Role of Tosyl Cellulose Acetate as Potential Carrier for Controlled Drug Release

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Abstract: Cellulose is a naturally occurring organic polymer. The chemical functionalization of cellulose is conducted to adjust its properties for different purposes. In the present study, cellulose was extracted from bagasse, derivatized to acetate, and chemically modified again to prepare tosylated cellulose acetate. The prepared cellulose derivatives were investigated by Fourier transform infrared spectroscopy and scanning electron microscopy. Tosyl cellulose acetate was evaluated as a potential carrier for the controlled release of pH-sensitive drugs. The release was investigated as a function of pH and time at various pH values. The results find their use in controlled release applications.
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1. Introduction

Chemical modifications of cellulose can drastically change its properties. Moreover, cellulose is suitable for preparation of many advanced materials for use in various applications; because of its structural uniformity as a β-1-4-linked polyglucan Typical cellulose modification techniques include esterification and etherification of its hydroxyl groups (Klemm *et al*., 1998; Heinze *et al*., 2006; Ibrahim *et al*., 2014). Other modification techniques include ionic and radical grafting, acetalization, deoxyhalogenation, and oxidation (Akira, 2001).

Cellulose derivatives are advantageous compared to other synthetic polymer derivatives; with regards to environmental safety and abundance of natural cellulose. Cellulose is a major component of all woods, grasses, fibers, and seed hairs. Other sources of cellulose include agricultural residues such as straws, sugar cane, banana plants, and the cell walls of some algae and bacteria (Hanley *et al*., 1997; Liu *et al*., 2005; Yu *et al*., 2005). One of the agricultural residues abundantly available in Egypt is bagasse, a byproduct resulting from sugar manufacture. This lignocellulosic biomass feedstock is a complex mixture of three structural biopolymers (lignin, cellulose, and hemicelluloses) and minor, non-structural components (Brodeur *et al*., 2011).

Because cellulose is insoluble in water and most common solvents (Bochek, 2003), it is usually dissolved in non-derivatizing solvents in non-aqueous media such as *N,N*-dimethylacetamide/lithium chloride (*N,N*-DMA/ LiCl). This particular system is used to prepare a wide variety of derivatives in which dissolution is possible with negligible degradation, even for high-molecular weight polysaccharides like cotton linter and bacterial cellulose.

The present study was completed to better understand the synthesis of tosyl-modified cellulose acetate and to characterize its properties. In the present study, there was a focus on the use of such chemically modified cellulose derivatives as carriers for the controlled release for pH-specific drugs. These experiments were carried out with tosyl cellulose acetate as carrier matrix for an anti-acid drug.

2. Experimental Materials

Cellulose isolation

Bagasse was kindly provided by Qena Pulp and Paper Company (Qena, Egypt) and was used as the lignocelluloic raw material for the isolation of cellulose. It consists of 85.95% holocellulose, 21.13% lignin, and 2.73% ash. Isolation of the cellulose was done *via* delignification followed by bleaching.

Delignification of the bagasse was carried out with 10% sodium hydroxide at 170°C for 2 h with a liquor-to-bagasse ratio of 1:10 (water: raw material). After the allotted time had elapsed, the fibers were washed until a neutral pH was achieved, and another treatment with 5% sulfuric acid at 160°C for 2 h with a liquor-to-bagasse ratio of 1:10 was performed. At the end of the pretreatment process, the unbleached bagasse fibers were air-dried and stored for further analysis and use.

Bleaching was carried out in one stage in which the unbleached bagasse pulp was subjected to sodium hypochlorite solution equivalent to 60% of the active

chlorine requirement needed to bleach the pulp for 1 h at 80 °C. The liquor-to-fiber ratio was 10:1, and the pH was maintained at 9.0 during the hypochlorite bleaching process. At the end, the bleached bagasse pulp was thoroughly washed with water until a neutral pH was achieved, left to air-dry, and stored for further use.

Methods

Preparation of cellulose acetate (CA)

Cellulose acetate was prepared using a method described by Schaller and Heinze (2005) in which approximately 3.3 g of cellulose fiber from bagasse pretreatment was dewatered twice with glacial acetic acid. Then, 6 mL of acetic anhydride and 100 µL of 96% sulfuric acid were combined in a 100-mL round-bottom flask. The flask was stoppered and placed in an oil bath at 55 °C. The reaction mixture was stirred slowly with a magnetic stirring bar for 2 h. After the completion of the reaction, the material was filtered using a coarse ground glass disc. The cellulose acetate was washed extensively with water, then with methanol, and was dried at 60 °C under vacuum.

