CELLULOSE-*GRAFT*-POLY(L-LACTIDE) AS A DEGRADABLE DRUG-DELIVERY SYSTEM: SYNTHESIS, DEGRADATION AND DRUG RELEASE

LIN DAI, YUE SHEN, DAN LI, SHU XIAO and JING HE[#]

[#] - *corresponding author*

Institute of Materials Science and Technology, Beijing Forestry University, 10083, Beijing, China

Received March 12, 2013

A cellulose-based degradable material, cellulose-*graft*-poly(L-lactide), was successfully attained via ring-opening polymerization (ROP) in an ionic liquid. The microsphere was prepared by the phase separation method, and the optimum reaction conditions were established as follows: dispersant dosage, 15% (g/g cellulose/AmimCl solution); oil/water volume ratio, 4:1; stirring speed, 350 r/min. Using wide-angle X-ray powder diffraction (WAXD), swelling and degradation tests, the changes resulting from degradation in the crystalline structure were also investigated. The hydration and degradation of cellulose-*g*-PLLA demonstrate significantly different characteristics, which dominated the drug-release mechanism of the cellulose-*g*-PLLA microspheres. It showed that the drug-release rate increased with the decrease in the grafting degree of the cellulose-*g*-PLLA, which may be due to the increased hydration ability of the cellulose-*g*-PLLA microspheres. Consequently, the cellulose-*g*-PLLA microspheres might be used as a potential polymer for the controlled release of drugs.

Keywords: cellulose, poly(L-lactide), microsphere, degradable, drug delivery

INTRODUCTION

In recent years, an increasing number of investigations have evaluated the potential of polymeric microcapsules as drug-delivery systems and also of modifying and retarding the drug release process.[1] Several techniques are currently in use to produce sustained release dosage vectors, including physico-chemical processes (solvent evaporation or phase separation methods), mechanical processes (spray drying), and a non-solvent addition process.[2,3] For example, the phase separation method involves a phase separation of a polymer solution by adding an organic nonsolvent.[4,5] Drugs are firstly dispersed or dissolved in a polymer solution, then an organic nonsolvent is added to this mixture solution under continuous stirring, by which the polymer solvent is gradually extracted and soft coacervate droplets containing the drug are generated. In order to develop a therapeutically effective dosage form, this complex process requires strict control of several processing parameters, such as stirring speed, drug polymer ratio, volume ratio between inner phase and outer phase, and the amount of surfactant.

Cellulose and its derivatives have been actively investigated to produce degradable polymers.[6,7] A significant amount of work has particularly focused on cellulose-based microcapsules. Also, a variety of drugs have been loaded and studied, such as naproxen, indomethacin, ibuprofen, sulindac, curcumin and folic acid.[8,9] Despite intensive research, there remain some challenges to the chemical modification of cellulose due to its high molecular weight, high crystallinity, rigidity of backbone chain and insolubility. Meanwhile green solvents, for example, ionic liquids 1-n-butyl-3-methylimidazolium chloride[10,11] and 1-allyl-3-methylimidazolium chloride,[12,13] have received great attention recently as reaction media of cellulose.

Graft polymerization could be one of the most promising and effective ways to increase the utility of cellulose by incorporating different polymer ingredients at a molecular structural level.[14,15] ROP might effectively synthesize aliphatic polyesters, which control general material properties, including degradability.[16,17]

As an authentic biopolymer, since PLLA is usually derived from agricultural products, its monomer can be produced by microbial fermentation. PLLA is a non-toxic biopolymer, compostable to CO_2 and water. Based on this excellent degradability, PLLA and its polymers have aroused great interest in their applications as biomedical materials, such as degradable sutures, drug delivery systems, and temporary scaffolds for tissue. Many articles are available on the physical and chemical properties of modified cellulose and the relationship with degradation.[18,19]

This main objective of the study reported in this paper was to synthesize well-defined graft polymers based on the cellulose backbone with L-lactide (L-LA) in an ionic liquid AmimCl, using DMAP as an organic catalyst, as well as to obtain the controlled release microcapsules of vitamin C, using cellulose-*graft*-poly(L-lactide) as a retarding material, by applying the phase separation methods. NMR and TEM were employed in analyzing the samples, and the study of degradability and drug release characteristics of the microspheres was emphasized.

