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Cellulose/poly(ethylene glycol) blend and its controllable drug release behaviors in vitro

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Abstract

By preparation of a cellulose/poly(ethylene glycol)(PEG) blend and using DSC to analyze its thermal properties, this paper reported that such polymer blend might be applied as a drug carrier to provide novel drug release behavior. According to DSC analysis, such polymer blend has a controlled phase change property, and changing the ratio of these two polymers capably controls this property. For detailed drug release, this temperature response phenomenon was found visibly to depress drug released from blend that absolutely different than that of other temperatures. The pH response of this polymer blend has been found only suitable for releasing drug in an acidic media, e.g. pH about 4, multi-pulse type and forbidden in a base liquor.
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Keywords: Drug release; Phase change; Control; Cellulose; Poly(ethylene glycol); Polymer blend

1. Introduction

With respect to the fact that the conventional drug delivery system, DDS, is usually presented a problem, e.g. an unexpected great drug concentration above the therapeutic range at the initial stage and followed by a suddenly decrease in concentration below the therapeutic range, the controlled drug delivery system is thus being developed (Edlund & Albertsson, 2002; Fan & Singh, 1989; Grayson et al., 2003; Langer, 1990; Siepmann & Gōpferich, 2001; Tanquay & Lacey, 1980; Wichterle & Lim, 1960). Of numerous cases reported elsewhere, the degradable polymer is found usually employed not only as a carrier, but also to affect the drug release behavior. This means that the development of a polymer-based carrier is important for developing DDS with desired drug release behavior.

In this work, we blend cellulose with poly(ethylene glycol) (PEG) as a drug carrier and a typical drug, vitamin C, as a probe to study the release behavior. Of this case, a solid-to-solid phase change phenomenon was significantly observed for fabricated polymer, especially relating to the drug release behavior. This thus suggested that we can use the phase change property of polymer or polymer blend to affect a drug release process to fit the request of controlled DDS. Experimentally, the pH and temperature responses were conduced and the drug release was recorded dynamically by means of the electric conductivity measurement as recent Frenning, Fichtner, and Alderborn (2005) described in detail.

2. Experiments

2.1. Materials

A commercial cellulose provided by Shanghai Chemical Fiber Co. was used as received in this case. Based on the company determination, the cellulose has a degree of polymerization, DP, of about 500 and is composed of the α-cellulose above 90%. Previously, this cellulose has been also employed to fabricate a bio-fiber in

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our lab (Wang, Shen, & Gu, 2004). A commercial poly(ethylene glycol), PEG, with the molecular weight of about 4000, purchased from the Shanghai Chemical Products Co. was directly used in this case without further treatment.

The analytical grade solvents of polyoxymethylene, PF, and DMSO, both purchased also from the Shanghai Chemical Products Co. were used as received. The distilled water was always used through experiment.

The commercial vitamin C obtained from Shanghai Medicine Co. was employed as a probe without any further treatment.

2.2. Fabrication of the cellulose/PEG/drug blend

Initially, a solvent of DMSO/PF(10%) was prepared as the same as previously described (Wang et al., 2004), then weighted cellulose and PEG (75/25 wt%) were added under a stirring condition for several minutes. After that, the vitamin C powder, 0.1 g, was added. By heating the triplet-components blend to about 60 °C and kept for 1 h, a further heating run was continuously conducted until the temperature up to about 110 °C when the blend present a visible transparent behavior. Then, the residual formaldehyde within the blend was subsequently extracted using a vacuum pump at 80 °C for several hours.

The drug blend was finally fabricated as a membrane by casting it at a cleaned surface of glass substance. This drug film was dried in an oven under 50 °C condition for 24 h.

2.3. Measurement and characterization

The thickness of the drug film was measured using a CHY-3 instrument (Shanghai). According to the producer, this instrument can measure the thickness of a membrane from 0 to 3 mm with a precision of small 5%.

The thermal properties of the drug blends prepared with different ratios of cellulose/PEG were studied using a Mettler-Toledo 822e Different Scanning Calorimeter, DSC. In this test, the temperature was increased from 0 to 100 °C with a rate of about 10 °C/min.

The drug release was recorded dynamically by means of a glass electrode of conductivity meter, DDSJ-308A (Shanghai), as literature described (Frenning et al., 2005). Before releasing, the relationship between the concentration of vitamin C and the conductivity unit was initially investigated to fit the request of knowing the release content quantitatively. During releasing measurement, weighted drug film was immersed in 100 ml distilled water then the glass electrode was immersed to start and record the release process. Of this process, the influence from different ratios of blend/water, and the responses from pH and temperature were studied, respectively.