Preparation of tosyl cellulose acetate

First, 20 g of CA was immersed in 300 mL of 18% aqueous sodium hydroxide at room temperature for 5 h. The solution was filtered using G3 sintered glass and washed with distilled water 6 times before a final washing with dimethylacetamide (DMAc). The cellulosic material was transferred with 800 mL of DMAc solution in a 3-necked flask and stirred for 2 h at 120 °C under reflux. When the allotted reaction time elapsed, the temperature was decreased to 100°C. When the temperature reached 100 °C, 60 g of dried lithium chloride (LiCl) was added and stirring continued for 24 h at room temperature to ensure complete dissolution.

The solution was cooled to 8 °C and a mixture of 25 mL of triethylamine and 25 mL of DMAc was added, dropwise, while stirring. A solution of 17.5 g of tosylchloride in DMAc was then added to the reaction mixture and stirring continued for 24 h. Precipitation to acquire tosyl cellulose acetate was carried out in ice water with vigorously stirring. The precipitate was filtered in a G3 funnel crucible and washed six times with distilled water and with ethanol six times further. Finally, excess ethanol was removed by distillation and the precipitate was dried in a vacuum oven at 40 °C.

Loading and releasing of pH-sensitive drug

An anti-acidic drug was selected to measure the effect of the prepared cellulose and tosyl cellulose acetate on drug release. Solutions at pH values of 2.0, 3.5, and 5.0 were prepared for testing and to mimic the pH of the stomach during the period of drug release. First, 0.5 g of the anti-acidic drug was dissolved in 10 mL of ethanol and was placed in the different pH solutions containing 0.1 g of the modified cellulose acetate. The pH of each solution was measured initially and for another 2 h. After that, another 10 mL of the respective pH solution was added to the existing solution and the pH was recorded after 1 h. This method was repeated with each tested pH.

Scanning electron microscopy (SEM)

The SEM characterizations of bagasse, cellulose acetate, and tosyl cellulose acetate and the drug-loaded compounds were made using a JEOL JXA-840A electron microprobe analyzer (JOEL USA Inc., Peabody, MA) operating at an accelerating voltage of 30 kV.

Fourier transform infrared (FT-IR) analysis

The FT-IR spectroscopy was used to evaluate the fiber resulting from bagasse, cellulose acetate, and tosyl cellulose acetate. The IR spectra were generated using a JASCO FT/IR 6100 Instrument (Japan). Samples (roughly 2 mg) were mixed and thoroughly ground with approximately 200 mg KBr to reduce their particle size and uniformly disperse the sample in the disks. All spectra were recorded in the absorbance range from 4000 to 400 cm^{-1}.

3. Results and Discussion

Isolation of the Cellulose

An alkaline pulping process was selected to break down the ligocellulosic structure. The resulting pulp was brown due to degradation of the cell wall components and incomplete removal of lignin (Ibrahim *et al*., 2010). The fibers were bleached such that they consisted of 81% α-cellulose and 15% extractable hemicellulose. The Klason lignin content after pulping and bleaching was approximately 0.1%. Ibrahim *et al*., (2013) indicated that alkaline treatment is a delignification process in which a significant amount of the lignin is dissolved and separated from the fiber in the resulting black liquor. After delignification and bleaching, an increase in the α-cellulose content is achieved, producing cellulose fibers.

Figure 1 shows the infrared spectrum of bleached bagasse pulp. The peak at 1735 cm^{-1}, assigned to the C=O stretching vibrations typical of the structural features of lignin, disappeared after bleaching (Ibrahim *et al*., 2010). Further absorption bands of lignin at approximately 1595 cm^{-1} (Agblevor *et al*., 2007) and 1510 cm^{-1} (aromatic ring stretching) also disappeared following bleaching fibers, as shown in Fig. 1. Moreover, bands from 3300 to 3413 cm^{-1} related to O-H groups, and at 2912 cm^{-1} related to C-H bonds, occurred beside bands between 800 and 1628 cm^{-1}, specific to cellulose. Generally, typical bands for pure cellulose at 1431, 1372, 1322, 1162, 1033, and 896 cm^{-1} appear in FT-IR spectra. Bands at 897 and 1165 cm^{-1} are designated C-O-C stretching at the β-(1-4) glycosidic linkage, the linkage characteristic of cellulose, while bands at 1337 cm^{-1} are designated C-

O-H bending at C_2 or C_3 and the band at 1431 cm^{-1} is assigned to C-O-H in-plane bending at C_6. This band occurs when the environment at C_6 is changed.

