Carbohydrate Polymers 111 (2014) 393–399

Contents lists available at ScienceDirect

Carbohydrate Polymers

journal homepage: www.elsevier.com/locate/carbpol

Preparation of cellulose based microspheres by combining spray coagulating with spray drying

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ARTICLE INFO

Article history:
Received 8 February 2014
Received in revised form 11 April 2014
Accepted 3 May 2014
Available online 10 May 2014

Keywords:
Cellulose microspheres
Spray coagulating
Coagulating bath
Spray drying
Drug delivery

ABSTRACT

Porous microspheres of regenerated cellulose with size in range of 1–2 μm and composite microspheres of chitosan coated cellulose with size of 1–3 μm were obtained through a two-step spray-assisted approach. The spray coagulating process must combine with a spray drying step to guarantee the formation of stable microspheres of cellulose. This approach exhibits the following two main virtues. First, the preparation was performed using aqueous solution of cellulose as precursor in the absence of organic solvent and surfactant; Second, neither crosslinking agent nor separated crosslinking process was required for formation of stable microspheres. Moreover, the spray drying step also provided us with the chance to encapsulate guests into the resultant cellulose microspheres. The potential application of the cellulose microspheres acting as drug delivery vector has been studied in two PBS (phosphate-buffered saline) solution with pH values at 4.0 and 7.4 to mimic the environments of stomach and intestine, respectively.

1. Introduction

Science and technology keep moving toward environmentally friendly and sustainable resources and processes. Cellulose, as a complex carbohydrate and the most abundant renewable natural polymer on earth, nowadays, is of growing importance in the development and application of renewable materials. This progression has triggered a renaissance of cellulose research and application around the world during the last decade (Klemm, Heublein, Fink, & Bohn, 2005; Peršin et al., 2014). Traditionally, cellulose is a promising raw material in chemical, biological and energy industries (McGovern et al., 2013; Sharma & Varma, 2013; Fu, Zhang, & Yang, 2013). Meanwhile, regenerated cellulose in spherical morphology, which possesses large surface area, porosity, hydrophilicity and abundant hydroxyl groups, showed potential applications in fields of chromatographic separation, (Kuga, 1980; Luo & Zhang, 2010) purification (Cao et al., 2007) and sorption (Luo & Zhang, 2009).

As a kind of biocompatible material, various forms of cellulose are generally recognized as safe (GRAS) food substances according to the Food and Drug Administration (JECFA database for the specifications of additive(s), INS No. 460(ii)). Therefore, besides the technological applications described above, powdered cellulose or cellulose pellets have been widely used as food additive or detoxification agent for human body. The past decades have witnessed a significant advance in the application of water soluble derivatives of cellulose as the controlled drug releasing hosts (Tas, Özkan, Savaser, & Baykara, 2003). However, due to their solubility in water, most of the derivatives achieved the function of controlled releasing through complicated preparation processes and post-modification (Berthier, Herrmann, & Ouali, 2011; Chang, Price, & Whitworth, 1987; Ghorab, Zia, & Luzzi, 1990; Kök, Arıca, Gencer, Abak, & Hasırcı, 1999; Mi, Wong, Shyu, & Chang, 1999; Uekama et al., 1990). While, pristine cellulose microspheres and composite microspheres of cellulose coated with a functional layer with size in micrometer scale were expected to show advantages as drug delivery vector or controlled releasing host in comparison with particles of cellulose with irregular morphology and microspheres of other kinds of soluble carbohydrates, such as cellulose derivatives and starch (Luo, Liu, Zhou, & Zhang, 2009). For example, in order to deliver drug from mouth to intestine, a kind of vectors, which is biocompatible and unharmful to live organisms but can withstand the digestion of stomach, is desirable. Thus, owing to their low solubility in water and bioresistance to human body, microspheres of cellulose will show special virtue when they are used as drug delivery vector. However, the preparation of microspheres of pristine cellulose encounters difficulties due also to the

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http://dx.doi.org/10.1016/j.carbpol.2014.05.002
0144-8617/

low solubility of cellulose in aqueous solvent. Therefore, there is a lack of efficient and environmentally friendly method to maximally utilize the abundant cellulose raw material. Up to date, most of the reported methods generated cellulose spheres through a sol–gel transition process involving organic solvent, surfactant and crosslinker or using cellulose viscose solution as starting materials (Kuga, 1981; Neill, Roxana, & Reichardt, 1951; Peska, Stamberg, & Blace, 1977). Unfortunately, the organic solvent, surfactant and viscose solution are harmful to cells and to environment, which impedes the mass production of cellulose microspheres and limits the large-scale application of this promising spherical matrix. Recently, the mixture of sodium hydroxide and urea aqueous solution has been developed by Zhang's group as a green solvent for rapid dissolving of cellulose and the resultant transparent cellulose solution was exploited for various applications (Cai & Zhang, 2005, 2006).

