Synthesis and Application of CDA-beta-CD in Controlling Release of Drug

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ABSTRACT: To chemically attach beta-cyclodextrin (beta-CD) molecules to cellulose diacetate (CDA), an isocyanate containing preformed polymer was synthesized by prepolymerization of CDA and toluene-2,4-diisocyanate (TDI), which was then grafted with beta-CD. Effects of reaction temperature, time, and mixture ratio on reactions were observed. The structure of CDA-beta-CD was characterized by ^{1}H- and ^{13}C-NMR spectra; the release of CDA-beta-CD with medicament naproxen by dynamic dialysis in the artificial simulated intestinal fluid (pH = 7.4) was studied in vitro. Results indicated that the release time could reach more than 8 h at a graft ratio of 68.7%, which showed a good controlled-release drug effect. © 2009 Wiley Periodicals, Inc. J Appl Polym Sci 113: 1811–1815, 2009

Key words: cellulose diacetate; beta-cyclodextrin; graft copolymer; drug delivery system; NMR spectra

INTRODUCTION

Cyclodextrin (CD) is externally hydrophilic and internally hydrophobic, which can form inclusion complex with many organic compounds such as drugs and flavors, etc. The polymer materials comprising the cyclodextrin segment in molecular structure are called CDP. The polymer has not only cyclodextrin's inclusion and controlled-release capability but also the excellent mechanical strength, better chemical stability, and adjustable function of polymer. At present, CDP is one of the most active functional polymer materials in research and application of biomedicine engineering, biotechnology, and environmental protection fields.[1–4] Cellulose acetate (CA) is a kind of polymer made by acetylation of cotton or lumber fiber. All of hydroxyl groups on cellulose glucose residue were esterificated to produce cellulose triacetates, which may be hydrolyzed to obtain cellulose diacetate containing 48.5%–58.5% combined acetate acid. Cellulose diacetate (CDA) can be processed into fibers and films and is widely used in the fabrication of paintings, textile fibers, plastics, cigarette filter tips, films, artificial kidneys, slow drug release, etc.

So far, many investigations have been conducted on carrying cyclodextrin directly onto polymers. For example, cyclodextrin is graft-copolymerized with polyethylene glycol, polypropylene, polystyrene, chitosan, cellulose, and starch, etc.,[5–9] but no report has been published about graft copolymerization of cyclodextrin on cellulose diacetate.[10] For synthesis techniques, numerous studies are related to graft reactions on cellulose material.[11–17] In the process, epoxy chloropropane is used mainly as an intermediate for direct graft of cyclodextrin on cellulose,[18] but cellulose diacetate is not dissolved in water and is hydrolyzed easily in alkali condition, thus being unable to react with epoxy chloropropane. To avoid above difficulties,[19,20] isocyanate has been used as an intermediate to synthesize graft copolymer of cellulose diacetate and cyclodextrin (Scheme 1). The investigation was also carried out in the drug naproxen's controlled-release behavior of graft copolymer.

EXPERIMENTAL

Materials

CDA (commercial product, Nantong Cellulose Acetate Factory) and beta-cyclodextrin (beta-CD) (analytical reagent, Shanghai Sanpu Chemical) were vacuum-dried for 12 h, *N*,*N*-dimethylfomamide (DMF) (analytical reagent, Shanghai Chemical Reagent Corporation of China Medicine), ethanol (analytical reagent, Shanghai Chemical Reagent Corporation of China Medicine), Tin dibutyl dilaurate (analytical reagent, Shanghai Chemical Reagent Corporation of China Medicine), toluene-2,4-diisocyanate (TDI) (analytical reagent, Shanghai Chemical Reagent Corporation of China Medicine), and

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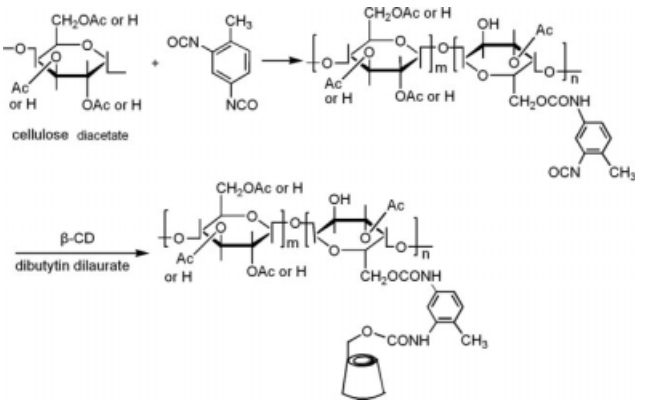

Scheme 1 Synthesis of CDA-beta-CD.

naproxen (China Medicine Biologicals Verification Agency) were used as received without further purification. NMR spectra were obtained by UNITY-400 NMR from Varian Corporation USA in CD_3COCD_3 with Me_4Si as internal standard, and the UV and visible spectra were measured by LAMDA-19 ultraviolet and visible spectrophotometer from PE Corporation USA in ethanol.