A SEM micrograph of the bleached bagasse fiber is shown in Fig. 2. The micrograph suggests that hemicelluloses, lignin, and pectin were partially removed. It is clear from the micrograph that the treatment improved fiber separation.

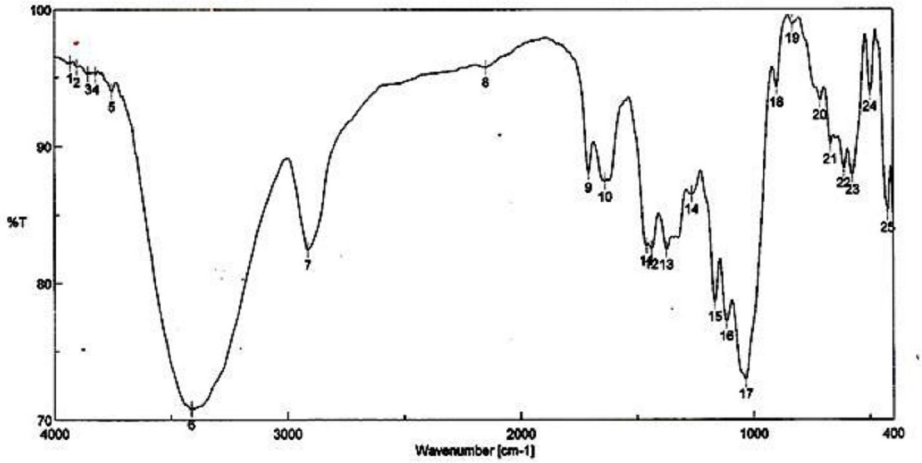

Fig. 1. FT-IR spectrum of bleached bagasse pulp

Fig. 2. SEM micrograph of bleached bagasse pulp

Preparation of Cellulose Acetate

Cellulose acetate is widely used in the medical and food production fields. Here, CA of degree of substitution (DS) 2 was prepared from bleached bagasse pulp. Using a method described by Schaller and Heinze (2005), IR spectroscopy was used to determine the functional groups and molecular structure of the macromolecules. The IR spectrum, shown in Fig. 3, indicates some characteristic functional groups. The band at 1753 cm^{-1} was assigned to the C=O functional group of cellulose acetate and the peak at 1428 cm^{-1} was attributed to CH_2 vibration. In addition, the sharp absorption peak at 1041 cm^{-1} was assigned to C-O stretching and the peak for C=C was at 1631 cm^{-1}. Moreover, the peak at 3477 cm^{-1}, related to O-H stretching, appears much smaller compared to the same peak in the spectrum for pure cellulose (see Fig. 1). This is attributed to the formation of cellulose acetate. On the other hand, the SEM micrograph of the resulting CA, as shown in Fig. 4, illustrates different a

morphological structure than that of cellulose (Fig. 2). It is clear from Fig. 4 that the resulting CA had a spongy structure, potentially important for its application.