Herein, we reported on a two-step spray-assisted green approach for the preparation of pristine cellulose microspheres and their composite microspheres (including drug loaded microspheres of cellulose) using cellulose dissolved in NaOH/urea aqueous solution as precursor in the absence of organic solvent, surfactant and crosslinking agent. Moreover, we have also explored their potential applications as drug delivery host and precursors for other kinds of functional systems.

2. Experimental

2.1. Materials

Cellulose with a viscosity-average molecular weight of 8.5×10^4 was obtained from Hebei Jigao Chemical Fibre Co., Ltd. Sodium hydroxide, urea, acetic acid and chitosan were of analytical grade (Sinopharm Chemical Reagent Co., Ltd. Shanghai, China) and used without further purification. Distilled water was used in the experiments.

2.2. Preparation of cellulose microspheres

A typical procedure for the preparation of stable microspheres of cellulose is as follows: an aqueous solution containing 7 wt% NaOH and 12 wt% urea was cooled to −12 °C, and then was utilized for the rapid dissolving of cellulose. The obtained transparent cellulose solution was infused into an air-atomizing device and then sprayed into a coagulating bath consisting of diluted aqueous solution of acetic acid. The cellulose solution was fed into the atomizing nozzle from the side inlet, while pressurized air was introduced from the top one. The cellulose solution was pulverized by the shear forces of the pressurized air with a pressure in range of 200–400 kPa, and tiny droplets of cellulose solution were generated through the orifice of the nozzle. Subsequently, the droplets were pushed into the coagulating bath and therein they coagulated, forming the as-coagulated microgels (details on the process, see Scheme 1, process I). The pH value of the coagulating bath was kept below 7 during the spraying process by continually adding aqueous solution of acetic acid into the bath. The as-coagulated cellulose microgels were washed three times with deionized water to remove the salt and acetic acid residua. Then they were re-dispersed into deionized water and dried through a lab-scale spray dryer at 120 °C, resulting in stable cellulose microspheres (see process II of Scheme 1).

2.3. Preparation of chitosan coated cellulose spheres

Composite microspheres of cellulose coated with a chitosan thin layer were fabricated by two different procedures: (1) the aqueous solution of chitosan containing 0.5 wt% acetic acid was utilized as the coagulating bath during the spray coagulating process (process I of Scheme 1), and the droplets of cellulose solution were sprayed directly into it. The as-coagulated composite microspheres were washed twice with water, and then solidified and dried by spray drying method; (2) the obtained stable pristine cellulose microspheres (see Section 2.2) were re-dispersed into an aqueous solution of chitosan containing 0.5 wt% acetic acid, and then dried by a spray drying process.

2.4. Ibuprofen loading and releasing

Loading of ibuprofen into the cellulose microspheres was achieved by the following procedure: ibuprofen solution was prepared by dissolving the drug (0.01 g) into a mixture of alcohol and water (1:2, V/V). Fresh microgels were obtained by removing the water inside the as-prepared microgels of cellulose using a suction filtration method as quick as possible, and then the fresh microgels (5.0 g) were immersed into a 20 mL ethanol/water solution of ibuprofen swiftly. The suspension was kept stirring for 24 h, ensuring an adequate absorption of ibuprofen by the microgels. The suspension of drug-infiltrated microgels was then dried by a spray drying process, resulting in ibuprofen encapsulated cellulose microspheres (see process II' of Scheme 1). To understand the drug delivery properties of the cellulose microspheres in a human body, the release of ibuprofen from the drug encapsulated cellulose microspheres were investigated in vitro using a shaker incubator (100 rpm) filled with 30 mL of PBS (phosphate-buffered saline) solution of different pH values (pH = 7.4 and pH = 4.0) at 37 °C. 4 mL of PBS solution was collected at predetermined time interval after centrifugation and then equivalent volume of fresh buffer solution was added to the incubator to maintain the total volume of the solution constant.

