# Carboxymethyl and carbanilated cellulose modified with tosyl and trimethylsilyl groups: Preparation, characterization, and applications in controlled release of anti-acid drugs

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**Abstract:** To adjust the properties of the macromolecular structure of cellulose, chemical modification can take place to find different applications. In the current study, cellulose was extracted from bagasse, where it was derivatized to carboxymethyl cellulose, and carbanilated cellulose. These two cellulose derivatives were further chemically modified in homogenous system by tosyl and trimethylsilylation to synthesize cellulose macromolecular derivatives, namely tosylcellulose derivatives and trimethylsilylcellulose derivatives. The compositional microstructure of the synthesized cellulose derivatives was investigated by $^1$HNMR analysis, FT-IR and SEM. This study demonstrated that cellulose, cellulose derivatives and both tosyl and trimethylsilyl cellulose derivatives formed under homogeneous conditions can be evaluated as potential carriers for controlled release of anti-acid drugs. The release was investigated as a function of pH and time in various pH solutions, namely 2.0, 3.5 and 5.0. The results indicated that the release is controlled by the type of the modified cellulose and thus it was concluded that modification is important for the use in slow drug release.
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## 1. Introduction

Cellulose is a naturally occurring organic polymer which forms a major component of all woods, grasses, fibers, and seed hairs. Other sources of cellulose are found in the agricultural residues such as straws, sugar cane, banana plants and the cell wall of some algae and bacteria [1–3]. Bagasse is one of the agricultural harvesting residues abundantly available in Egypt, which results as a byproduct from the sugar manufacture. This Lignocellulosic biomass feedstock is a complex mixture of three structural biopolymers, i.e. lignin, cellulose and hemicelluloses, and minor non-structural components [4].

Cellulose is a promising biopolymer for the formation of many advanced materials for various applications due to the structural uniformaty being a β 1-4 linked polyglucan. Thus the conversion of the OH moieties like esterification including carbanilation, etherification, and nucleophilic displacement reaction [5-7] is of inceasing interest.

It is known that cellulose is insoluble in water and most common solvents [8]. The poor solubility is attributed primarily to the strong intramolecular and intermolecular hydrogen bonding between the individual chains [9]. In spite of its poor solubility characteristics, cellulose is used in a wide range of applications including composites, netting, upholstery, coatings, packing, paper, etc. Chemical modifications for the cellulose lead to a drastic change of its propertiesand it is performed to produce cellulose derivatives (cellulosics), which can be tailored for specific industrial applications [7], where cellulosics are in general reproducible, recyclable and biocompatible [10].

Cellulose is dissolved using non-derivatizing solvents in non-aqueous media, i.e. *N,N*-dimethylacetamide/lithium chloride (*N,N*-DMA/LiCl). This system is used in preparing a wide variety of derivatives where the dissolution succes without or at least with negligable degradation even in case of high molecular weight polysaccharides, e.g. cotton linter and bacterial cellulose. According to McCormick et al. [11], lithium ions are linked with a carbonyl group of *N,N*-dimethylacetamide tightly while the chloride ions remain unencumbered. Chloride ion acts as a necleophilic base plays a role in breaking of intra- and inter- hydrogen bonds of cellulose making the cellulose dissolve. Some researchers attribute to chlorine anion the ability to complex three OH groups of an hydroglucose unit by hydrogen bonding, while Li-*N,N*- dimethylacetamide macro cation is loosely bound [12]. Moreover, it was proposed that the cellulose takes part in lithium

catian coordination sphere as driving force of dissolution of cellulose [13].

Most of cellulose derivatives, such as carboxymethyl cellulose (CMC), are used succesfully in the pharmacetical application especially as a carrier for many drugs which releases in a certain measuring time to reach its beneft effect. The flexibility in polymer processing plays an important role in the development of controlled delivery devices for a range of applications related to drugs, food-related bioactive ingredients and genes. The release of bioactive agents from a delivery system may be caused by diffusion-controlled, i.e. diffusion of drug through a rate-controlling barrier/matrix, degradation-controlled, i.e. chemical or physical breakdown of the matrix leading to bioactive agent release, or via an environmental trigger, i.e. change in pH, ionic strength or pressure tailors the release of the bioactive agent. Release mechanisms can be chemical or physical in nature, but always involve some form of diffusion [14].

Our present study aims to synthesis and characterize CMC and carbanilated cellulose as well as their modifications by tosyl and trimethylsilyl groups. The study also reflects the use of these chemically modified cellulose derivatives as controlled release carriers for pH specific drug delivery, where they were used as carrier matrices for anti-acid as drug model.

## 2. Experimental

### 2.1. Materials

A bagasse, which was provided kindly by Quena for Pulp and Paper Industrial Company, Quena, Egypt, was used in this study as the lignocelluloic raw material. Characterizations for the raw materials, i.e. moisture content, ash, lignin, holocellulose, alpha cellulose and extracted hemicellulose were carried out before and after pulping and bleaching.

### 2.2. Treatment of Raw Material

Cellulose was isolated from bagasse raw material by delignification and bleaching. Delignification of the bagasse was carried out with 10.0% (wt/wt) sodium hydroxide (NaOH) at 170 °C for 2 hours with liquor ratio of 1:10 (raw material:water). After the desired time, the fibers were washed till neutrality then another treatment with 5.0% sulfuric acid ($H_2SO_4$) at 160 °C for 2 hour with liquor ratio of 1:10 was carried out. At the end, the unbleached bagasse fibers were air dried and stored for further analysis and use.

Bleaching was carried out for the unbleached bagasse fibers in one stage, where the unbleached bagasse pulp was subjected to sodium hypochlorite solution equivalent to 60% of the chlorine requirement 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 process. At the end, the bleached bagasse pulp was thoroughly washed with water till neutrality and then left to dry in air and stored for further use.

### 2.3. Synthesis of Cellulose Derivatives

The produced cellulose was first solubilized according to the method described by Rahn et al. [15]. Briefly, in our work, 1.0 g of bleached bagasse fiber, as the cellulose material, was transferred into 20 ml of 18% NaOH (wt/v) solution and stirred at room temperature for 1 h. The slurry was then filtered and thoroughly washed with distilled water until the wash water was neutral. The resulting cellulosic fibers were then suspended in *N,N'*-dimethylacetamide (DMAc), filtered and washed twice with DMAc. After that, 36 ml of DMAc was added to the bleached bagasse fibers and were kept at 120 °C for 2 h under stirring. After that, the slurry was allowed to cool to 50 °C then 3.5 g of anhydrous lithium chloride (LiCl) were added. The cellulose was completely dissolved by cooling down to room temperature under stirring.