EXPERIMENTAL

Materials

Microcrystalline cellulose (MCC) with 255 degree of polymerization (DP) and N-methylimidazole of 99% concentration were provided by the J&K Chemical Reagent Co., Ltd, China. Allyl chloride of 98% concentration was purchased from Acros Organis, USA. 1-allyl-3-methylimidazolium chloride (AmimCl) was synthesized according to the literature.[13] L-LA with a purity of 98% was purchased from A Johnson Matthey Co., Great Britain. 4-dimethylaminopyridine (DMAP) with a purity of 99.5% was provided by Haili Chemical Industry Co., Ltd. Liquid paraffin and Span 80 were procured from Guangdong Guanghua Sci-Tech Co., Ltd. The lipase L3126 used in the hydrolysis test (optimum conditions for the enzymatic hydrolysis: 37 °C, pH 7.40) from porcine pancreas was provided by Beijing Solarbio Science & Technology Co., Ltd. The dialysis bags (Viskase/MD34-7, MWCO 7000) were purchased from Beijing RuiDaHengHui Science & Technology Co., Ltd. All other reagents and solvents used were of analytical grade.

Preparation of cellulose-*g*-PLLA microspheres

A typical polymerization procedure was employed as follows. 4% (w/w) microcrystalline cellulose/AmimCl solution was firstly prepared by mechanical stirring at 60 °C under nitrogen atmosphere for 1 h in a previously dried Schlenk tube. Then L-LA, DMAP were added into this tube. After dissolving, the tube was degassed for three times in vacuum/N_2 during 1 h cycles. Finally, the reaction was kept at 90 °C under nitrogen atmosphere, with vigorous stirring for 11 h.

The resultant dispersion was poured into light liquid paraffin with certain concentration, containing 10% (15%, 20%, 25%) w/v of a dispersing agent Span 80, in a 250 mL beaker, which was rotated in a water bath at 250 (300, 350, 400) rpm at 80 °C for 1 h. After the reaction was completed, the flask was cooled to room temperature. The product was subsequently isolated by precipitating into excess of deionized water, filtered, (initially washed with deionized water for several times, then with ethanol aqueous solution to remove any unreacted monomer). Ultimately, the grafted polymer microsphere sample was extracted with acetone in a Soxhlet apparatus for 24 h to dissolve all the homopolymer.

Determination of cellulose-*g*-PLLA microsphere yield

The microspheres were weighed and the yield of microspheres was calculated using the following equation:

$$\text{Yield}\% = (A/B) \times 100\% \quad (1)$$

where A is the weight of microspheres obtained and B is the theoretically expected weight of microspheres.

Hydration of cellulose-*g*-PLLA microspheres

The water uptake capacity of each cellulose-*g*-PLLA microsphere was determined by the hydration of microsphere in deionized water at 37 °C. The cellulose-*g*-PLLA microsphere (200 mg) was placed in deionized water for a required period of time. Concurrently, after blotting the surface water with a piece of filter paper, the hydrated samples were taken and weighed immediately on an electronic balance. The percentage water content of the cellulose-*g*-PLLA microsphere was calculated as follows:

$$P_{WC}\% = \left[(W_e - W_0)/W_0 \right] \times 100\% \quad (2)$$

P_{WC} is the percent water content of the cellulose-*g*-PLLA microsphere at equilibrium. W_e is the weight of the cellulose-*g*-PLLA microsphere at equilibrium of water uptake and W_0 is the initial weight of the cellulose-*g*-PLLA microsphere. Each water uptake experiment was repeated for three times and the

average value was taken as the final percentage water content value.

Degradation of cellulose-*g*-PLLA microspheres

PBS hydrolysis

The specimens were put in vials filled with pH 7.40 phosphate-buffered saline solutions (PBS), seal saved and placed in a thermostat for various periods at 37 °C, then cleaned and weighed after a period of time.

Enzymatic hydrolysis

The specimens (250 mg) and PBS solution (25 mL, pH 7.40) were placed in a conical flask with 25 mg lipase and incubated at 37 °C. After degradation, the enzyme solution was diluted 200 times and examined by a spectrophotometer at 210 nm. The concentration of lactic acid in solution was obtained based on the standard curve: C_{LA} (g/L) = A_{LA}/0.6298, where A_{LA} is the UV absorbance at 210 nm. The weight loss of the polymer was calculated from the formula: weight loss% = (C_{LA} × 5000) / 250 × 100, where C_{LA} is the concentration of lactic acid in solution.

Drug loading and *in vitro* drug release

Cellulose-*g*-PLLA (60.0 mg) and vitamin C (60.0 mg) were dissolved in 2 mL PBS solution. Then the solution was put into a dialysis bag and subjected to dialysis against 1000 mL distilled water for 24 h (refreshing the water after 12 h). After dialysis, the dialysis bag was directly immersed into a 400 mL phosphate buffer solution mimicking the pH of intestinal fluid (pH 7.40) at 37 ± 0.5 °C. Aliquots of the medium of 2 mL were withdrawn periodically at predetermined time intervals and analyzed at λmax values of 245 nm for vitamin C. The volume of the solution was held constant by adding 2 mL phosphate buffer solution after each sampling.