2.5. Characterizations

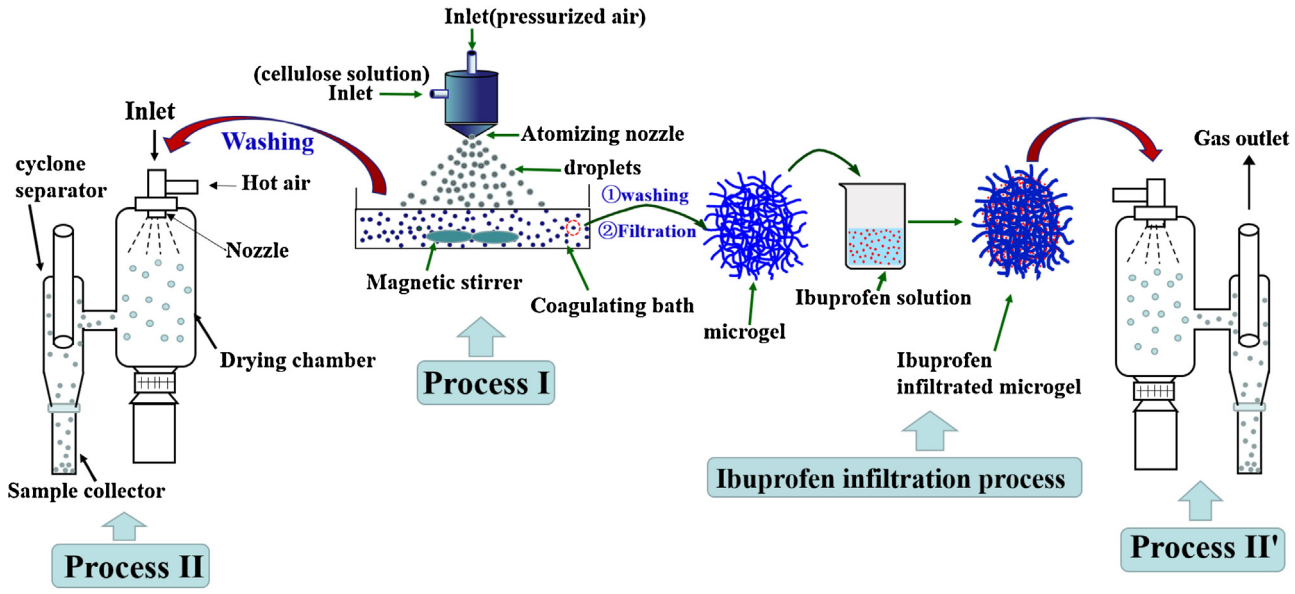
A Microtrac NPA253 instrument (Microtrac, USA) was used to perform dynamic light scattering for samples 4 mL in volume. A JSM-6390LV SEM (JEOL, Japan) was used for morphological studies by coating the sample onto a glass slide (~1 cm^2) and then was deposited with a conductive thin layer of gold. A JEM 2100F transmission electron microscope (JEOL, Japan) was utilized for the TEM and HR-TEM images measurements by simply dispersing the sample on the surface of a copper grid. Powder X-ray diffraction (XRD) were performed on a Bruker D8 advance diffractometer (Germany) employing Cu-$K\alpha$ radiation (λ = 0.15418 nm) in order to identify the crystallinity of the prepared samples. The amount of ibuprofen in the PBS solution at different time intervals were monitored by measuring the absorbance of the solution at wavelength of 222 nm through a TU-1901 UV–vis spectrophotometer (Purkinje General, China), and then the absorbance was converted into the mass of ibuprofen.

3. Results and discussion

3.1. Principles of the preparation methods

3.1.1. Pristine cellulose microspheres

A two-step spray-assisted process, i.e. the combination of spray coagulating with spray drying has been developed for the preparation of pristine cellulose microspheres (see Scheme 1). The coagulation is a typical process in industry for the preparation of viscose fiber using viscose solution as precursor and mixed aqueous solution of sodium salt and inorganic acid as coagulating bath. During the coagulating process, viscose fibers formed in the bath and then were stretched in-situ in order to get stable viscose fibers. Herein, the coagulation process as in the viscose fiber industry



Scheme 1. Illustrative diagram of the spray coagulating process (I), the spray drying process of as-coagulated pristine cellulose microgels (process II), the infiltration and spray-assisted encapsulation of ibuprofen into the cellulose microspheres (process II′).