Carboxymethylation and carbanilation were applied for the synthesis of both CMC and carbanilated cellulose, in which CMC was synthesized according to a method described by Heinze et al. [16], where 2.5 g of air-dried cellulose (from bleached bagasse pulp) in 75 ml isopropanol was stirred vigorously, while 6.7 ml of 15% (w/v) aqueous NaOH was added drop wise during 10 min at room temperature. Stirring was continued for 1 h and 3 g of sodium monochloroacetate was then added. The mixture was placed on a water bath at 55 °C for 5 h with stirring. The mixture was filtrated, suspended in 300 ml of aqueous methanol and neutralized with acetic acid. The product was washed three times with 300 ml of 80% (v/v) aqueous ethanol and dried in vacuum oven at 45 °C.

On the other hand, carbanillation of cellulose was synthesized according to Barthel et al. [17], where the cellulose was converted with phenyl isocyanate, 7 ml, for 5 h at 70 °C in dimethylacetamide/lithium chloride (DMAc/LiCl) applying pyridine, 3 ml, as co-solvent. The reaction mixture was poured drop wise into 300 ml of aqueous mixture of methanol/water (8:1) under stirring. The mixture was filtered and the product was washed with 100 ml of methanol then left in another methanol solution for 3 to 4 min and filtered. This method was repeated for three times and at the end the product was dried in vacuum oven at 45 °C.

### 2.4. Synthesis of Macromolecular Tosylcellulose Derivatives

The synthesized cellulose derivatives, namely CMC and carbanilated cellulose, were then converted to tosylcellulose derivatives, where 20 g of the cellulosic material was first stirred in 18% aqueous NaOH (300 mL) at room temperature for 5 h and the solution was the filtered in G3 sintered glass and washed with distilled water for 6 times followed finally with DMAc.

The resulting cellulosic material was transferred with DMAc solution (800 mL) in a 3 nicked flask and stirred for 2 h at 120 °C under reflux. At the end of the time, the temperature was down to 100 °C then 60 g of dried LiCl was added and stirring was continued for 24 h at room temperature till complete dissolution.

The solution was then cooled to 8 °C and a mixture of 25 mL triethylamine and 25 mL DMAc was added drop wise with stirring followed by the addition of a solution of 17.5 g tosylchloride in DMAc and stirring was continued for 24 h.

At the end of the reaction time, precipitation was carried out in ice water with vigorously stirring. The precipitate was filtered in G3 funnel crucible, washed for 6 times with distilled water then with ethanol for further 6 times. Finally, the excess ethanol was removed by distillation and the precipitated was dried in a vacuum oven at 40 °C.

**2.5. Synthesis of Macromolecular Trimethylsilyl cellulose Derivatives**

Conversion of hydroxy to trimethylsiloxy groups is extensively used in organic and in particular in carbohydrate chemistry to improve volatility and solubility in non-polar solvents. In the present work, the CMC and carbanilated cellulose were activated firstly as mentioned in the preparation of tosyl cellulose. After dissolution of the activated cellulose derivatives in DMAc/LiCl, 100 mL of hexamethyldizalane (HMDS) was added drop by drop in about 20 to 30 min to the homogenous cellulosic solution with 0.5 mL of chlorotrimethylsilane, as catalyst, with continuous stirring and the temperature was raised to 100 °C and left overnight. The solution was cooled down to 8 °C and filtered in G3 sintered glass. The product was washed with ethanol twice then with distilled water for 5 times. Finally, the product was removed and dried in vacuum oven at 50 °C.

**2.6. Loading and Releasing of Drug on Macromolecular Derivatives**

An Anti-acidic drug was selected for measuring the effect of the prepared cellulose derivatives on the drug release by testing the pH change in different pH solutions at different time interval. Different pH solutions, namely 2.0, 3.5 and 5.0, respectively, were prepared for the test. 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 from the cellulosic derivatives. The pH of each solution was measured at time zero then reported after 2 h.

After the first 2 hours, another 10 mL of pH solutions, namely 2.0, 3.5 and 5.0, respectively, were added to the tested solutions and the pH of each solutions were reported after 1 h. This method was repeated once again and the pHs of the different solutions were reported.

**2.7. FT-IR analysis (FT-IR)**

FT-IR spectroscopy was used to confirm fiber results from bagasse, cellulose derivatives and modified cellulose derivatives. The IR spectra were performed using JASCO FT/IR 6100 Instrument. Samples (~ 2 mg) were mixed and thoroughly ground with ~ 200 mg KBr to reduce particle size and to obtain uniform dispersion of the sample in the disks. All the spectra were recorded in the absorbance mode from 4000 to 400 $cm^{-1}$ at room temperature.

**2.8. Scanning Electron Microscope (SEM)**

SEM characterization of bagasse, cellulosic derivatives and modified cellulosic derivatives as well as drug loaded compounds was performed using a JEOL JXA-840A electron microprobe analyzer (JOEL USA Inc, Peabody, MA).

**3. Results and Discussions**

Being interested in modifying cellulose derivatives into macrostructure molecules, we studied in this work the modification of carboxymethyl and carbanilated cellulose with tosyl and trimethylsylil groups toward the direct formation of tosylation and trimethylsilylation-cellulose derivatives in DMAc/LiCl media.

**3.1. Characterization of Lignocellulosic Biomass Raw Material**

Before converting of lignocellulosic biomass to cellulosic products it is necessary to release of the cellulose portion from the tightly woven lignocellulosic structure. For this, the biomass needs to be treated to make it more amenable to subsequent cellulose production [18]. From Table 1 (A), one can notice that the holocellulose for the bagasse raw material can reached up to ~ 86% with higher lignin content of 21.13%. Thus, the most important features of an effective treatment strategy include breaking off the lignocellulosic complex.