Drug concentrations were calculated based on the calibration curves determined for each drug at their specific maximum absorption wavelengths. C_{VC} (mg/L) = 3.262 × A_{VC} - 20.4011, where A_{VC} is the UV absorbance area at 245 nm. A simple, semi-empirical equation using the Higuchi simplified model (Eq. 3) and the Korsmeyer-Peppas model (Eq. 4) was used to kinetically analyze the data on the drug release from the studied matrix system applied in the initial stages (approximately 60% fractional release).

$$M_t / M_\infty = kt^{0.5} \quad (3)$$

$$M_t / M_\infty = k_r t^{n_r} \quad (4)$$

where M_t/M_∞ represents the fraction of the drug released at time t; M_t and M_∞ are the absolute cumulative amounts of drug released at time t and at infinite time (in this case, the maximum amount released under the experimental conditions used, at the plateau of the release curves); k and k_r are the constant incorporating the characteristics of the macromolecular matrix-drug of the Higuchi simplified model and the Korsmeyer-Peppas model respectively; and n_r is the diffusion exponent, indicating the release mechanism.

In the equation above, a value of $n_r = 0.5$ indicates a Fickian diffusion mechanism of the drug from the matrix, while a value of $0.5 < n_r < 1$ indicates an anomalous or non-Fickian behaviour. When $n_r = 1$, a case II transport mechanism is involved, while $n_r > 1$ indicates a special case II transport mechanism.[20]

Characterization

^{1}H NMR spectra of cellulose-*g*-PLLA were recorded on a Bruker AV400-MHz NMR spectrometer. DMSO-d_6 was used as solvent with a drop of trifluoroacetic acid-d to shift active hydrogen to lower field area, and tetramethysilane (TMS) as an internal standard. WAXD was performed by XRD-6000 X-ray diffractometer (Shimadzu, Japan) using Ni-filtered CuKα radiation (40 kV, 30 mA) with a 4°/min scanning rate at room temperature. Diffraction intensity was measured in the range of 2θ = 5-40°. A drop of sample dissolved in DMSO 0.01% (w/v) was placed on a copper grid with formvar film and dried before measurements by JEM-100CXa TEM at an acceleration voltage of 100 kV. Ultraviolet analysis was carried out on a UV2000 spectrophotometer (UNICO, China). High performance liquid chromatography (HPLC) was performed using an Agilent 1200 (Agilent, USA) liquid chromatograph equipped with a XDB-C18 phase column. The mobile phase was H_2O:methanol (20:80 by vol.), the flow rate was 0.8 mL/min and accurate injection device for 20 μL was used.

RESULTS AND DISCUSSION

Preparation of cellulose-*g*-PLLA microspheres

The homogeneous ROP reaction of L-LA with DMAP catalyst was shown in Figure 1. Table 1 showed the results obtained by using various feed ratios of L-LA/MCC. Based on previous experiments, the polymerization temperature was set at 90 °C.

It seemed to indicate that the grafting content of PLLA in polymers increased with the rise of weight ratio of L-LA and DMAP to cellulose in feed. One possible reason behind this experiment was that L-LA reacted with DMAP to form intermediates, which can attack alcohol hydroxyl groups of cellulose easier than L-LA. Although there were many PLLA branches on the cellulose chain, with the amount of lactic acid increasing, the gain of each PLLA branch was limited. As indicated in Table 1, the highest DP value of cellulose-*g*-PLLA polymer was 3.98. These values were much higher than those reported in the DMAc/LiCl system.[21]

The optimal conditions of the formation of the polymer microsphere were selected from the tests and sample 9 was chosen as a standard sample.