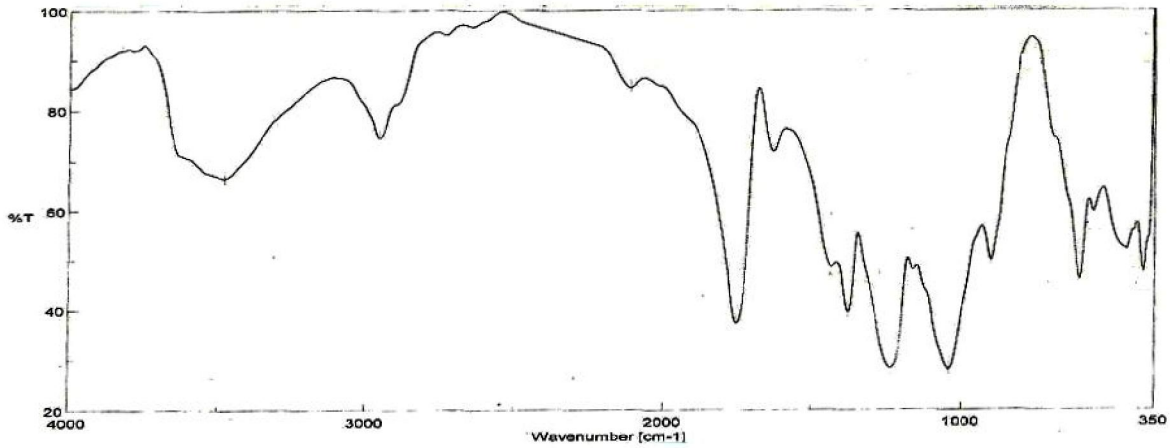

Fig. 3. FT-IR spectrum of cellulose acetate

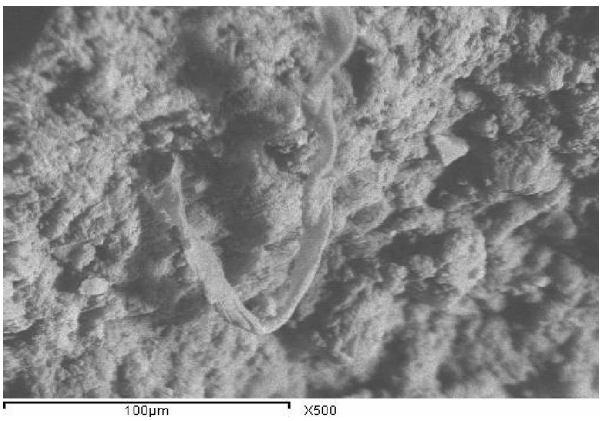

Fig. 4. SEM micrograph of cellulose acetate

Tosyl Cellulose Acetate Preparation

The prepared tosyl cellulose acetate was analyzed using FT-IR and SEM. The IR spectra for both tosyl cellulose acetate, as shown in Fig. 5, and CA, as shown in Fig. 4, were similar, except for bands at 1118 (SO_2), 1364 (S-O), 2973 (C-H aromatic), 815 (S-O-C), and 1616 cm^{-1} (C=C aromatic). These bands are bands for the tosyl group. The similarity of the two IR bands is because the DS of the starting CA was 2, meaning that tosyl groups were introduced to C_3 or may have bonded to the acetate group. The SEM micrograph of tosyl cellulose acetate, as shown in Fig. 6, is significantly different from that of cellulose acetate; tosyl cellulose acetate had much greater porosity.