For un-mentioned release cases, the temperature was about 25 °C, the pH was about 7 and the ratio of solid/water was about 0.5.

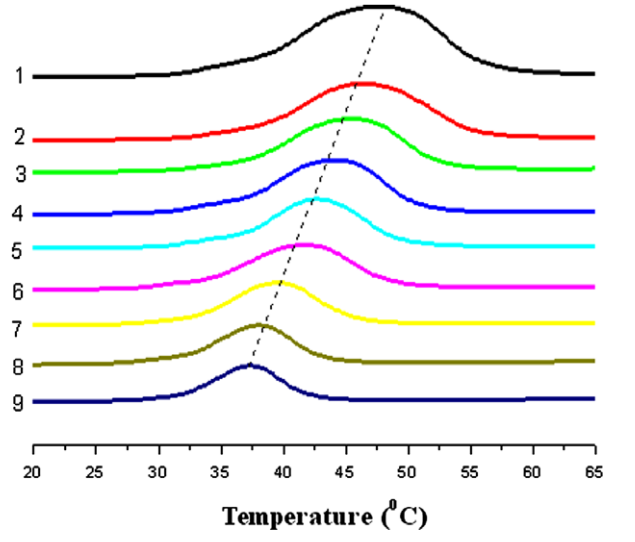
3. Results and discussion

3.1. Characterization of polymer/drug blend

According to several independent determinations, the averaged thickness of all prepared drug films was found to be 0.033 ± 0.003 mm. This means that these drug films were prepared uniformity.

The DSC curves of cellulose/PEG blends with different ratios were showed in Fig. 1. Observed that the heating absorption was evidently presented as a unique peak in described temperature range and this can be shifted to the low temperature direction if the cellulose percent was increased. Obviously, this phenomenon has two suggestions, the first is that the change of the ratio of cellulose/PEG the varied is the thermal property; and the second is such polymer blend might be employed as a drug carrier to control the drug release by using this visible temperature-based thermal response behavior. In fact, such thermal behavior is possible for a cellulose/PEG blend as literature described in relation to a solid-to-solid phase change occurrence (Liang, Guo, Gu, & Ding, 1995).

In order to further understand the relationship between the observed thermal phenomena and the polymer blend, the heat absorption behavior was taken as a function of the ratio of cellulose/PEG blend showed in Fig. 2. According to illustrated a good linear fit, the expected relationship was thus principally obtained as: $T_{abs} = 314.93 – 5.53\mathrm{Ln}(W_{Cell}/W_{PEG})$. Where the T_{abs} represents the heat absorption related temperature, W represents the weight of polymer and Ln is a natural logarithm. This equation implies that the increase of the cellulose percent, the heat adsorption of the blend would be occurred in a low temperature. This also



1. Cell/PEG=25/75, 2. Cell/PEG=30/70, 3. Cell/PEG=35/65, 4. Cell/PEG=40/60

5. Cell/PEG=45/55, 6. Cell/PEG=50/50, 7. Cell/PEG=60/40, 8. Cell/PEG=65/35

9. Cell/PEG=70/30

Fig. 1. DSC curves of cellulose/PEG blends with different ratios.