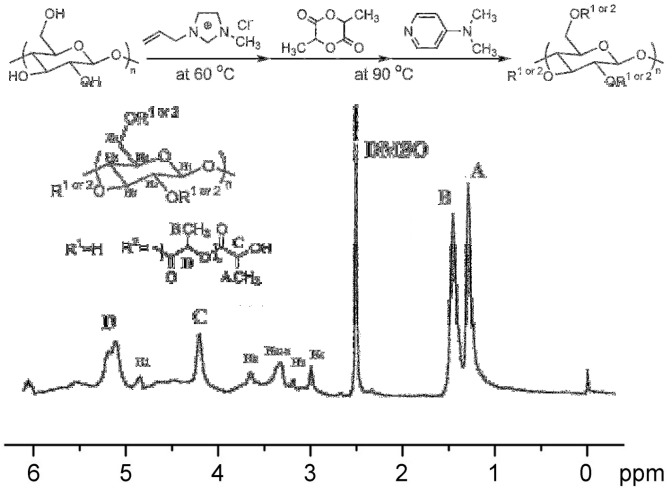

Figure 1: ^{1}H NMR spectrum of cellulose-*g*-PLLA (DP_{PLLA}=3.15) in DMSO-d_6

Table 1
Results and reaction conditions of the graft polymerization of PLLA on cellulose in AmimCl

No.	L-LA/MCC (mol/mol)	-OH/DMAP (mol %)	DP_{PLLA}	MS_{PLLA}
1	6/1	0.5	2.55	3.95
2	8/1	0.5	2.99	4.08
3	10/1	0.5	3.27	4.13
4	6/1	1.0	2.84	4.00
5	8/1	1.0	3.28	4.15
6	10/1	1.0	3.62	4.35
7	6/1	1.5	3.15	4.10
8	8/1	1.5	3.61	4.37
9	10/1	1.5	3.98	4.45

Test conditions: MCC = 0.6 g; AmimCl/ MCC (wt/wt) = 4%; 90 °C; 11 hours

Table 2
Yield of microspheres (DP_{PLLA} = 3.98)

No.	Factors			Yield (%)
	Dispersant dosage (%)	Oil/water volume ratio	Stirring speed (r/min)	
1	15	4:1	250	45.6
2	15	4:1	300	73.5
3	15	4:1	350	78.1
4	15	4:1	400	72.5
5	15	2:1	350	--
6	15	3:1	350	62.5
7	15	5:1	350	69.3
8	10	4:1	350	--
9	20	4:1	350	50.2
10	25	4:1	350	63.8

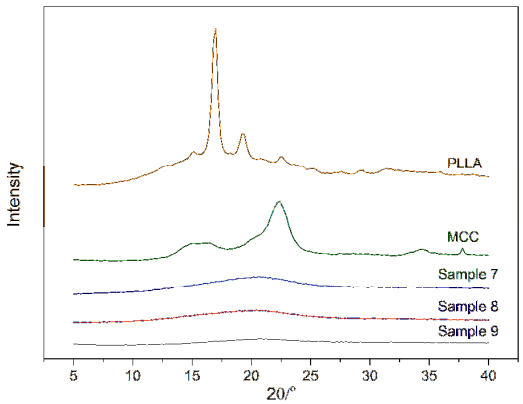

Figure 2: WAXD spectra of PLLA, MCC and cellulose-*g*-PLLA (DP_{PLLA} = 3.98, DP_{PLLA} = 3.61, DP_{PLLA} = 3.15)

Table 2 contained three independent variables: dispersant dosage, oil/water volume ratio and stirring speed, each at four levels.

The dispersant dispersed the droplet and ensured the stability of the microsphere morphology. The volume ratio of oil and water influenced the diameter and stability of the microsphere.

For the spheroidizing process, the stirring rate was an important influencing factor, which could control the stability of water in the oil emulsion system and the diameter of the polymer microsphere. According to the quantitative characteristics of the microspheres shown in Table 2, the optimum reaction conditions were as follows: dispersant dosage, 15% (g/g cellulose/AmimCl solution); oil/water volume ratio, 4:1; stirring speed, 350 r/min.

^{1}H NMR analysis of cellulose-*g*-PLLA

The homogeneous ROP reaction of LA with DMAP catalyst and the ^{1}H NMR spectrum of cellulose-*g*-PLLA (DP_{PLLA} = 3.15) are shown in Figure 1; the area from the terminal methyl protons of lactyls was labeled A, the area from terminal methyl protons of lactyls in PLLA side-chains was labeled B, the area from terminal methine protons of lactyls in PLLA side-chains was labelled C, and the resonance peak area derived from internal methine protons of lactyls in PLLA side-chains was designated as D. The degree of lactyl substitution (DS) was defined as the average number of hydroxyls substituted for lactyls per anhydroglucose residue of cellulose and the molar substitution (MS) was defined as the average number of introduced lactyl units per anhydroglucose residue of cellulose. The average degree of polymerization of the PLLA-side chain (DP_{PLLA}), which was equal to the molar amounts of combined LA per glucopyranoside unit of cellulose-*g*-PLLA was estimated directly by ^{1}H NMR analysis according to the following equation:

$$DP_{PLLA}=\frac{MS}{DS}=\frac{IA_{(a+b)}/3}{IA_b/3}=\frac{IA_a}{IA_b}+1 \quad (5)$$

where molar substitution IA_a and IA_b are the resonance peak areas deriving from internal methine protons of lactyls in PLLA side-chains and terminal methine protons of lactyls in PLLA side-chains, respectively.