Synthesis of CDA-beta-CD

5.7 g of CDA, 2.5 g of TDI, and 60 mL of DMF were added to a 250-mL three-necked reactor equipped with a mechanical stirrer, thermometer, and condenser. The prepolymerization reaction was performed at room temperature for 1 h; 6.0 g of beta-CD and 0.2 mL of tin dibutyl dilaurate were added and stirred for 75 min at 60°C. The product was purified by pouring the mixture into boiling water for 2 h to remove unreacted TDI and CD. The CDA-beta-CD product obtained was dried at 60°C in a vacuum for 1 h. The graft yield was calculated by the following formula:

$$\text{Graft yield } \% = [(m_1 - m_0)/m_0] \times 100 \qquad (1)$$

where m_0 and m_1 are the weights of CDA (g) and homopolymer, respectively.

Analyses of isocyanate content

1.0 g of sample was added into the DMF solution containing 1 mL di-*n*-butylamine in an iodine flask; this was shaken, laid for 20 min to fully dissolve, and 25 mL of DMF was added. The solution was titrated with 0.1 mol/L hydrochloric acid to yellow. The indicator was methanol solution of 1% bromcresol green solution.

$$-\text{NCO } \% = (V_0 - V)M \times 42 \times 100/1000W \qquad (2)$$

where V_0 is hydrochloric acid volume consumed in the blank experiment (mL); W is mass of samples (g); V is volume consumed in experimental titration (mL); M is hydrochloric acid concentration (mol/L).

Standard curve of naproxen

The concentration of naproxen was monitored using a UV spectrophotometer at 331.2 nm. Quantitative naproxen was weighed out and dissolved in aqueous alcohol solution ($V_{alcohol}/V_{water} = 4$). The absorbance measurement of a series of standard solution is performed at 331.2 nm to prepare calibration curves. A linearity was obtained with good correlation ($r = 0.9996$) in the range of concentration of 30–80 μg/mL.

Preparation for the drug films of compositions of CDA-beta-CD and naproxen

The copolymer was dissolved in DMF solution and poured into circular film tools of the same size. Water was added to separate the product and formed a 0.5-mm-thick film, with an average diameter of 15 mm; an aqueous alcohol solution ($V_{alcohol}/V_{water} = 4$) of naproxen was then added into this flask to conduct drug embedding and was soaked at 15°C for 1 week to reach the equilibrium of absorption.

Controlled-release behavior of naproxen in copolymer

A dynamic dialysis method was used to measure in vitro drug release performance: The solution was stirred in a shaker at 100 r/min for 10 h. At predetermined time intervals, aliquots of the aqueous buffer solution were taken and equivalent aliquots of 0.01*M* phosphate buffer solution (PBS) (pH = 7.4) put into medium. The concentration of the naproxen released was monitored using a UV spectrophotometer at 331.2 nm. Three milliliter of buffer solutions was taken out at intervals of certain time, followed by supplement of 3 mL fresh buffer solutions. Absorbance of the solutions was measured at 331.2 nm. Concentration was determined from the standard curve equation of the drug.

RESULTS AND DISCUSSION

Prepolymerization reaction

The reaction courses of CD and CDA with TDI were studied by using —NCO% consumption levels. Figure 1 shows that the reaction of CDA and TDI has basically completed after 60 min. However, reaction of CD with TDI was much faster than CDA, a polymer undissolved in DMF forms in 20 min, and —NCO was exhausted in solution. With respect to polymer reactions of grafting CD on diacetate fibers,

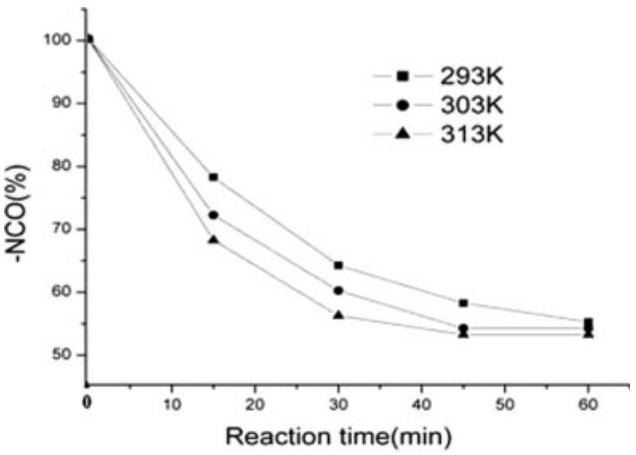

Figure 1 Effect of reaction temperature on prepolymerization reaction of CDA and TDI.