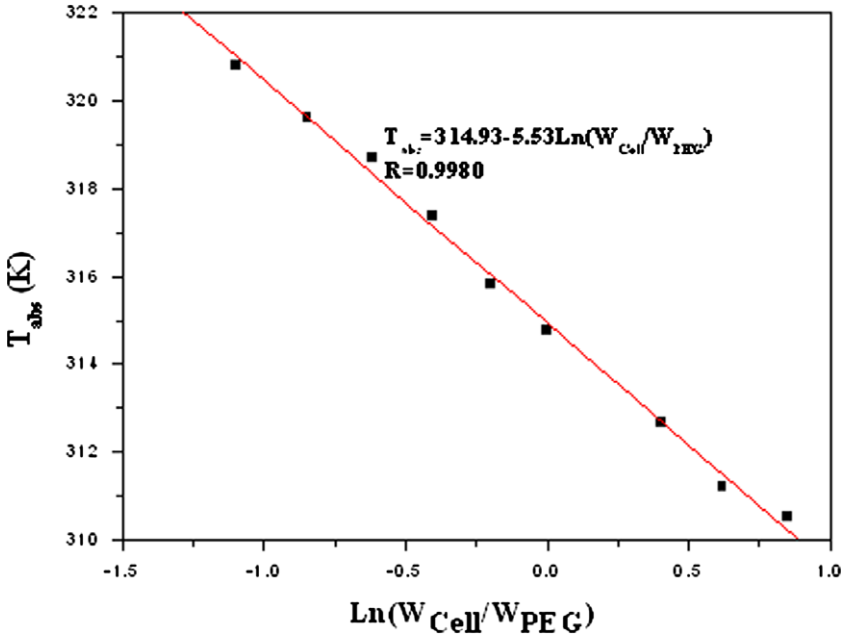


Fig. 2. The relationship between the ratio of cellulose/PEG and heat absorption temperature described with a good linear fit and associated formula.

means that the heat absorption behavior for such cellulose/PEG blend is changeable dependence of their mixing ratio. Obviously, this finding is of importance for preparation of polymer-based drug carrier.

Based on Figs. 1 and 2, a drug film was therefore prepared with a heat absorption possibility at about 59 °C (Fig. 3). Assuming this drug film has the expected phase change property, it was thus further expected to show a temperature-based response to affect the drug release.

3.2. Drug release

Generally, the utilization of the conductivity, κ, as a measure to study the drug release is possible (Frenning et al., 2005). However, before studying detailed case, to know the correlation between the conductivity and drug concentration is necessary. Based on two independence measurements, Fig. 4 presented a plot indicated that the relationship between the κ and the drug concentration could be described as: $\mathrm{Ln}\,\kappa = 5.364 + 0.503\mathrm{Ln}\,C$, where the κ

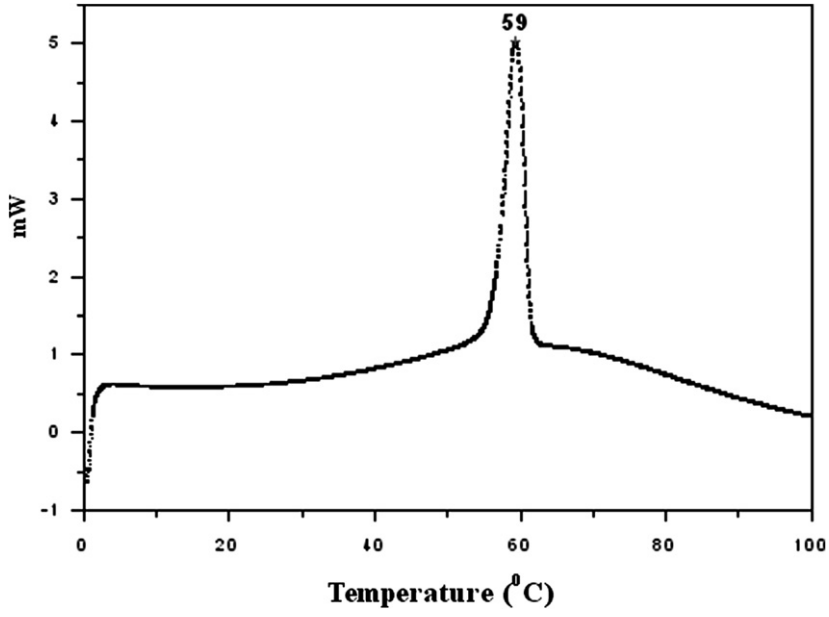


Fig. 3. A DSC curve of fabricated cellulose/PEG/vitamin C blend illustrated a heat absorption at about 59 °C relating to the solid-to-solid phase change occurrence.