Crystalline structure analysis of Cellulose-*g*-PLLA microspheres

The crystalline structures of PLLA, cellulose, and cellulose-*g*-PLLA were examined by WAXD measurements (Figure 2). PLLA showed the strongest diffraction peak at 2θ = 17°, whereas cellulose showed the strongest diffraction peak at 2θ = 22.4°. However, neither the crystallization peak of PLLA, nor that of cellulose was observed on cellulose-*g*-PLLA polymers. Only a dispersive broad peak around 2θ = 20.6° (20.4°, 20.8°) was obtained, indicating that the cellulose became amorphous when grafted by PLLA. In a study made by Teramoto *et al.*,[22] it was suggested that CDA-*g*-PLLA polymers had a crystalline diffraction pattern, which could be caused by the relatively long PLLA side-chains.

Morphology characterization of cellulose-*g*-PLLA microspheres

As indicated in Figure 3, TEMs of polymer microspheres showed the general appearances of microspheres and the increase of their diameters

when specific surface area reduced with the rise of DP_{PLLA}. These results strongly supported the idea that the cellulose-*g*-PLLA microsphere is a promising candidate as a drug-delivery system.

Hydration properties

The cellulose-*g*-PLLA microspheres were degraded via hydrolytic breakage of the ester branch chains. Water accessibility to these bonds would determine the rate of degradation. Accordingly, the rates for the degradation may depend on the hydrophilicity and crystallinity of the cellulose-*g*-PLLA. PLLA is hydrophobe. Cellulose is relatively hydrophilic, but with a semi-crystalline structure. Cellulose-*g*-PLLA is expected to produce different degrees of matrix hydration.

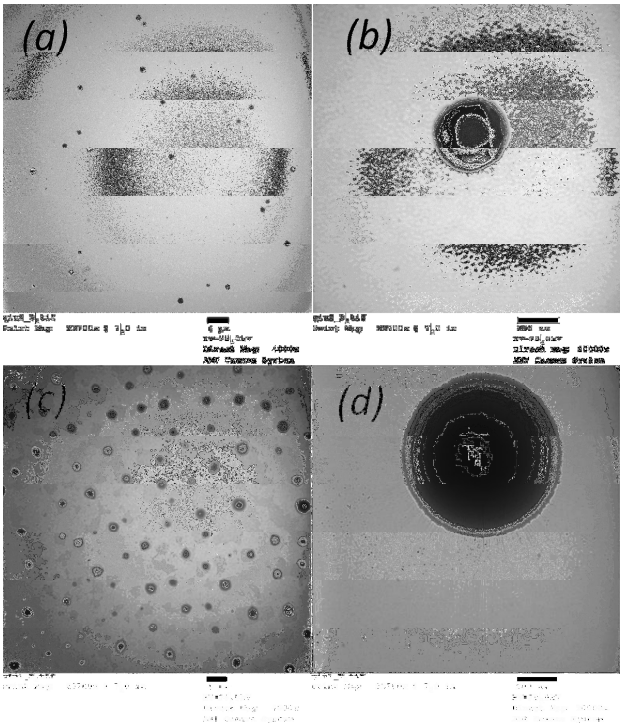

Figure 3: TEM of the polymer microsphere, DP_{PLLA} = 3.15 (a, b) and DP_{PLLA} = 3.98 (c, d)