were shifted to our preparations, however, droplets of cellulose dissolved in an NaOH/urea aqueous solution were produced with a spray method in our case instead of the tiny flow of viscose solution derived from extrusion in the viscose fiber industry. Furthermore, in contrast to the mixed aqueous solution of inorganic acid and sodium salt, which was used as coagulating bath in the viscose fiber industry, aqueous solution of acetic acid was chosen as the coagulating bath in our case (see process I of Scheme 1). The droplets of the NaOH/urea aqueous solution of cellulose were coagulated upon contacting with the coagulating bath. The reaction between acetic acid and sodium hydroxide broke the hydrogen bonds existing in the droplet of the cellulose solution, resulting in as-coagulated cellulose microgels. At this stage, spherical structures of cellulose named as microgels formed. However, the as-coagulated microgels contain an abundance of water and also a trace of acetic acid and sodium acetate. The purpose of the following washing step is to remove the acetic acid and sodium acetate in the microgels. The suspension of the microgels was evaporated subsequently to dryness by a spraying dryer as has been shown in Scheme 1 process II. During the spray drying process, water included in the microgels was evaporated transiently, which induced the shrinkage of the microgels and led to stable cellulose microspheres (see Section 3.2). The dried stable cellulose microspheres were simultaneously collected by a connected cyclone separator (see process II of Scheme 1). Control experiments indicated that when the spray coagulating combined with freezing dry or with normal evaporation dry, or the spray drying was applied to the cellulose solution directly, only aggregations or particles of cellulose with irregular morphology were obtained (see Section 3.3 SEM and TEM measurements).

3.1.2. Chitosan coated cellulose microspheres

Two different spray-assisted procedures have been developed for the preparation of chitosan coated cellulose microspheres: in procedure (1), an aqueous solution of chitosan with 0.5 wt% acetic acid was utilized as coagulating bath instead of the diluted aqueous solution of acetic acid as has been used in the preparation of pristine cellulose microspheres. Herein, acetic acid played double roles as both the solvent of chitosan and a coagulating agent for the cellulose droplets. The as-coagulated cellulose microgels were simultaneously coated by chitosan since the hydroxide within the as-coagulated cellulose microgels provided an alkaline condition and made the chitosan deposit in-situ onto the external surface of the cellulose microgels, resulting in composite microgels. After washing, the composite microgels were re-dispersed into water to form a suspension. The suspension was then evaporated to dryness by a spray drying process, resulting in stable composite microspheres of cellulose coated with chitosan. While in procedure (2), stable pristine cellulose microspheres were initially prepared via the two-step spray-assisted process and subsequently re-dispersed into an aqueous solution of chitosan containing 0.5 wt% acetic acid. The suspension was then dried by a spraying dryer. During the spray drying step, the chitosan was solidified and deposited onto the external surface of the cellulose microspheres, generating chitosan coated cellulose microspheres as well.

3.1.3. Drug loading

The loading of Ibuprofen was performed based on the as-coagulated microgels with the assistance of a spray drying process as has been depicted in Scheme 1, process II′. The Ibuprofen molecules, which were dissolved in solvent and then infiltrated into the freshly prepared as-coagulated cellulose microgels, were encapsulated into the solid cellulose microspheres during the spray drying process by taking advantage of the shrinkage effect evoked by the evaporation of water/ethanol solvent from the microgels (see Section 3.2. dynamic light scattering (DLS) measurements).

3.2. Dynamic light scattering (DLS) measurements

The size distributions of as-coagulated microgels and spray dried solid cellulose microspheres were studied by dynamic light scattering (DLS) method, and the results are presented in Fig. 1. It can be seen that the as-coagulated microgels showed a relatively wide size distribution (Fig. 1(a)) than those of the cellulose microspheres derived from the microgels by spray drying (Fig. 1(b)). More than 90% of the particles with hydrodynamic diameter distributed in range of 3–6 μm for the as-coagulated microgels and 1.2–2 μm for the stable cellulose microspheres, respectively, were observed. The average hydrodynamic diameter of the stable cellulose microspheres is 2–3 μm smaller than that of the as-coagulated microgels, indicating that the shrinkage phenomena took place during the spray drying process of the microgels. This shrinkage effect offers