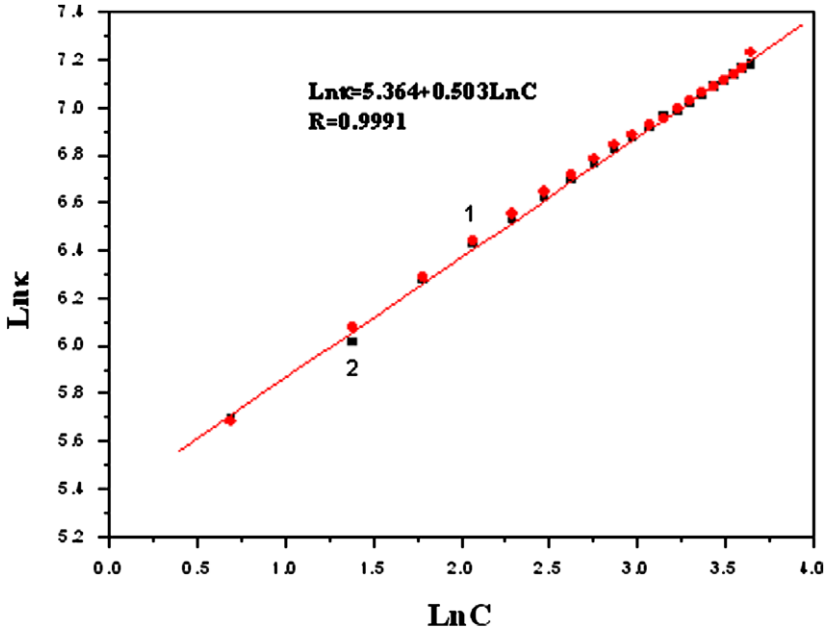


Fig. 4. A relationship between the drug concentration and the conductivity value.

represents the conductivity and the *C* stands for the concentration of drug, respectively.

Considering the ratio of solid/water is exactly reflecting to the drug amount loaded, Fig. 5 presented four release curves related to four different ratios of solid/water. Since the big ratio means the great drug loaded in blend, the observed release behavior is suggested that the great drug loaded in blend is benefit for release. The similar release evidence was also observed by Frenning et al. (2005).

The pH response is usually a basic function for preparation of novel DDS (Edlund & Albertsson, 2002; Fan & Singh, 1989; Grayson et al., 2003; Langer, 1990; Siepmann & Gōpferich, 2001; Tanquay & Lacey, 1980; Wichterle & Lim, 1960). To investigate this release behavior, the drug release was further conducted in two different pH-based liquids, i.e. one was prepared at about pH 4 by adding HCl to water and another was prepared at about pH 10 by adding NaOH to water. Fig. 6 showed that the pH response was evidently for prepared drug membrane because the release in acid solution is in period while in a base solution is impossible. Moreover, it is of interest to note that the pH response-based drug release was presented in multi-pulses, that is similar as that of Grayson et al. (2003) recently reported. Therefore, this drug release behavior suggests that this polymer blend is also capable for applying to new type DDS.

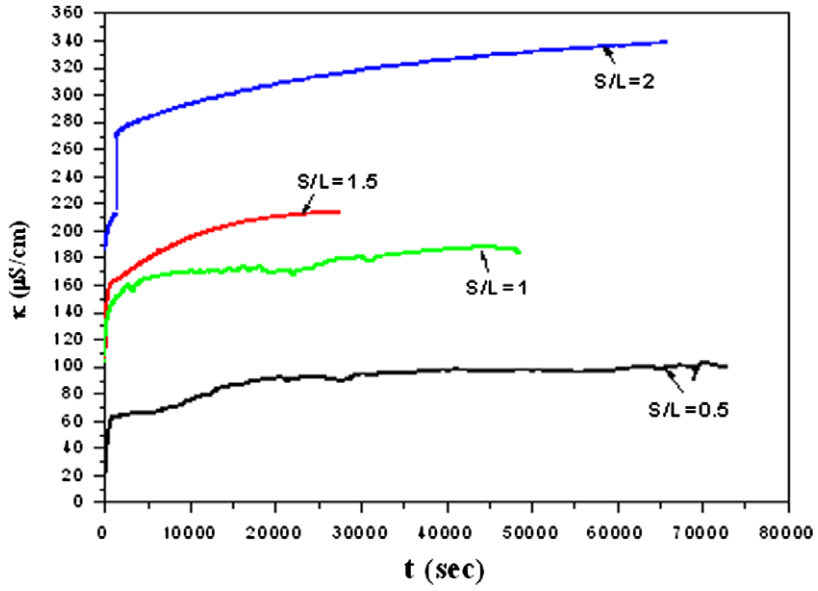


Fig. 5. Dynamic drug release behavior for cellulose/PEG/vitamin C blend in water corresponding to four different solid/liquid ratios.

