345 °C and the total weight loss reached 77.4% from 285 °C to 389 °C. Regarding the

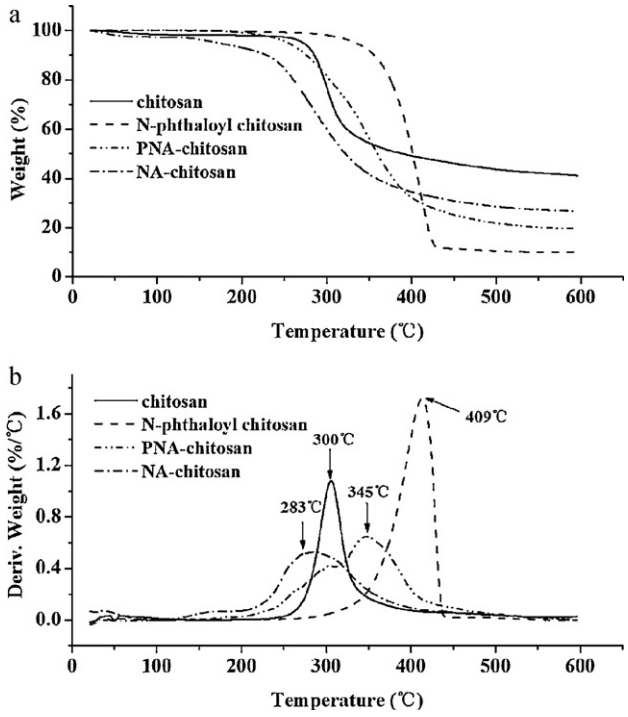

Fig. 3. (a) TGA thermograms of chitosan and chitosan derivatives and (b) DTG curves for chitosan and chitosan derivatives.

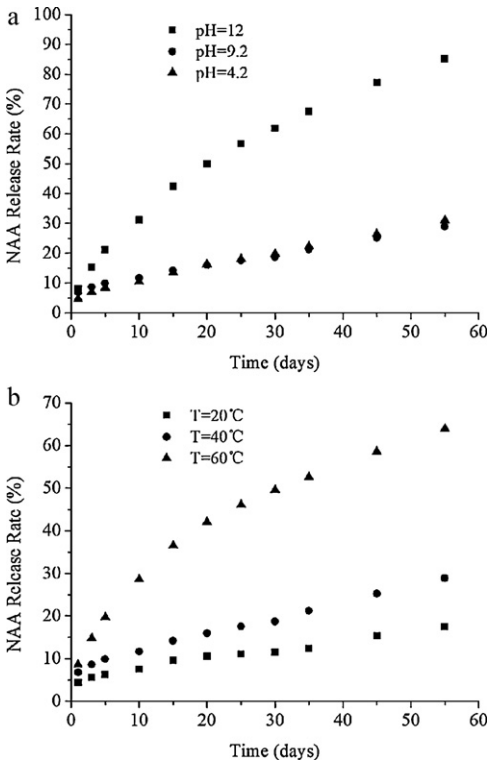

Fig. 4. The release behavior of NAA after heterogeneous hydrolysis at different conditions: (a) under various pH values, 40 °C and (b) at various temperatures, pH 9.2.

NA-chitosan, there were three degradation stages: the first stage started at about 25–75 °C with a weight loss of 2.6% ascribed to the volatile low molecular products and water; the second degradation stage was at about 125–175 °C, which could be explained as the solvent of DMF; the third degradation stage was at about 200–400 °C and reached a maximum at 342 °C with weight loss of 63.4%. It was clear that the thermal stability decreased in this order: N-phthaloyl chitosan > chitosan > PNA-chitosan > NA-chitosan.