The alkaline pulping was selected as a chemical pulping method for breaking down the ligocellulosic structure. The resulting pulp had brown color, where the color changes during the pulping and could have resulted from the degradation of the cell wall components and extractives as well as incomplete lignin removal [19].

The chemical characterization revealed the proportion of each component of the fibers from

agricultural residues. As seen in Table 1 (A) and (B), the main effect of the treatment on the composition of the biomass is the decrease in both the lignin and ash contents. The content of the Klason lignin after pulping and bleaching is less than that for the raw material, i.e. ~ 0.1% compared to 21.13% for the raw material, Table 1 (A) and (B). This can be due to the fact that alkaline treatment is basically a delignification process, in which a significant amount of the lignin is dissolved and separated in the resulting black liquor [18]. Consequently, after delignification and bleaching of the treated material, an increase in the α-cellulose can noticed and it reached ~ 81%. This can give indication of the suitability of the treated bagasse to be used as a source for cellulose for further application.

**3.2. Characterization of the Prepared Cellulose**

Figure 1 (A) showed the infrared spectrum of bleached bagasse pulp. It can be seen that the peak at 1735 $cm^{-1}$, which is assigned mainly to C=O stretching vibration of the carbonyl and acetyl groups in the xylan component of hemicellulose and also typical for structural features of lignin [19], disappeared after bleaching. Further absorption bands of lignin at approximately 1595 $cm^{-1}$ and, in particular, 1510 $cm^{-1}$ (aromatic ring stretch) disappeared in the bleached fibers as well [20], Fig. 1 (A). Moreover, bands at 3300-3413 $cm^{-1}$, related to O-H groups, and at 2912 $cm^{-1}$, related to C-H band, can be seen beside bands between 800 $cm^{-1}$ and 1628 $cm^{-1}$ where they are specific for cellulose.

Generally, typical bands for pure cellulose at 1431, 1372, 1322, 1162, 1033, 896 $cm^{-1}$ can be seen in the FT-IR, where bands at 897 $cm^{-1}$ and 1165 $cm^{-1}$ are assigned as C-O-C starching at the β-(1-4) glucosidic linkage, the linkage which is characteristic for the cellulose, while bands at 1337 $cm^{-1}$ is assigned as the C-O-H bending at C2 or C3 and band at 1431 $cm^{-1}$ is assigned to the absorbance of C-O-H bending in plane at C6 which arise by changing the environment at C6.

In order to further investigate the structural changes in the fibers, SEM of the bleached bagasse fiber was studied and is shown in Fig. 1 (B). This picture visually suggests the partial removal of hemicelluloses, lignin and pectin, which are the cementing materials around the fiber bundles, after high pressure chemical treatment. Fig. 1 (B) shows also the structure and appearance of bagasse fibers in micro-scale. It is clear from the SEM micrograph that the high pressure chemical treatment helps in fiber separation.

**3.3. Synthesis of Carboxymethylcellulose (CMC)**

In the present work, CMC, structure 1, was prepared starting with the dissolution of the prepared cellulosic material, i.e. bleached bagasse pulp, with *N,N*-DMA/LiCl, as mentioned in the experimental part. Activation step was subjected first for its important before dissolution to open the polymer chain of cellulose into relaxed conformation which enhances solvent solution kinetics to the crystalline regions that are parked tightly. The activation step was performed with NaOH (18% w/v) for 1 hour with stirring at room temperature then washed with water and followed by DMAc, where this step causes swelling and the celluolse structre is opened in which the intra- and inter-hydrogen bonds are replaced by hydrogen links with water and DMAc. Solvent system of DMAc/LiCl is very hygroscopic, and water is excluded from this solvent system [21], where the presence of water accelarates the formation of aggregates of polymers and prevents complexation of solvent with cellulose.

The prepared CMC was analyzed using FT-IR and SEM and were illustrated in Fig. 2 (A) and (B). The FT-IR, Fig. 2 (A), shows the typical absorption of cellulose backbone as well as peaks at about 1632 $cm^{-1}$ and 1429 $cm^{-1}$ indicate the presence of CMC ether group. The peak of OH group is clear at the absorption band of 3423 $cm^{-1}$, while the peak at 2908 $cm^{-1}$ is for the C-H stretching and the peak of 1040 $cm^{-1}$ is special for the C-O stretching from the asymmetric oxygen bridge.

SEM, Fig. 2 (B), shows that the image of the cellulose derivative fibers was greatly different, which transferred to a tube like that gave the CMC absorbing property to absorb water or any solvent and changes to very viscous part that enables it to be as thickener for a great variety of products.

**3.4. Synthesis of Carbanilated Cellulose**

Another aim of the present work was the preparation of carbanilated cellulose, Scheme 1, which was prepared as mentioned in the experimental part and characterized using FT-IR, elemental analysis, $^1H$ NMR and SEM.

The nitrogen content, results from the elemental analysis, was used for calculating the DS of the prepared carbanilated cellulose which gives a DS of 2.7. On the other hand, the FT-IR, Fig. 3 (A), shows very weak peak at 3391 $cm^{-1}$ which indicates that OH groups where replaced by phenyl-isocyanate groups, while the absorption band at 1723 $cm^{-1}$ were characterized for the cellulose carbanilate. It was noticed that the C-O peak is appeared at 1066 $cm^{-1}$, while the C=C peak appeared at 1602 $cm^{-1}$ and the characteristic peak for C-N was clear at the absorption peak of 1222 $cm^{-1}$. Moreover, the introduction of the carbanilated group was confirmed from the phenyl ring signal at δ = 6.0–8.0 ppm in addition to the cellulose functional groups in the $^1H$ NMR spectra in DMSO, Fig. 3 (B).

The SEM shows great difference between cellulose, Fig. 1 (B), and carbanilated cellulose, Fig. 3 (C), which appears like net with huge porous that gives great promising for more absorbing of water or solvent.

**3.5. Synthesis of Tosylcellouse Derivatives**

The *p*-toluenesulfonyl (tosyl) group is commonly used as a leaving group in nucleophilic substitution ($S_N$) reactions making it a practical intermediate for subsequent cellulose modification reactions. In this work, the prepared cellulose derivatives, namely CMC and carbanilated cellulose were further modified for the preparation of tosylcellulosed derivatives. Homogeneous reaction yielding tosylated cellulose derivatives was carried out by allowing CMC and carbanilated cellulose to react with tosyl chloride in DMAc/LiCl in the presence of trimethylamine as a base. For the carbanilated cellulose with DS of 2.7, the tosyl group can enter either in C3 or bounded with the N atom of the carbanilated cellulose. Moreover, Scheme 2 shows the preparation of tosylcarboxymethyl cellulose and tosylcarbanilated cellulose.