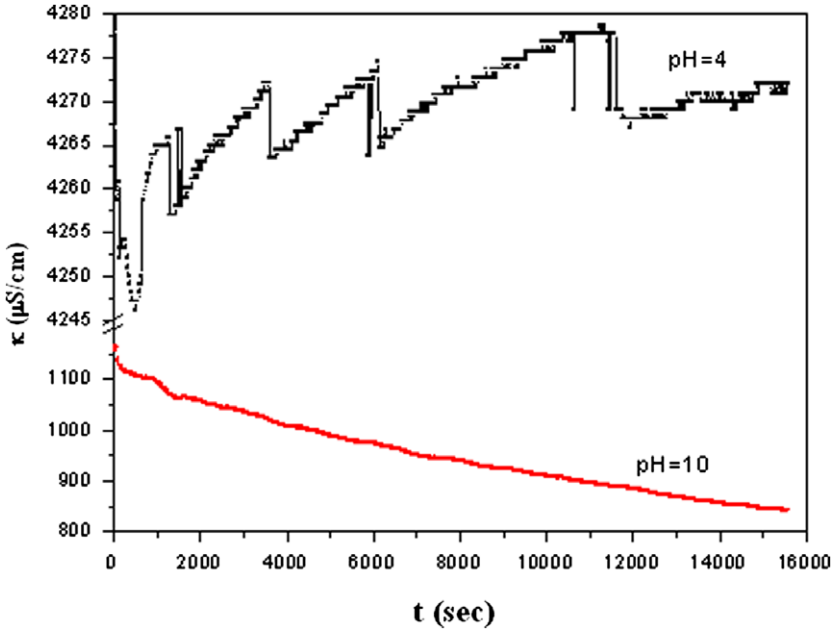


Fig. 6. The pH response for cellulose/PEG/vitamin C blend released in acid and base liquors, respectively.

For this case prepared drug film, the temperature response is greatly expected. To release drug in water relating to different temperatures including the human body temperature, 37 °C, and phase change taking place temperature, 59 °C, Fig. 7 indicated that the temperature response is certainly because the higher the temperature the greater is the drug released. However, as expected, Fig. 7 clearly indicated that the drug release conducted in a temperature that related to the phase change occurrence would be strongly influenced or controlled. Moreover, such influence presented is that the drug release would be depressed by the solid-to-solid phase change property of polymer blend. In other words, this suggests that the phase change occurrence in a polymer blend would be a tool for applying to control drug release with desired temperature response. Though this case we reported phase change temperature is high than the human body temperature, it should be addressed that some novel therapy methods need application of the high temperature, e.g. for reducing or controlling the size of cancer.

4. Conclusion

Based on experiments, the cellulose/PEG blend has been found with the possibility to apply for preparation of a novel drug delivery system with desired pH and temperature

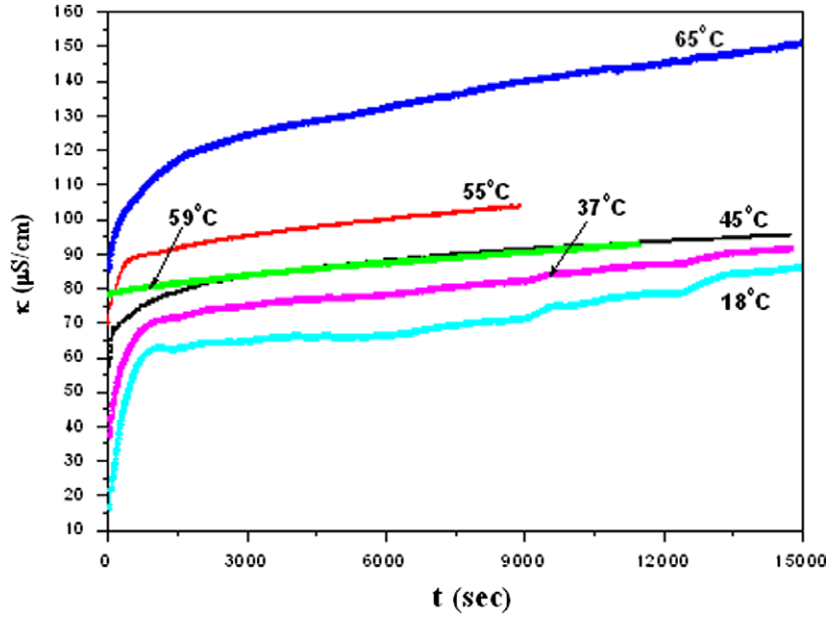


Fig. 7. The temperature response for cellulose/PEG/vitamin C blend released in water corresponding to different temperatures.

responses. However, to prepare such polymer blend for applying to DDS, the ratio of cellulose/PEG should be chosen to fit the required temperature-response, and the pH response is only suitable for releasing drug in an acidic media.

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