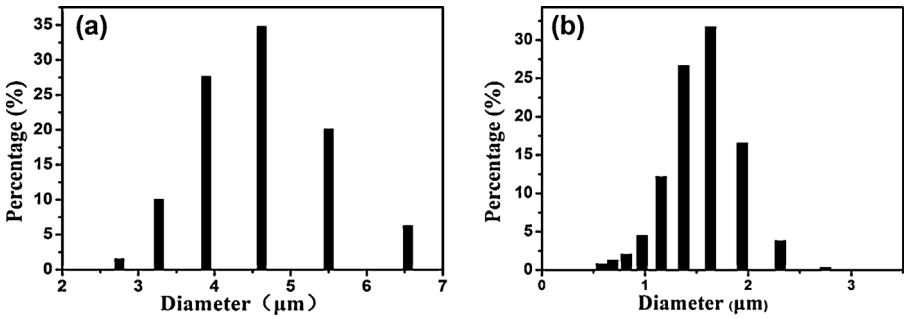


Fig. 1. DLS plots of (a) the as-coagulated microgels and (b) the cellulose microspheres derived from the as-coagulated microgels by a spray drying process.

us an opportunity to encapsulate guest, e.g. drug, into the cellulose microspheres (see Section 2.4.).

3.3. SEM and TEM measurements

3.3.1. The pristine cellulose samples

SEM image of the stable cellulose microspheres was depicted in Fig. 2 as picture A, which clearly shows the formation of cellulose microspheres with smooth surface and size between 1 and 2 μm. The SEM image is consistent with the DLS results described above. In order to verify the necessity of an acidic condition for the coagulating bath, SEM image of the microspheres coagulated in a pure water bath is given as picture B in Fig. 2 for comparison. In comparison with the perfect microspheres prepared using acetic acid solution as coagulating bath, cellulose microspheres with poor size distribution and morphology were obtained when pure water was used as coagulating bath (see picture B of Fig. 2). The different results indicate that it is necessary to maintain the pH value of the coagulating bath below 7. Undoubtedly, the acidic coagulating bath can supply enough protons to neutralize the OH^- in the droplets of cellulose solution and generate the spherical cellulose microgels with more homogenous size distribution. In contrast, when pure water was used as coagulating bath, the alkalinity of the coagulating bath increased with time. Then the coagulating solution turned into a poor coagulating agent to the droplets of the cellulose solution. As a result, cellulose microspheres with wide size distribution and irregular morphology formed since the cellulose tends to swelling in an alkaline condition. Control experiments revealed that the combination of spray coagulating with spray drying is crucial to the formation of perfect microspheres. As has been described in Section 3.1, the spray coagulating process produced the droplets of cellulose solution and made them coagulated upon contacting with the coagulating bath, generating loose microgels with abundance of water. However, the microgels are too weak to maintain the spherical structure after the regular evaporation or freeze drying process. While, the spray drying process could play two functions to the microgels: drying and stabilizing. During the spray drying process, the microgels were dried in transient during the falling process. Thus, they can easily keep the original spherical morphology and stay in separated state after drying. The transient evaporation of solvent from microgels induced the homogenous shrinkage of them and resulted in stable cellulose microspheres with smaller size than those of the original microgels. The shrinkage and stabilization induced by the spray drying played a similar function as the crosslinker in the conventional preparations of cellulose microspheres, microspheres of cellulose derivatives or synthetic polymer. Whereas, in our case no crosslinker is required owing to the spray drying induced transient shrinkage effect and the low solubility of the regenerated pristine cellulose microspheres. This point was confirmed by comparing SEM image of Fig. 2A with that of Fig. 2C, where the former showed the image of solid cellulose microspheres derived from spray drying, while the latter one is an image of the solid derived from as-coagulated microgel by freeze drying. The comparison revealed that a bulk cellulose agglomeration rather than regular microspheres formed when the microgels were dried by a freeze drying method. The same is true when cellulose microgels were dried by a thermostatic evaporation process. The above observations demonstrated that the application of spray drying to the microgels is a vital step in guaranteeing the formation of stable microspheres of regenerated cellulose. Otherwise, only cellulose agglomeration will be obtained. Nevertheless, if the spray drying process was applied directly to the cellulose solution without the spray coagulating pre-process, only particles of cellulose with irregular morphology were achieved due to the disturbing of NaOH and urea in the droplets of cellulose solution.