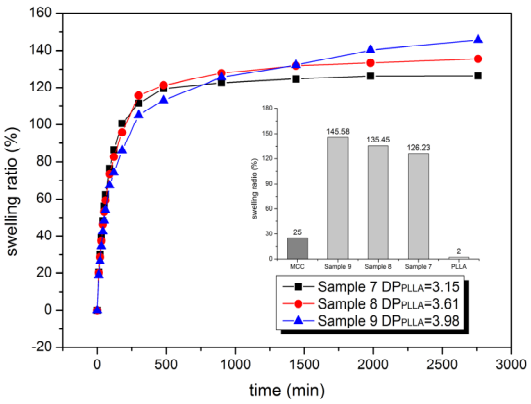

Figure 4: Hydration degrees of cellulose-*g*-PLLA microsphere

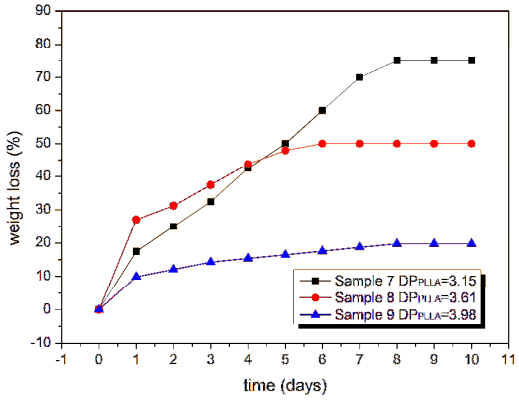

Figure 5: Influence of DP_{PLLA} on the degradability of cellulose-*g*-PLLA in PBS

Figure 4 shows the hydration degrees of microspheres prepared from different DP_{PLLA} of the cellulose-*g*-PLLA. Interestingly, all the cellulose-*g*-PLLA presented high water uptake capabilities relative to pure cellulose and the water content increased with the rise in the amounts of DP_{PLLA}, which may be attributed to the increase of the degree of network structures, but the rate of water uptake decreased with the increase in the amounts of DP_{PLLA}, which may be ascribed to the decrease of the specific surface areas.

Degradations

PBS hydrolysis

Hydrolysis has well-known great effects on biodegradation of polymers in enzyme solution, therefore the hydrolysis of polymers should be researched initially. As indicated in Figure 5, the weight loss decreased with the increase of the DP of the polymers. Hydrolysis of PLLA was the main reaction of cellulose-*g*-PLLA in PBS, the good water affinity of cellulose allowed water to penetrate into the polymer molecules and break the ester bond inside, leaving a low molecular mass polymer. Moreover, the bulk hydrolytic chain scission of PLLA was proportional to water and ester concentration, and autocatalysis by the generated carboxylic end groups. Consequently, PLLA was transformed into carboxylic acid and alcohol.

The PBS solution entered the amorphous regions and the crystalline regions subsequently. The hydrolysis proceeded more preferentially in amorphous regions than in crystalline regions. The biodegradation process of PLLA was also indirect.[23] In the first stage, PLLA was hydrolyzed by cutting the unstable bonds and hydrolysis into oligomers; in the second stage, it could be further degraded by enzymes into lactic acid. So, the performance of polymer biodegradation was greatly affected by its hydrolysis ability.

Enzymatic hydrolysis

Cellulose-*g*-PLLA is hydrolyzed by lipase to produce lactic acid, which can produce strong absorption at 210 nm wavelength. UV absorption represents the dissolved amount of aqueous lactic acid in a solution; that is, PLLA materials in enzyme solution are degraded to lactic acid, and the concentration of lactic acid is quantified for the analysis of UV absorption. As may be noted from Figure 6, the weight losses of samples 9, 8 and 7 at last decreased in sequence. Meanwhile, we found that the weight loss increased by the extension of the processing of the lipase, but three days later, weight loss rose slower towards a balance. The results strongly proved that this polymer could be hydrolyzed by lipase and when the ester bonds of the branched chains were hydrolyzed in a certain degree, even if the lipase processing time was extended, the reaction in the fluid of lactic acid would not be stronger and the weight loss curve tended towards the balance finally.

The correlation was examined between actual degradability data and the properties of the samples which were presumed to affect degradability. Based on correlation analysis results, the degree of polymerization appeared to be the most influential factor on degradability, whereas crystallinity proved to be negatively correlated. The amphiphilic cellulose-*g*-PLLA polymer was hydrolyzed initially and then further degraded by enzymes.

Drug loading and *in vitro* release studies

Drug loading

The final drug release quantity (drug loading) of samples 7, 8, 9 was 48 mg, 51 mg and 55 mg, respectively. The increase in drug loading with the rise of DP_{PLLA} may be attributed to the growth in polymer viscosity.