The FT-IR was used to study the function groups of the resulted product, where FT-IR spectroscopy is of importance for studying molecular structures and the conformations of macromolecules. The FT-IR spectrum of tosyl cellulose exhibits some characteristic functional groups. Beside the peaks for the OH group at 3404 $cm^{-1}$, the C-H stretch at 2897 $cm^{-1}$, the C=O at 1628 $cm^{-1}$ and the C-O at 1038 $cm^{-1}$ and weak peaks at 858 $cm^{-1}$, 807 $cm^{-1}$, 749 $cm^{-1}$, 696 $cm^{-1}$, we can detect an additional absorption peaks around 1370 and 1180 $cm^{-1}$ corresponding to $SO_2$ and a peak at 2139 $cm^{-1}$ for C=S for the FT-IR spectra of the tosylcarboxemethy cellulose, Fig. 4 c.

For the FT-IR of the tosylcarbanilated cellulose, Fig. 4 e, we can detect a peak for the OH group at 3388 $cm^{-1}$, peak for the C-H stretch at 2956 $cm^{-1}$, peak for C=S at 2186 $cm^{-1}$, peak for C-N at 1224 $cm^{-1}$, peak for C=O at 1735$cm^{-1}$, peak for C=C at 1604 $cm^{-1}$, and a peak for the C-O at 1065 $cm^{-1}$.

On the other hand, the SEM of tosylcarboxymethyl cellulose and tosylcarbanilated cellulose show great cavity with tabulated shape of the fibers which make the product more absorbent, Fig. 5 a & b.

**3.6. Synthesis of Trimethylsilyl Cellulose Derivatives**

Silylation of cellulose represents an attractive route for the preparation of soluble derivatives of the biomacromolecule and hence broaden the spectrum of applications [22]. The trimethylsilyl (TMS) group is widely used in the protection of hydroxyl functional groups as it easily deprotected in mild conditions [23,24].

Silylation of carbanilated cellulose and CMC may be an effective way to develop new application, while retaining the reactivity of hydroxyl functionalities. The product is a novel type of derivative possibly characterized by some favorable properties. Such cellulose derivative containing the easily deprotected-TMS group is expected to be applied as a new cellulose derivative of a functional material.

On the other hand, the carbanilation of cellulose using DMAc/LiCl as solvent has a number of advantages like high reaction rate and good yield under relatively mild conditions. Also, the solubility in DMAc/LiCl system is preferred to adjust the DS to be below 2, where DS can be well controlled via the molar ratio of reagent to the anhydro-glucose unit (AGU) [22]. Moreover, carbanilated cellulose is used in drug and food and thus, the properties of carbanilated group, which introduced into the cellulose-backbone, is to fulfill of this backbone with the porous which increases the absorbance of the cellulose molecules and introducing trimethylsilyl (TMS) group to increase the solubility of the molecules that makes the molecule more available for carrying the drug inside those porous.

From the FT-IR spectrum, Fig. 6, one can notice an absorption band at 3394 $cm^{-1}$ for the N-H instead of the OH group for the cellulose material. Moreover, the small peak for C-OH bending in plane at C6 for the cellulose material that appears at 1437 $cm^{-1}$ became sharp and appears at 1445 $cm^{-1}$ in case of trimethylsilyl-carbanilated cellulose (TMS-carbanilated cellulose). Furthermore, the band for C-OH bending of C2 and C3 that appears at 1376 $cm^{-1}$ in case of carbanilated cellulose disappeared in case of TMS-carbanilated cellulose, while the band at 1224 $cm^{-1}$ for Si-C became very sharp, Fig. 6. From the functional group appears on the FT-IR, one can suggests that the trimethylsilyl group can exists either on the three available atoms of C2, C3 and C6 or on both C6 and C2 through a bond with the nitrogen atom of the carbanilation group as can be illustrated in structure 2.

On the other hand, a second set of trimethylsilyl cellulose derivative, namely trrimethylsilyl-carnboxymethyl cellulose (TMS-CMC) was prepared and characterized for its functional groups as well as its morphological structure. From the FT-IR spectrum of TMS-CMC, one can notice that the absorption bands are, in general, appears to be stronger and sharper compared to those of cellulose and CMC, Fig. 6, where the bands for OH group and C-O group appears stronger at 3425 and 1602 $cm^{-1}$, Fig. 6 e. A strong peak at 1421 $cm^{-1}$ was noticed which represents the C-H in plane for C6. An important peak at 1327 $cm^{-1}$ was noticed stronger in case of

TMS-CMC indicating the presence of CMC and TMS group. Moreover, the $CH_3$-Si-O absorption peak at 1060 $cm^{-1}$ was noticed for TMS-CMC. Furthermore, the introduction of TMS group was confirmed from the methyl proton signal at $\delta$ = 0.9 ppm in addition to the methyl proto signal of the carboxyl groups at $\delta$ = 1.2 ppm in the $^1H$ NMR spectra in DMSO (Fig. 7).

On the other hand, the SEM micrographs of the trimethylsilyl cellulose derivatives are shown in Figure 8 a & b. A porous structure can be observed in case of the trimethylsilylcarbanilated cellulose, Fig. 8 a, while a smooth surface can be observed in case of trimethylsilylcarboxymethyl cellulose, Fig. 8 b. The SEM indicated that the surface area depends on the cellulose derivative type. Therefore, the influence of the absorption will depend on the surface morphology of the prepared trimethylsilyl cellulose derivative.

**3.7. Anti-acid Drug Loading of Cellulose**

Cellulose derivatives, in general, are widely used in different pharmaceutical formulations primarily for its viscosity-increasing properties. CMC is always used as a tablet binder and disintegrates [25,26] and also to stabilize emulsions [27]. Currently, controlled drug release techniques have attracted much attention due to their advantages to the conventional forms of dosage, such as prolonging the release time, and decreasing the poisoning effect reducing the drug release rate [28,29].