CD, TDI, and CDA should not be added simultaneously in the reaction solution, and CD should not be also reacted first with TDI and then with CDA. Therefore an investigation was carried out into optimum conditions for reactions of CDA with TDI and then with CD.

Figure 1 shows that, according to analyses of isocyanate content, the pre-reaction of CDA and TDI proceeds at different temperatures, and the reaction is fastest at 40°C, next at 30°C, and slowest at 20°C as early as 45 min. However, the discrepancy is not significant, and their reactive degree was substantially consistent after 60 min. 30°C was selected as the working control temperature of these reactions. The reaction of CDA and TDI is very rapid as early as 15 min and subsequently slowed down gradually. The reactions are close to completion after 45 min, with the isocyanate consumption being $\sim$ 50%. The —NCO conversion gradually nears 50% and levels off with time increase. Whatever the reaction at high or low temperature, only one —NCO group in TDI reacts with CD at this stage. This indicates that electronic and steric effects result in a sharp decrease in reactive activation of the other one after one isocyanate group reacts with cellulose diacetate.

Grafting reaction

Effect of temperature

The effect of reaction temperature on graft yield after adding CD is shown in Figure 2, according to formula (1) calculation. Graft yield increases with increasing reaction temperature, and the increased extent is no longer large after the temperature reaches 60°C.

Effect of reaction time

Figure 3 shows that graft yield increases with increasing reaction time and reaches a maximum at the reaction time of 75 min. Graft yield is substantially unchanged as reactive time is prolonged further.

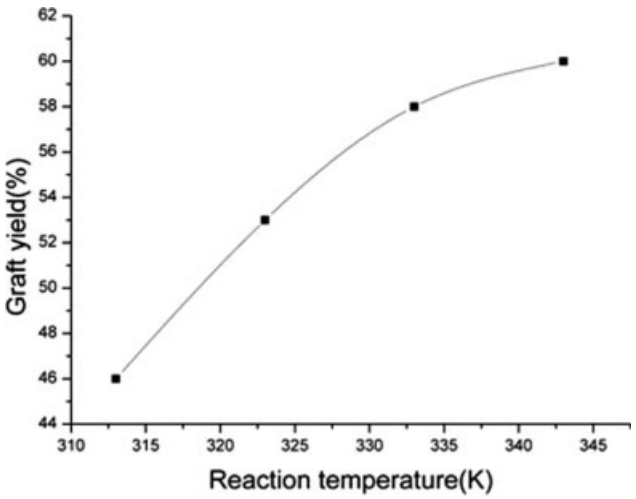

Figure 2 Effect of reaction temperature on the graft yield.

Effect of feeding ratios

In the investigation into the effect of feeding ratio on graft reactions, the following research condition was used: at CDA mass 5.7 g, the mass of the CD varied from 3.0 to 7.0 g, reaction time 75 min, and temperature 60°C. Experimental results are shown in Figure 4. It showed that graft yield increases when addition of CD increases, and the advance is not obvious after the amount reaching to 6.0 g.

Structure and characterization

Figure 5 shows ^{1}H-NMR spectrum for CDA-beta-CD in D_3CCOCD_3.

The chemical shifts are obtained according to ^{1}H-NMR spectra for CDA-beta-CD in Figure 5: ^{1}H-NMR

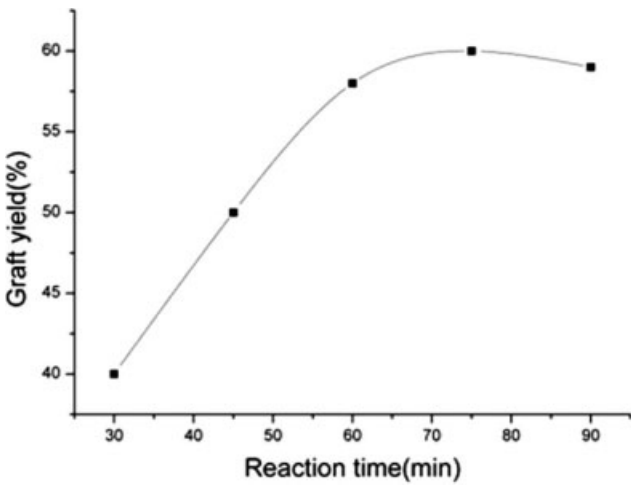

Figure 3 Effect of reaction time on graft yield.