Picture A of Fig. 3 presents the TEM image of a cellulose microsphere derived from spray-dried microgel. It can be seen clearly that the spheres are abundant with porous structures, indicating that the spray drying can not only solidify the network of the cellulose microspheres but also keep their porosity. While, TEM image of the particles deduced from microgels by a normal evaporation drying method at ambient temperature reveals the formation of a loose network, which might be induced by the hydrogen-bond-network existing in the cellulose molecules (Fig. 3B) (Cai et al., 2007). In comparison with the loose agglomeration (Fig. 3B), the stable microsphere showed a more condensed surface (Fig. 3A), which can be attributed to the formation of a hard shell on the external surface of the cellulose microsphere.

3.3.2. Composite microspheres

SEM and TEM images of the composite microspheres of chitosan coated cellulose prepared by procedure (2) (see Section 2.3) are given in Fig. 4 as pictures A and B, respectively. In comparison with that of the spheres of pristine cellulose (see Fig. 2A), the size of the composite microspheres of chitosan coated cellulose increased slightly (Fig. 4A), especially for the large sized ones. Additional differences between these two kinds of samples are concerning the morphology and appearance. After the coating of a chitosan layer, spheres with a rough appearance were observed. TEM image shows clearly the preserving of pores inside the composite microsphere and also reveals the successful coating of a solid layer. Similar results have also been observed for composite microspheres produced with procedure (1).

3.4. X-ray measurements

As has been indicated in Section 3.3, the drying method can influence the final morphology of the microspheres. To understand the effect of drying method on the crystallinity of the cellulose materials, powder X-ray diffraction measurements were performed to the cellulose microspheres derived from the spray drying method and the cellulose particles obtained from freeze

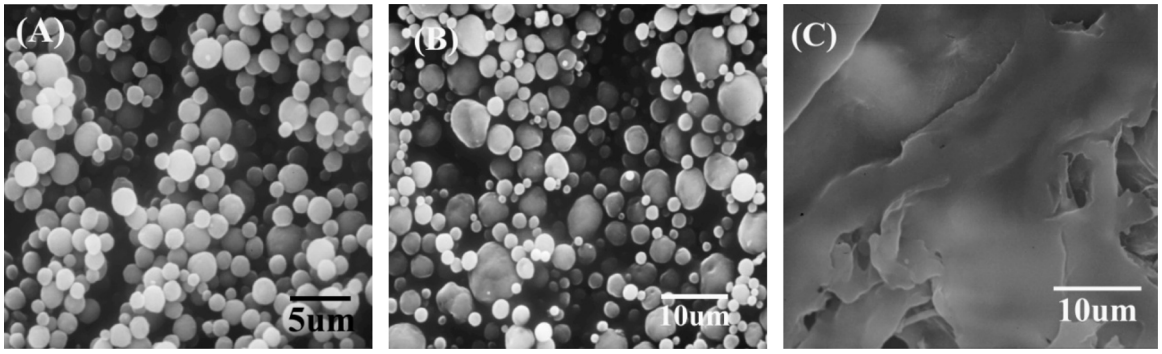


Fig. 2. SEM images of the regenerated cellulose samples: (A) prepared by spray coagulating using acetic acid as coagulating bath and then dried by spray drying; (B) prepared by spray coagulating using pure water as coagulating bath and then spray dried; (C) prepared by spray coagulating using acetic acid as coagulating bath and then freeze dried.

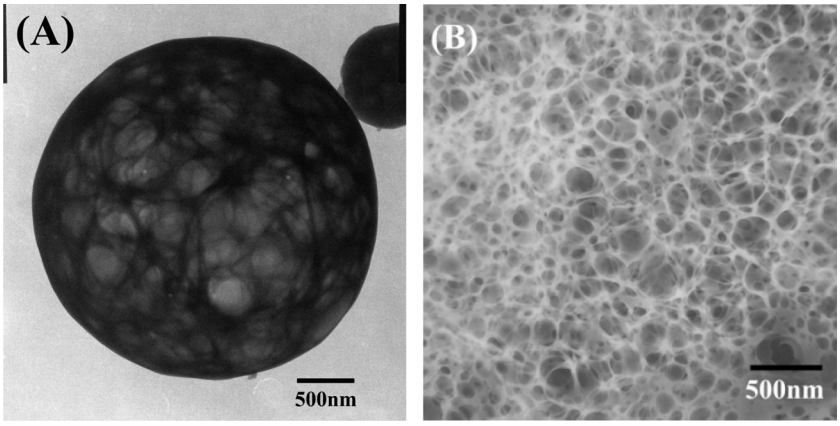


Fig. 3. TEM images of the cellulose microsphere obtained by spray drying (A) and the solid derived from the microgel dried by a normal evaporation at ambient temperature (B).