Cellulose and its derivatives has the biocompatible and biodegradable properties and has been investigated extensively for the application in industry and pharmacy [30–39], also cellulose and its derivatives are safe, non-toxic, hydrophilic and come from renewable resources in nature so they have economic advantages over synthetic polymers.

In this work, cellulose and both its derivatives and modified derivatives; i.e. tosyl and trimethylsilyl cellulose derivatives, were used as carrier for the active ingredient of the anti-acidic drug, mainly magnesium carbonate ($MgCO_3$), in which 0.1 g of the tablet drug were loaded over 0.1 g of the cellulose and their macromolecular derivatives. The exactly weight of active ingredient of drug, which had been loaded on the cellulose and their functionally modified derivatives, was calculated from the loading percent of the active ingredients on each tablet, where the weighed of one tablet is 1.5 g and contains 15% (w/w) from the active ingredient material. Thus, the actually weight of active material of the drug used is equal to 0.225 g.

According to that, 0.1 g of the drug containing 0.015 g of the active ingredient material was loaded on 0.1 g of either cellulose or modified cellulose derivatives. The loaded cellulose and macromolecular cellulose derivatives drug were immersed in three different acidic solutions, namely solution with pH 2.0, solution with pH 3.5 and solution with pH 5.0, as mentioned in the experimental part. Anti-acid tablet, without any cellulose or cellulose derivatives, was immersed in each acidic solution to be used as control to show the comparison with the loaded ones. For the controlled tablet, the pH of each solution became neutral when the anti-acid tablets were immersed in the solutions and this does not maintain for more than an hour. Following up the time of release and measuring the pH at the different time release for the cellulose and modified cellulose derivatives drug loaded, Table 2, indicates that for pure cellulose, as a carrier for the drug, the pH for all the solutions raised between 2 to 3 grades during the first two hours, i.e. between 0-2 h, while after the first 2 h all the pHs reached neutrality, i.e. the pH for all the solutions become 7.0. The neutrality for the solutions remains for solutions of pH 3.5 and 5.0, while that for solution of pH 2.0 the solutions start to be acidic again after 3 h of release, where the pH decreased to 6.0 after 3 h and reached to 4.0 after 4 h. For solutions of pHs 3.5 and 5.0, it was noticed that using the cellulose as drug loading was very effective for releasing the drug and neutralizes the solution for long time, while in case of a pH solution of 2.0, which is the drastic conditions of the stomach, the cellulose was good drug loading till only the first 3 h.

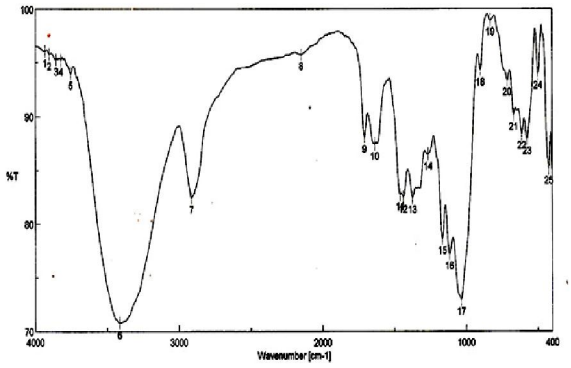
For using both tosylcarboxymethyl and tosylcarbanilated celluloses as drug loadings, Table 2, the results indicate that both modified cellulose derivatives were good drug loading and the pH of the three solutions reached neutrality after the first 2 hours. This means that, they both fast neutralize the solutions and the drug continues to release for longer time. Moreover, for the drastic acidic solution, i.e. solution with pH 2.0, we increased the time of the release to reach more than 4 h (results are not included in Table 2), i.e. till 6 h, and we found that after 5 hours the drug was still has an effect in neutralizing the solution and the pH was hold at pH 6.0, while it reached to pHs 4.0 and 5.5 after 6 h for tosylcarboxymethyl cellulose and tosylcarbanilated cellulose, respectively.

On the other hand, using both trimethylsilylcarboxy methyl and trimethylsilylcarbanilated cellulose showed the same effect as cellulose material, i.e. they showed good release for solutions of pHs 3.5 and 5.0. Furthermore, it was noticed that the release was in a good effective at solution of pH 2.0 for the first 3 hours, while the solution slightly starts to be acidic in case of trimethylsilylcarbanilated cellulose after 4 h release, i.e. the pH turned to 6.0, Table 2.

Generally, the above results were illustrated in Figures 9 (A) and (B), where a comparison between the cellulose and both tosyl and trimethylsilyl cellulose derivatives were made to indicate the suitability for the drug release.

On the other hand, SEM was used to study the morphological structure of the cellulose and its modification as drug loading. For both cellulose and trimethylsilylcarboxymethyl cellulose, Figs. 10 a & d, the drug appears as particles sticks on the surface of both cellulose and trimethylsilylcarboxemethyl cellulose confirming that the surface of both of them plays as a carrier of the drug particles, and this may give the reason why the release in the solution of pH 2.0 do not remain for longer time, thus acting as the anti-acid tablet without loading. In case of tosylcellulose derivatives, Figs. 10 b & c, and trimethylsilylcarbanilated cellulose, Fig. 10 e, the SEM illustrated that the drug particles do not only adsorbed on the surface but also penetrated inside the porous of the modified cellulose derivatives. This enables the drug to have slow release in the different acidic solutions and thus remain neutral for longer time.