To study the active ingredient release, polymeric derivatives were hydrolyzed heterogeneously. Commonly, the release behavior of bioactive agents from polymer-bioactive compound adducts depends on a number of factors, including the sample form, the hydrophilic character of the compound, the pH value of the medium, and the incubation temperature (Arranz & Sánchez-Chaves, 1995). The NAA release behavior of the NA-chitosan under different pH values of the media at 40 °C was investigated. It could be found (Fig. 4a) that at pH 12.0, the cumulative release rate was significantly higher than that of pH 4.0 and pH 9.2, mainly due to the greater availability of OH^-. This was consistent with the results described in prior study (Ignatova et al., 1998). Release data at pH 9.2 of the compound adducts at 20 °C, 40 °C, and 60 °C are shown in Fig. 4b. As incubation temperature increased, the hydrolysis rate was even higher.

The FT-IR spectra of the residue samples from the heterogeneous hydrolysis at different release periods were carried out to monitor the structural changes of the NA-chitosan. Fig. 5 reveals that the typical absorption intensity of NA-chitosan at 1738 and 781 cm^{-1} representing O-naphthalene ester are weakened. As the hydrolysis time increased to 55 days, these peaks were almost invisible. Meanwhile, the peaks at 1659 and 1599 cm^{-1} attributed to —CH and $—NH_2$ stretching vibration in chitosan were becoming stronger which indicated that NA-chitosan turned out to be chitosan again.

From the data above, NA-chitosan displayed clearly slow release properties of NAA. The low molecular weight bioactive compound (NAA) was released from the polymer upon the hydrolysis of the ester groups, which was demonstrated in former literatures as well (Eynard, Gay, Occelli, Dolci, & Martini, 1986; Tsatsakis et al., 1995). The slow release of NAA from some isomeric hexyl 1-naphthylacetates made it possible to employ these esters every 2 years, which significantly reduced the cost of distribution and relieved the environmental stress (Dolci, Navissano, Gay, Eynard, & Rangone, 1999). As to NA-chitosan, the release period sustained up to 2 months at pH 12.0 in 40 °C, indicating its supply duration could be even longer under milder conditions. The persistent release of NAA provided a consecutive biological activity on crops. The presence of amino groups in NA-chitosan maintained the various unique functions of chitosan, and it may lead to great potential in biological functions such as antifungal activity (Kumar et al., 2004; Liu, Du, Wang, & Sun, 2004), and it could be exploited in chitosan-based seed coatings and other crop protection applications (Muzzarelli et al., 2012).

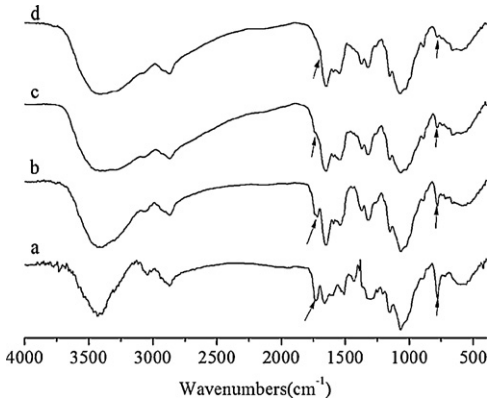

Fig. 5. FT-IR spectra of (a) O-naphthylacetyl chitosan; (b), (c), (d) represent the spectra of the residues after the heterogeneous hydrolysis at pH 12.0 at 60 °C for 15 days, 35 days, 55 days, respectively.

4. Conclusions

A novel O-naphthylacetyl chitosan (NA-chitosan) was synthesized for the first time, which possesses both naphthylacetyl and amino groups in the main chain of the polysaccharide. N-phthaloyl chitosan provided a reactive intermediate of chitosan which facilitated the immobilization of bioactive agrochemical carboxylic acids onto chitosan and the deprotection of N-phthaloyl-O-naphthylacetyl chitosan (PNA-chitosan) could be easily carried out after treatment with anhydrous hydrazine. The release of NAA linked to chitosan was strongly dependent on both pH value and incubation temperature, extreme condition such as higher pH and higher temperature would accelerate the hydrolysis rate.

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