drying process. The XRD patterns of regenerated cellulose derived from two different drying methods are shown in Fig. 5. The XRD curves revealed that both of the regenerated cellulose show three diffraction peaks at $2\theta = 12.1$, 19.8 and 22.0°, which can be indexed to the (1 -1 0), (1 1 0) and (2 0 0) characteristic planes of cellulose II crystal (Cai & Zhang, 2005). The degree of crystallinity, which is identified by MDI Jade 5.0 software based on the diffraction peaks (Bansal, Hall, Realff, Lee, & Bommarius, 2010), are 44% for the spray-dried cellulose microspheres and 68% for the freeze-dried particles, respectively. The values indicate that cellulose microspheres derived from spray drying process own more amorphous region, which might arise from the high increasing and dropping rates of the temperature during the spray drying process than those during the freeze drying process (Suslick, Choe, Cichowlas, & Grinstaff, 1991). Crystallinity can influence the swelling properties of the cellulose materials in alkaline conditions (Grignon & Scallan, 1980), while the swelling properties of the cellulose microspheres may affect the releasing properties of the cellulose microspheres when they were utilized as loading hosts.

3.5. Drug loading and releasing properties

The porous cellulose microspheres could act as a drug delivery vector with great potential due to their biocompatibility and bioresistance to human body. Fortunately, the shrinkage phenomena, taking place during the spray drying step of the microgels, offers us a chance to encapsulate drug into the dried stable microspheres of cellulose (see Sections 3.2 and 2.4). To verify this capacity, we

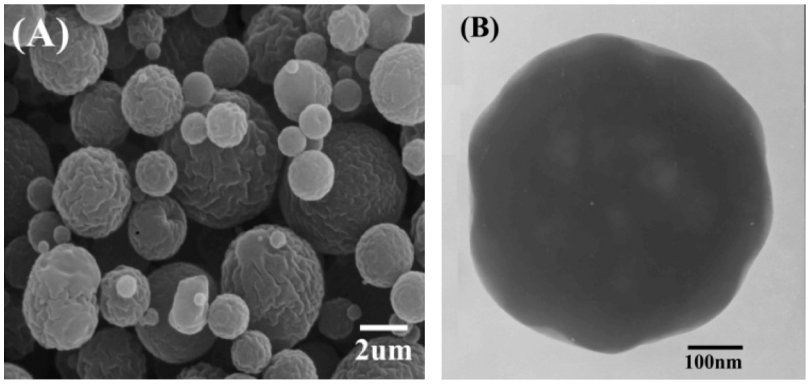


Fig. 4. SEM (A) and TEM (B) images of chitosan coated cellulose composite microspheres obtained by procedure (2).

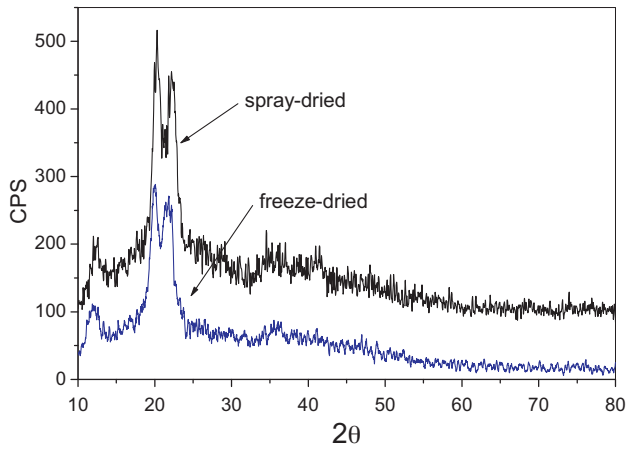


Fig. 5. The powder X-ray diffraction patterns of cellulose microspheres derived from microgels by spray drying and the particles derived from microgels by freeze drying, respectively.