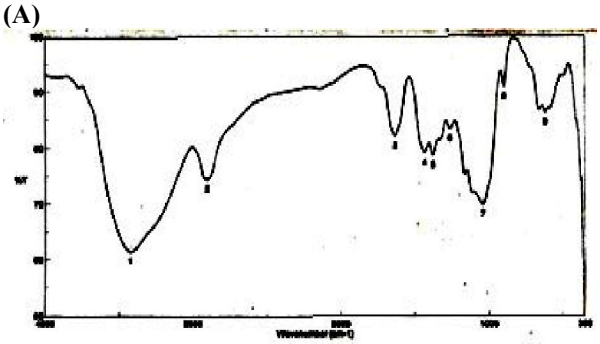
**(A)**




**(B)**


**Fig. 1. Characterization of bleached bagasse pulp (A) FT-IR spectra and (B) SEM.**

**(A)**



**(B)**

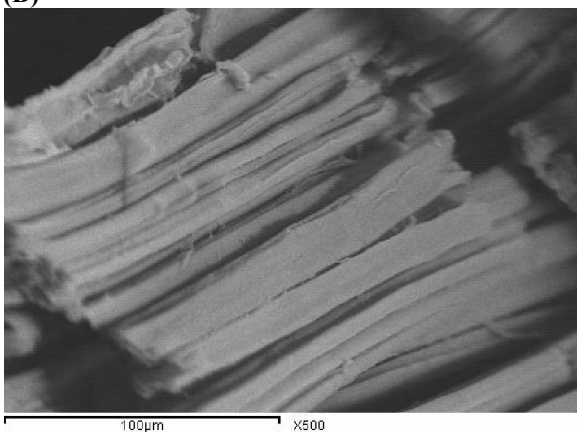



**Fig. 2. Characterization of CMC (A) FT-IR spectra and (B) SEM**

**Table 1:** Characterization for (A) bagasse and (B) bleached bagasse pulp

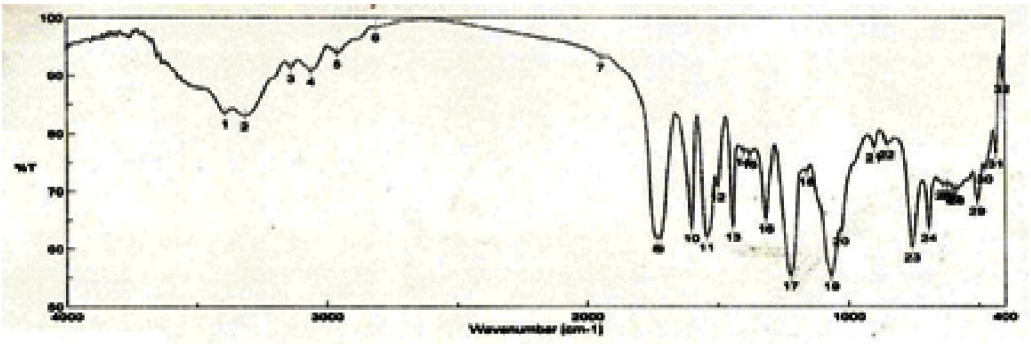
(A)

| Characterization | % |
|---|---|
| Moisture content | 8.59 |
| Ash | 2.73 |
| Lignin | 21.13 |
| Holocellulose | 85.95 |

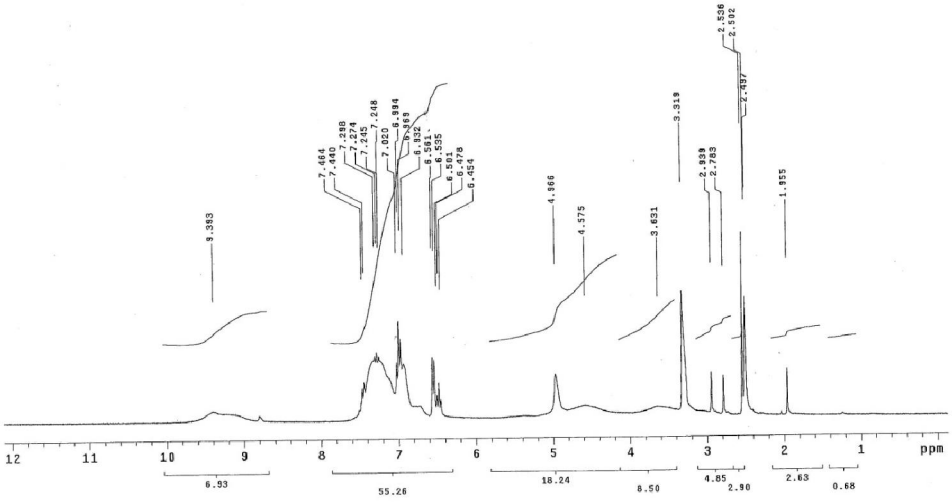
(B)

| Characterization | % |
|---|---|
| Moisture content | 5.3 |
| Ash | 3.7 |
| Lignin | 0.08 |
| α-cellulose | 80.9 |
| Extracted hemicelluloses | 15.1 |

**(A)**




(B)




(C)