In vitro *release studies*

In the present study, a release model was observed for the release of vitamin C from cellulose-*g*-PLLA microspheres (Figure 7). The drug-release rate increased with the decrease of DP_{PLLA}, which was due to the increase of the polymer viscosity and this, in turn, strongly shielded the drug and hampered the diffusion of the dissolution medium into the microsphere core to dissolve the drug, as well as that of the dissolved drug out of the microsphere. Moreover, the characteristics of the drug released from the cellulose-*g*-PLLA microspheres might be affected by hydrophilicity and degradability. The release of vitamin C from the cellulose-*g*-PLLA microspheres, via the penetration of water into the amorphous region to leach out the incorporated drug, was much quicker than the release of vitamin C via degradation of matrix. Vitamin C release from the hydrophobic part via bulk degradation was another factor that affected drug

release. Owing to the different hydrophilicities and degradability of the matrix, the drug-release mechanism of the microsphere remained complex. Over 60% of vitamin C released in the early stage of the quick release suggested that vitamin C was mostly incorporated in the amorphous regions. The following stage of slow release was sustained for over 200 h, due to the fact that the cellulose-*g*-PLLA microspheres were degraded. In conclusion, such a cellulose-*g*-PLLA microsphere presents interest, and might be used as a drug-delivery system.

Kinetic mechanism

The Higuchi model was defined for vitamin C release from the cellulose-*g*-PLLA microspheres (Table 3). R values for these studies ranged between 0.7817 and 0.8450, indicating that diffusion was not the only predominant factor controlling drug release from these dosage forms.

The Korsmeyer-Pappas model was defined for vitamin C release in Table 3. The n_r value release exponent determined for samples 7 and 8 were found to be 0.5124 and 0.5175, respectively, at approximately 60% fractional release, which suggested that the release mechanism of vitamin C from the cellulose-*g*-PLLA microspheres was predominantly controlled by Fickian diffusion as $n_r \approx 0.50$, whereas the n_r was found to be 0.6068 for sample 9, suggesting that the release mechanism was controlled by non-Fickian diffusion.

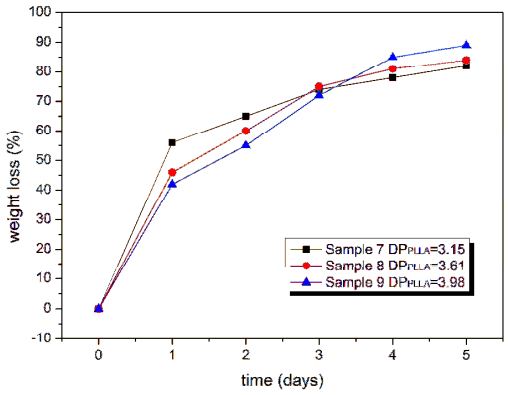

Figure 6: Influence of DP_{PLLA} on the degradability of cellulose-*g*-PLLA in enzyme solution

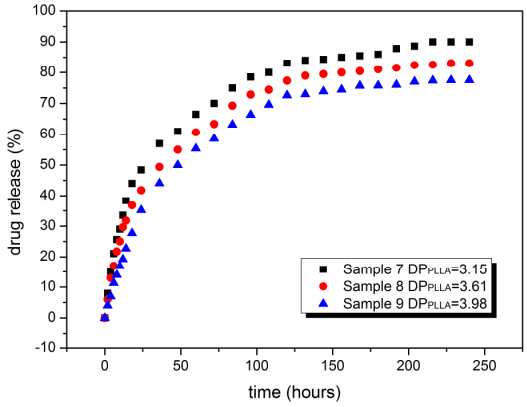

Figure 7: Effects of DP_{PLLA} on the release of vitamin C from microsphere

Table 3
Kinetic parameters of vitamin C released from cellulose-*g*-PLLA microspheres

No.	DP_{PLLA}	M_t/M_∞ (%)	Higuchi model		Korsmeyer-Pappas model		
			k (%/min$^{-0.5}$)	R	n_r	k_r (%/min^{-n})	R
7	3.15	61.0	1.2849	0.8450	0.5124	1.1054	0.9904
8	3.67	60.7	1.1040	0.8226	0.5175	0.9111	0.9902
9	3.98	63.2	1.0382	0.7943	0.6068	0.3775	0.9927
7	3.15	90.0	0.7165	0.7817	0.3372	3.8721	0.9912
8	3.67	83.0	0.6954	0.7818	0.3607	2.8952	0.9919
9	3.98	77.5	0.7128	0.7818	0.4164	1.6137	0.9938

The release mechanism elucidated was found to be 0.3372, 0.3607 and 0.4164, respectively, at approximately 100% fractional release, which indicated that the release mechanism from these dosage forms cannot be explained by the Korsmeyer-Peppas model, since the resultant n_r values ($n_r < 0.5$) did not fall within the specified range. The n_r value was affected by the change in matrix geometry.[24] Therefore, the mechanism of vitamin C release might be partly explained by the degradation of these microspheres, since n_r was affected by the change in the shape of the matrix undergoing investigation.