introduced ibuprofen, an extensively employed analgesic and anti-inflammatory drug, into cellulose microspheres and subsequently studied on their drug release properties in vitro with two simulated body fluids of stomach (pH = 4) and intestine (pH = 7.4), respectively, at the temperature of 37 °C. The releasing behaviors of ibuprofen from the ibuprofen-loaded cellulose microspheres at pH = 4 and pH = 7.4, respectively, were depicted in Fig. 6. There was a sharp release at the initial stage since the ibuprofen loaded close to the external surface could diffuse immediately from the microspheres to the solution when the microspheres were dispersed into the buffer solution. The subsequent release appeared to be a diffusion-controlled process. A comparison between the two release curves in Fig. 6 reveals that the release of ibuprofen from the microspheres at pH = 7.4 is more rapid than that at pH = 4. Nearly 80% of ibuprofen was released from the microspheres at pH = 7.4 within 100 h, while only 27% of ibuprofen was released at pH = 4 during the same time period. The different releasing rate of ibuprofen from the cellulose microspheres at pH values of 4 and 7.4 can be ascribed to the different solubility of ibuprofen therein. The low solubility of ibuprofen at low pH value combines with the biocompatibility and bioresistance properties of cellulose to human body make the microspheres of cellulose an ideal vector in assisting ibuprofen to survive the digestion of the acidic stomach and deliver it from mouth to intestine, where more than 50% of the ibuprofen can then be released in a period of about 3 days.

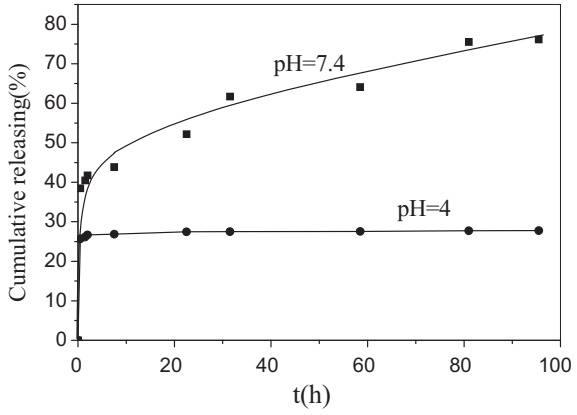


Fig. 6. Time dependence of ibuprofen releasing from the spraying dried cellulose microspheres in PBS solution of pH = 4 and pH = 7.4, respectively.

Additionally, the successful preparation of ibuprofen-loaded cellulose system intrigued us to anticipate that similar method can be easily transferred to the preparation of nanoparticles or biomolecules decorated cellulose composite microspheres.

4. Conclusions

In summary, an efficient and green approach to the preparation of cellulose based porous microspheres was developed. This method may evoke the mass-production and the large-scale application of cellulose based microspheres. Porous microspheres of pristine cellulose with size distribution more than 90% in range of 1–2 μm and composite microspheres of chitosan coated cellulose with more than 90% of the sphere sizes distributed between 1 and 3 μm were generated under a condition free of organic solvent and surfactant. The combination of spray coagulating procedure with spray drying process is critical to the formation of porous cellulose microspheres, whereas application only one of the processes independently cannot result in particles with spherical morphology. Cellulose microspheres derived from the spray drying process showed lower crystallinity than those obtained by the freeze drying method due to the high changing rate of temperature in the former case. By this two-step spray-assisted approach one can flexibly introduce functional guests into the cellulose microsphere hosts in-situ or ex-situ and endow them with further functions. For instance, ibuprofen-loaded cellulose microspheres, which showed potential ability to make ibuprofen survive in an acidic environment, were achieved by taking advantage of the shrinkage effect of the microgels during the spray drying process. It can also be anticipated that other kinds of functional guests, e.g. magnetic nanoparticles, can be incorporated into the cellulose microspheres in-situ during the spray coagulating process and the spray drying step or ex-situ after the spray drying step, which can then endue the cellulose microspheres with additional functions, such as magnet-assisted separability. Furthermore, the modification of the resultant cellulose microspheres with functional polymer or biomolecules can provide them with advanced controllability to drug releasing and recognition ability to the immune system of human body, which are two crucial requirements to the microspheres when they are used as drug delivery vehicle with controlled releasing properties. Moreover, carbonizations of the cellulose microspheres will result in porous carbon materials, which can be used extensively as adsorbents for adsorption and separation or as electrode materials for electrochemical energy storage. Such kinds of exploration to the cellulose microspheres are also underway in our group.

Acknowledgements

This work is supported by the National Key Project on Basic Research (grant no. 2012CB722705), the National High Technology Research and Development Program of China (2012AA110407 and 2014AA250323) and the Natural Science Foundation of China (no. 21103096 and U1232104). We also thank the Scientific Research Foundation of Department of Science and Technology of Shandong Province for financial support (ZR2010BM024).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carbpol.2014.05.002.

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