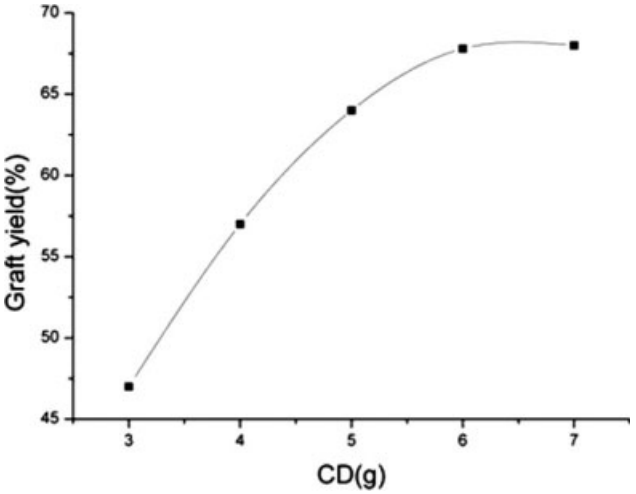

Figure 4 Effect of feeding ratio on graft yield.

(400 MHz, D_3CCOCD_3) δ : 8.03 (s, HCO of DMF), 7.40–7.10 (m, C_6H_3 of TDI), 6.00–5.82 (m, OH of CD), 5.10–3.50 (m, 1–6-H of CDA), 4.97 (s, 12-H of CD), 3.85–3.45 (m, 13–17-H of CD), 2.96, 2.75 (2 × s, CH_3 of DMF), 2.23 (s, CH_3 of TDI), 2.14–1.97 (m, 8-H of CDA, H_3CCO).

Figure 6 shows ^{13}C-NMR spectrum for CDA-beta-CD in D_3CCOCD_3.

The chemical shifts are obtained from ^{13}C-NMR spectra of CDA-beta-CD in Figure 6: ^{13}C-NMR (100 MHz, D_3CCOCD_3) δ : 171.0–169.0 (carbonyl 7-C of CDA), 162.5 (HCO of DMF), 153.4 (carbonyl 9-C of carbamate), 139.1, 130.8 (C_6H_3 of TDI), 113.2 (12-C of CD), 103.3 (1-C of CDA unesterized), 100.7 (1-C of CDA esterized), 82.9 (15-C of CD), 76.9–71.0 (2–5-C of CDA, 13–14-C, 16-C of CD), 62.9–59.0 (6-C of CDA esterized and unesterized, 17-C of CD), 36.5, 31.5 (CH_3 of DMF), 20.7 (CH_3 of CDA), 17.4 (CH_3 of TDI). It is demonstrated from ^{13}C spectra that CD is connected to CDA skeletons through chemical bonds because the characteristic chemical shifts of carbamate group carbonyl appears along with chemical shifts of CD cyclic carbon section and aromatic compound carbon.

As various carbon peaks, in general, are singlets and less overlap each other, proton noise decoupling

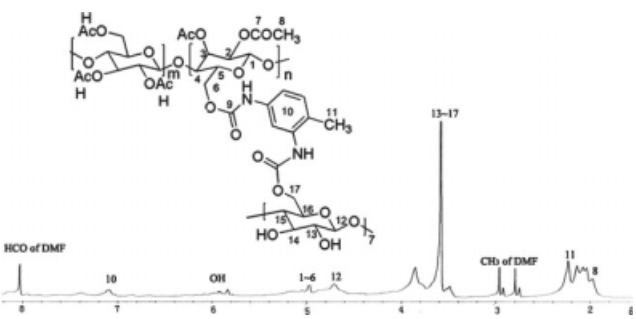

Figure 5 ^{1}H-NMR spectra of CDA-beta-CD.