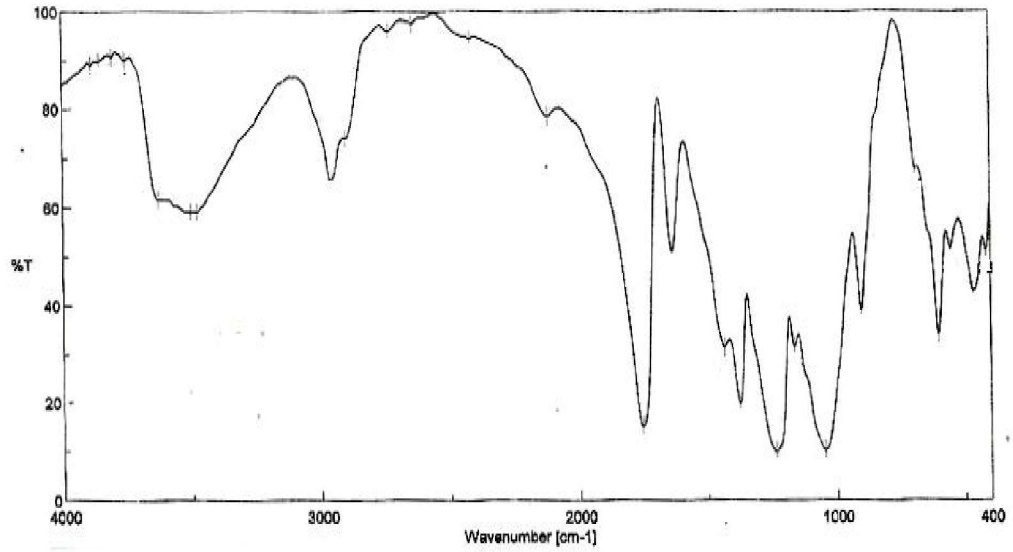

Fig. 5. FT-IR spectrum of tosyl cellulose acetate

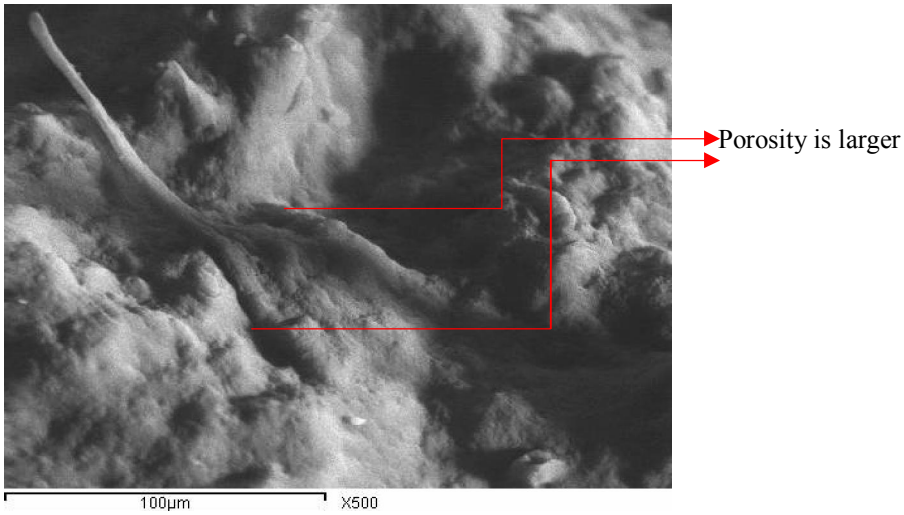

Fig. 6. SEM micrograph of tosyl cellulose acetate

Matrix Loading

Currently, controlled drug release techniques have attracted much attention due to their advantages over conventional dosing methods. Controlled drug release prolongs the release time and decreases the poisoning effect resulting from rapid drug release rate (Rosenau *et al*., 2009; Peng *et al*., 2010). Cellulose and most of its derivatives are safe, non-toxic, hydrophilic, and renewable, so they offer some economic advantages over synthetic polymers. They also have biocompatible and biodegradable properties and have been investigated extensively for applications in the pharmaceutical industry (Ohya *et al*., 1991; Li *et al*., 2000; Carlmark and Molmstron 2003; Gupto and Khandekar 2003; Sturcova *et al*., 2004; Metroglu *et al.* 2005; Bontempo *et al*. 2006; Tong *et al*. 2007; Meng *et al*. 2009; Ibrahim *et al*. 2014; 2015).

In the current work, tosyl cellulose acetate was used as a carrier for the active ingredient of the anti-acidic drug. Solutions with pH 2.0, 3.5, and 5.0, were prepared and the drug that was carried on the tosyl cellulose acetate was added to the solutions. As shown in Table 1, the pH of the three drug-loaded solutions rose to 7.0 over time.

Moreover, after 4 h from the elapsed time, another patch of the acidic solution with pH 2.0 was added and we found that the pH of the solution mixture was hold on 6.0, even after 6 h from the elapsed time, indicating that the drug that was carried on tosyl cellulose acetate is still active. This means that the rate of the drug release is still active holding the pH of the solution at 6.0. This observation is remarkable and can give an indication of using tosyl cellulose acetate as drug loading. On the other hand, the SEM, Fig. 7, illustrates that the particles of drugs are stocked on the surface of the film of the tosyl cellulose acetate, where it is adsorbed on the surface of the tosyl cellulose acetate. Due to that, the tosyl cellulose acetate can be considered as an effective carrier matrix for drugs as controlled release.

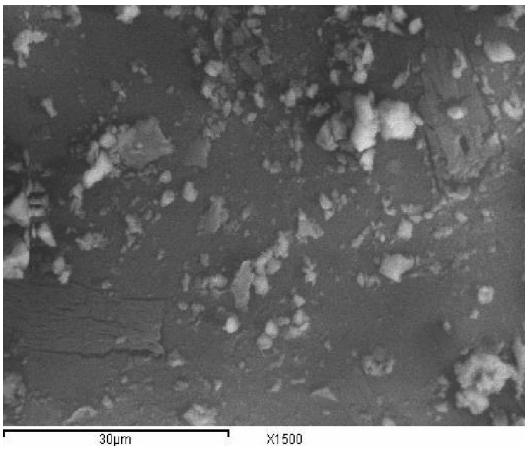

Fig. 7. SEM micrograph of tosyl cellulose acetate loaded with the anti-acid drug

Table 1. pH Variation of Tosyl Cellulose Acetate Loaded with Drug

Weight of drug (g)	Time Elapsed (h)						Time Elapsed (h)				Time Elapsed (h)			
	0	2	3	4	5	6	0	2	3	4	0	2	3	4
	pH = 2.0						pH = 3.5				pH = 5.0			
0.013	4	7	7	7	6	6	4	7	7	7	6	7	7	7

Conclusions

1. Cellulose extracted from lignocellulosic agricultural residue was derivatized to cellulose acetate and then further derivatized with a tosyl group to tosylated cellulose acetate macromolecules.
2. When tosyl cellulose acetate used as a drug carrier, it exhibited anti-acidic release behavior with constant rate of release after 3 and 4 h, controlling the pH of the solution at 7.0.
3. Tosyl cellulose acetate also exhibited a strong, constant rate of release after 5 and 6 h, controlling the pH of the solution at 6.0.
4. The excellent behavior of tosyl cellulose acetate demonstrates the feasibility of using cellulose derivatives for drug loading and should be further investigated.

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