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

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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. 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. For example, the phase separation method involves a phase separation of a polymer solution by adding an organic nonsolvent. 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. 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. 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 and 1-allyl-3-methylimidazolium chloride, have received great attention recently as reaction media of cellulose.
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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. ROP might effectively synthesize aliphatic polyesters, which control general material properties, including degradability.

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 CO₂ 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.

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) 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. 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/N₂ 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: YIELD% = (A/B)×100% (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:

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

\( P_{\text{WC}} \) 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), sealed 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 spectrophotometer at 210 nm. The concentration of lactic acid in solution was obtained based on the standard curve: 

\[ C_{LA} (\text{g/L}) = A_{LA}/0.6298, \]

where \( A_{LA} \) is the UV absorbance at 210 nm. The weight loss of the polymer was calculated from the formula: weight loss\% = \((C_{LA} \times 5000) / 250 \times 100 \), 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 buffer solution after each sampling. Drug concentrations were calculated based on the calibration curves determined for each drug at their specific maximum absorption wavelengths. 

\[ C_{VC} (\text{mg/L}) = 3.262 \times A_{VC} - 20.4011, \]

where \( A_{VC} \) is the UV absorbance area at 245 nm. 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. 

\[ C_{LA} (\text{g/L}) = A_{LA}/0.6298, \]

where \( A_{LA} \) is the UV absorbance at 210 nm. The weight loss of the polymer was calculated from the formula: weight loss\% = \((C_{LA} \times 5000) / 250 \times 100 \), where \( C_{LA} \) is the concentration of lactic acid in solution.

**Characterization**

\[^1\text{H}\text{ NMR}\] 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 tetramethylsilane (TMS) as an internal standard. WAXD was performed by XRD-6000 X-ray diffractometer (Shimadzu, Japan) using Ni-filtered CuK\(\alpha\) radiation (40 kV, 30 mA) with a 4°/min scanning rate at room temperature. Diffraction intensity was measured in the range of 20 = 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\(_2\)O:methanol (20:80 by vol.), the flow rate was 0.8 mL/min and accurate injection device for 20 \(\mu\)L 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.\(^{20}\)

\[ M_t / M_\infty = k t^{0.5} \]  
\[ M_t / M_\infty = k, t^{n} \]  

where \( M_t / M_\infty \) represents the fraction of the drug released at time \( t \); \( M_t \) and \( M_\infty \) 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 \( k_t \) are the constant incorporating the characteristics of the macromolecular matrix-drug of the Higuchi simplified model and the Korsmeyer-Peppas model respectively; and \( n_t \) is the diffusion exponent, indicating the release mechanism.

In the equation above, a value of \( n = 0.5 \) indicates a Fickian diffusion mechanism of the drug from the matrix, while a value of \( 0.5 < n < 1 \) indicates an anomalous or non-Fickian behaviour. When \( n = 1 \), a case II transport mechanism is involved, while \( n > 1 \) indicates a special case II transport mechanism.\(^{21}\)
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-$\gamma$-PLLA ($DP_{\text{PLLA}}=3.15$) in DMSO-$d_6$.

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

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

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

Table 2: Yield of microspheres ($DP_{\text{PLLA}} = 3.98$)

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

\[ \text{Crystalline structure analysis of Cellulose-g-PLLA microspheres} \]

The crystalline structures of PLLA, cellulose, and cellulose-g-PLLA were examined by WAXD measurements (Figure 2). PLLA showed the strongest diffraction peak at \( \theta = 17^\circ \), whereas cellulose showed the strongest diffraction peak at \( \theta = 22.4^\circ \). However, neither the crystallization peak of PLLA, nor that of cellulose was observed on cellulose-g-PLLA polymers. Only a dispersive broad peak around \( \theta = 20.6^\circ \) (20.4\(^\circ\), 20.8\(^\circ\)) was obtained, indicating that the cellulose became amorphous when grafted by PLLA. In a study made by Teramoto \textit{et al.}, \textsuperscript{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.

\[ \text{Morphology characterization of cellulose-g-PLLA microspheres} \]

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)](image)

![Figure 4: Hydration degrees of cellulose-g-PLLA microsphere](image)

![Figure 5: Influence of DP_{PLLA} on the degradability of cellulose-g-PLLA in PBS](image)
Figure 4 shows the hydration degrees of microspheres prepared from different DP<sub>PLLA</sub> 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<sub>PLLA</sub>, 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<sub>PLLA</sub>, 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. 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<sub>PLLA</sub> 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<sub>PLLA</sub>, 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 $n_r \approx 0.5$, 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<sub>PLLA</sub> on the degradability of cellulose-g-PLLA in enzyme solution](image)

![Figure 7: Effects of DP<sub>PLLA</sub> on the release of vitamin C from microsphere](image)

<table>
<thead>
<tr>
<th>No.</th>
<th>DP&lt;sub&gt;PLLA&lt;/sub&gt;</th>
<th>$M_0/M_∞$ (%)</th>
<th>$k$ (%/min&lt;sup&gt;0.5&lt;/sup&gt;)</th>
<th>$R$</th>
<th>$n_r$</th>
<th>$k_r$ (%/min&lt;sup&gt;-n&lt;/sup&gt;)</th>
<th>$R$</th>
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</thead>
<tbody>
<tr>
<td>7</td>
<td>3.15</td>
<td>61.0</td>
<td>1.2849</td>
<td>0.8450</td>
<td>0.5124</td>
<td>1.1054</td>
<td>0.9904</td>
</tr>
<tr>
<td>8</td>
<td>3.67</td>
<td>60.7</td>
<td>1.1040</td>
<td>0.8226</td>
<td>0.5175</td>
<td>0.9111</td>
<td>0.9902</td>
</tr>
<tr>
<td>9</td>
<td>3.98</td>
<td>63.2</td>
<td>1.0382</td>
<td>0.7943</td>
<td>0.6068</td>
<td>0.3775</td>
<td>0.9927</td>
</tr>
<tr>
<td>7</td>
<td>3.15</td>
<td>90.0</td>
<td>0.7165</td>
<td>0.7817</td>
<td>0.3372</td>
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<tr>
<td>8</td>
<td>3.67</td>
<td>83.0</td>
<td>0.6954</td>
<td>0.7818</td>
<td>0.3607</td>
<td>2.8952</td>
<td>0.9919</td>
</tr>
<tr>
<td>9</td>
<td>3.98</td>
<td>77.5</td>
<td>0.7128</td>
<td>0.7818</td>
<td>0.4164</td>
<td>1.6137</td>
<td>0.9938</td>
</tr>
</tbody>
</table>

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. 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.

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