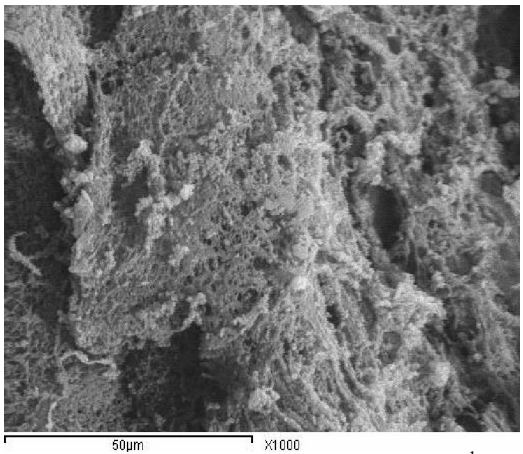



**Fig. 3.** Characterization of cabanilated cellulose (A) FT-IR spectra, (B) $^{1}$H NMR and (C) SEM (X 1000)

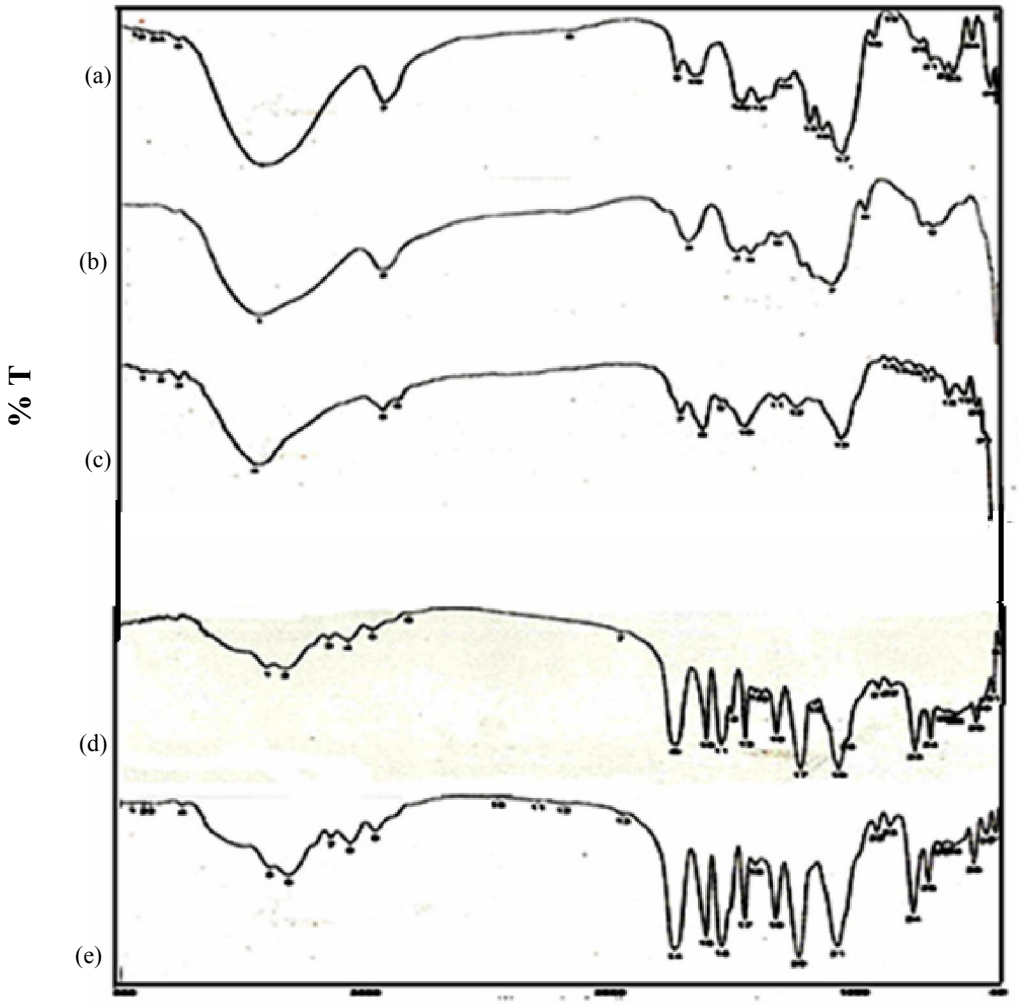



**Fig. 4. FT-IR spectrum for (a) baggase; (b) CMC, (c) tosylcarboxymethyl cellulose, (d) carbanilated cellulose and (e) tosylcarbanilated**