CONCLUSION

In this study, microspheres based on cellulose/PLLA grafting were prepared to be used for the delivery of drugs. The degradable material, cellulose-*g*-PLLA polymer, could be prepared successfully via ROP of cellulose and L-LA under homogeneous conditions in AmimCl. By NMR, WAXD, HPLC and UV measurements, the structures and thermal properties of the cellulose-*g*-PLLA graft polymers were investigated. Furthermore, the cellulose-*g*-PLLA microsphere was well dispersed by the phase separation method, using the AmimCl/liquid paraffin system, and the optimum reaction conditions were established as follows: dispersant dosage, 15% (g/g cellulose/AmimCl solution); oil/water volume ratio, 4:1; stirring speed, 350 r/min. The hydration and degradation of cellulose-*g*-PLLA demonstrated significantly different characteristics, which dominated the drug-release mechanism of the cellulose-*g*-PLLA microspheres. The results indicated that the cellulose-*g*-PLLA microspheres might be useful as a potential polymer carrier for the controlled release of drugs.

ACKNOWLEDGEMENTS: This study was financially supported by the Major State Basic Research Projects of China (973-2010CB732204), which is gratefully acknowledged.

REFERENCES

[1] G. F. Oliveira, P. C. Ferrari, L. Q. Carvalho and R. C. Evangelista, *Carbohyd. Polym*., **82**, 1004 (2010).
[2] A. Bohr, M. Yang, S. Baldursdóttir, J. Kristensen, M. Dyas *et al*., *Polymer*, **53**, 3220 (2012).
[3] M. Rafienia, F. Orang, and S. H. Emami, *J. Bioact. Compat. Pol*., **21**, 341 (2006).
[4] K. G. Carrasquillo, A. M. Stanley, J. C Aponte-Carro, P. De Jésus, H. R. Costantino *et al*., *J. Control. Release*, **76**, 199 (2001).
[5] D. Mallardé, F. Boutignon, F. Moine, E. Barré, S. David *et al*., *Int. J. Pharm*., **261**, 69 (2003).
[6] H. P. S. A. Khalil, A. H. Bhat and A. F. I. Yusra, *Carbohyd. Polym*., **87**, 963 (2012).
[7] J. Zhu, X. T. Dong, X. L. Wang and Y. Z. Wang, *Carbohyd. Polym*., **80**, 350 (2010).
[8] O. Suwantong, P. Opanasopit, U. Ruktanonchai and P. Supaphol, *Polymer*, **48**, 7546 (2007).
[9] S. Tungprapa, I. Jangchud and P. Supaphol, *Polymer*, **48**, 5030 (2007).
[10] A. S. Amarasekara and O. S. Owereh, *Carbohyd. Polym*., **78**, 635 (2009).
[11] C. Tsioptsias and C. Panayiotou, *Carbohyd. Polym*., **74**, 99 (2008).
[12] Y. Cao, H. Li, and J. Zhang, *Ind. Eng. Chem. Res*., **50**, 7808 (2011).
[13] J. Wu, J. Zhang, H. Zhang, J. He, Q. Ren *et al*., *Biomacromolecules*, **5**, 266 (2004).
[14] D. Klemm, B. Heublein, H. P. Fink and A. Bohn, *Angew. Chem. Int. Ed*., **44**, 3358 (2005).
[15] C. S. Wu, *Polymer*, **46**, 147 (2005).
[16] A. Carlmark, E. Larsson and E. Malmström, *Eur. Polym. J*., **48**, 1646 (2012).
[17] A. Maraisa, J. J. Kochumalayila, C. Nilssona, L. Fogelströma and E. K. Gamstedtb, *Carbohyd. Polym*., **89**, 1038 (2012).
[18] H. Lönnberg, Q. Zhou, H. Brumer, T. T. Teeri, E. Malmström *et al*., *Biomacromolecules*, **7**, 2178 (2006).
[19] P. Vlček, M. Janata, P. Látalová, J. Kríž, E. Čadová *et al*., *Polymer*, **47**, 2587 (2006).
[20] A. M. Oprea, D. Ciolacu, A. Neamtu, O. C. Mungiu, B. Stoica *et al*., *Cellulose Chem. Technol*., **44**, 369 (2010).
[21] A. Mayumi, T. Kitaoka and H. Wariishi, *J. Appl. Polym. Sci*., **102**, 4358 (2006).
[22] Y. Teramoto and Y. Nishio, *Polymer*, **44**, 2701 (2003).
[23] M. Vert, J. Mauduit, S. Li, *Biomaterials*, **15**, 1209 (1994).
[24] V. Pillay and R. Fassihi, *J. Control. Release*, **59**, 229 (1999).