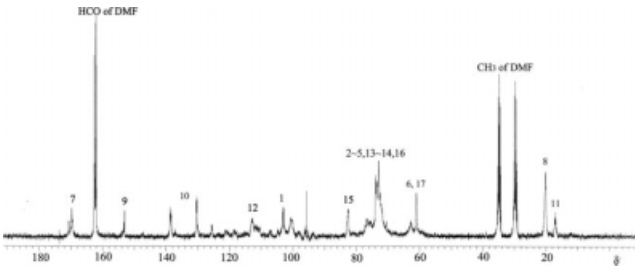

Figure 6 ^{13}C-NMR spectra of CDA-beta-CD.

carbon spectrum have certain predominance in quantitative determination of polymers compared with hydrogen spectrum. According to ^{13}C-NMR, δ 59 is the chemical shift of 17-CH_2 of CD, its integral intensity is 1.38; δ 17.4 is the chemical shift of CH_3 of TDI, its integral intensity is 0.5; and δ 62.9 is the chemical shift of 6-CH_2 of CDA, The graft ratio of TDI and CD contained on every cellulose loop of CDA may be calculated in the light of following formulas from reaction equations:

$$\mathrm{CD/CDA} = (1.38/7)/1 = 0.20 \quad (3)$$

$$\mathrm{TDI/CDA} = 0.5/1 = 0.5 \quad (4)$$

Therefore there are 0.2 CD and 0.5 TDI on every cellulose loop of CDA. Comparing with 68.7% obtained from gravimetric calculation shows a considerable difference, and this difference results probably from the following causes: water-immiscible products are produced by crosslinking of CD and unreacted TDI, and large amount of unreacted CD wrapped after formation of cellulose acetate films cannot be washed off with water.

Slow drug release

Copolymer with graft yields of 47.1%, 54.2%, and 68.7% were selected as drug release carriers; determination of drug concentration was performed after absorption by copolymer, and a different method was used to calculate drug absorption amount and release rate. Drug release data are shown in Figure 7.

It is shown in Figure 7 that release time of naproxen in CDA-beta-CD copolymer increases and release rate rises when graft ratio of CDA-beta-CD copolymer increase. The release time is 6 h and maximal release amount only 30% at a graft yield of 47.1%. At the graft yield of 68.7%, release time and amount reach to more than 8 h and 80%, respectively, thus obviously reducing times of taking medicine and side effects due to excessive once doses. It was demonstrated that CDA-beta-CD copolymer has a CD inclusion and controlled release capacity as well as the excellent mechanical strength, better

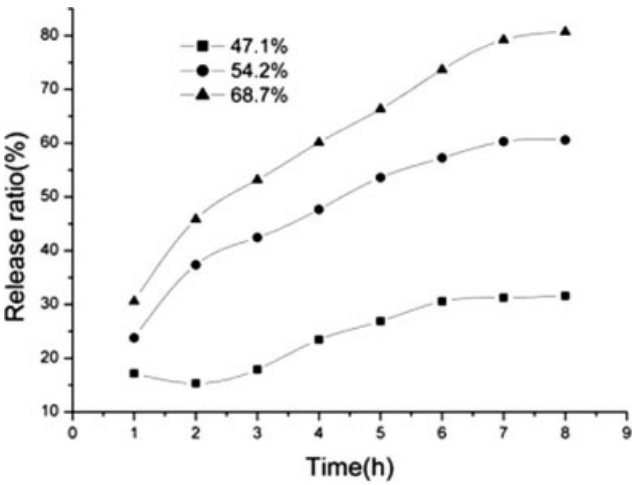

Figure 7 Release of naproxen in CDA-beta-CD copolymer.

chemical stability, and better function adjustability of diacetate fibers,[21] and this function polymer material has favorable potential application.

CONCLUSIONS

In this study, a kind of isocyanate containing preformed polymer was synthesized by prepolymerization of CDA and TDI, which was then grafted with beta-CD chemically. The optimum prepolymerization reactions were tested as to the feed weight ratio of CDA to TDI. The ratio 5.7 : 2.5 at room temperature was selected and set at beta-CD 6.0 g at 60°C for 75 min for the best results. The structures of CDA-beta-CD were characterized by ^{1}H- and ^{13}C-NMR spectra and the quantitative determination of CDA-beta-CD were measured by ^{13}C-NMR spectra; there were 0.2 CD and 0.5 TDI on every cellulose loop of CDA. The molecular inclusion complex of CDA-beta-CD with medicament naproxen was studied. Results indicated that in vitro, the release time of medicament naproxen by dynamic dialysis could reach more than 8 h at a graft ratio of 68.7% in the artificial simulation intestinal juice (pH = 7.4), showing a good controlled-release drug effect.

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