**Wavenumber $cm^{-1}$**

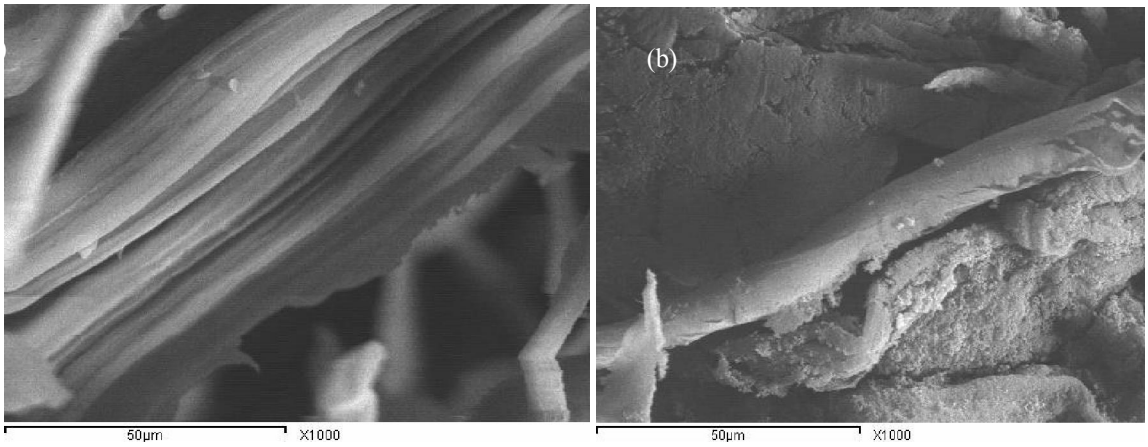



**Fig. 5. SEM for (a) tosylcarboxymethyl cellulose and (b) tosylcarbanilated cellulose**

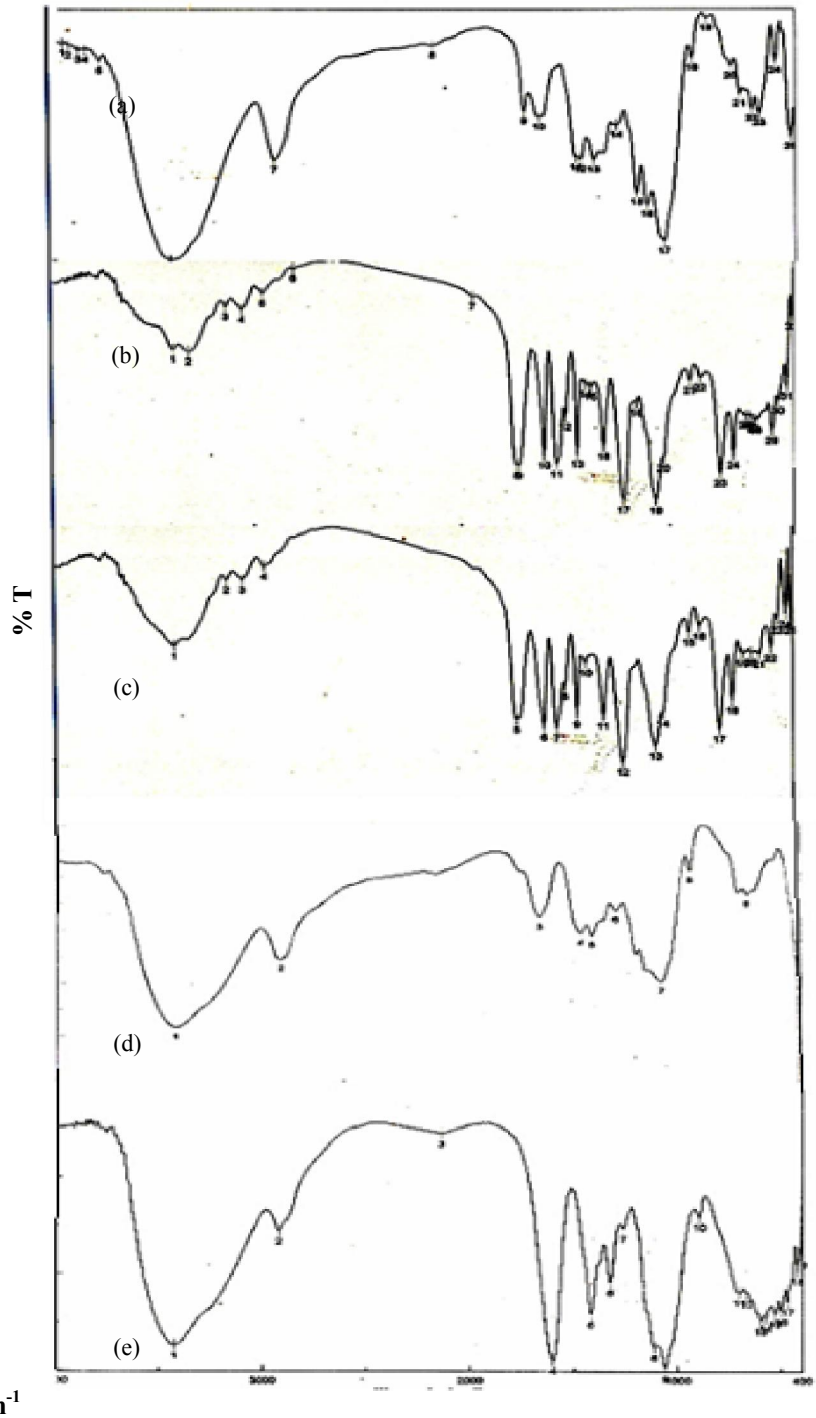



**Fig. 6. FT-IR spectrum for (a) cellulose, (b) carbanilated cellulose, (c) trimethylsilylcarbanilated cellulose, (d) CMC and (e) trimethylsilylcarboxymethyl cellulose (TMS-CMC)**

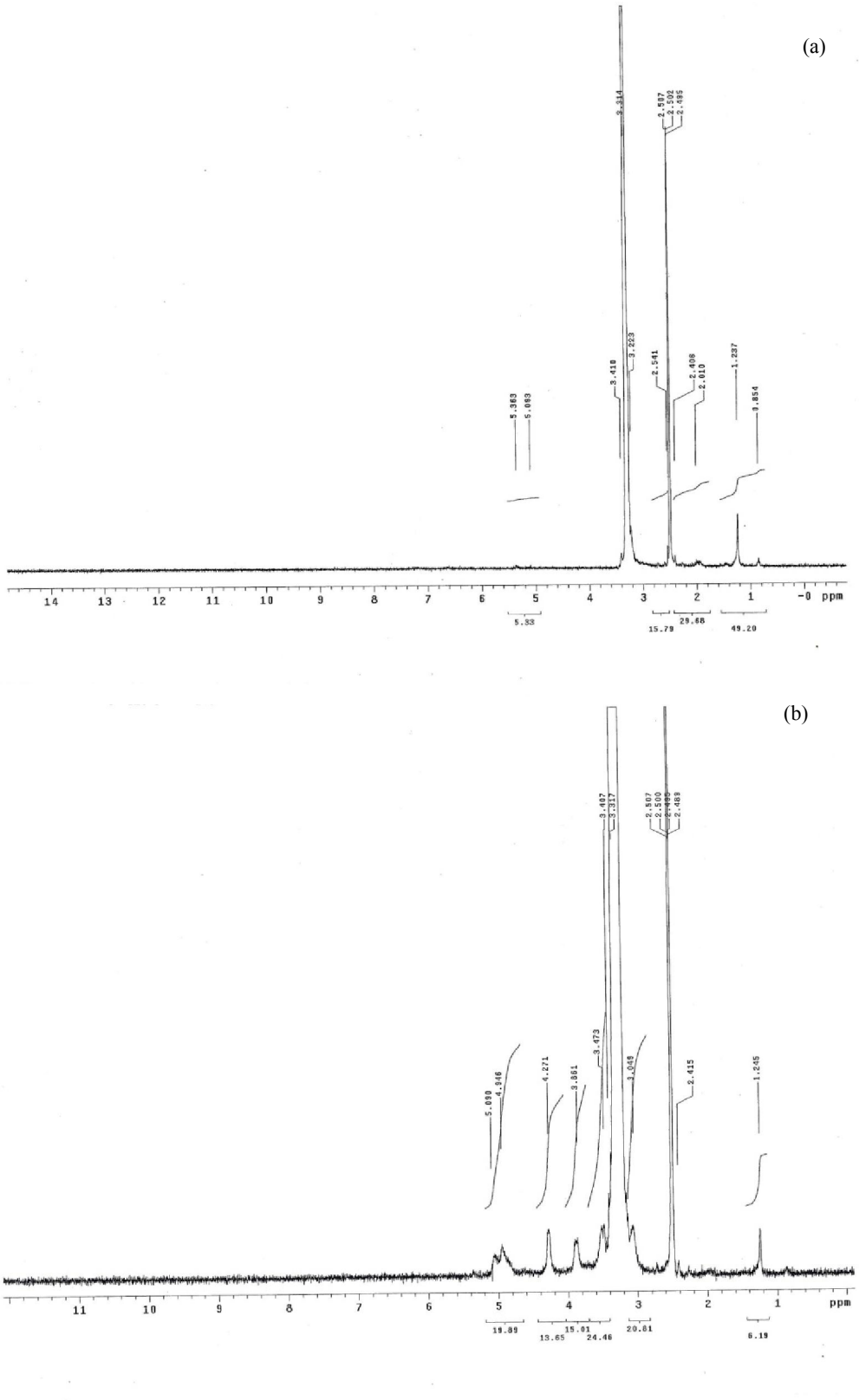



**Fig. 7. $^{1}$H NMR for (a) trimethylsilylcarboxymethyl cellulose and (b) carboxymethyl cellulose**

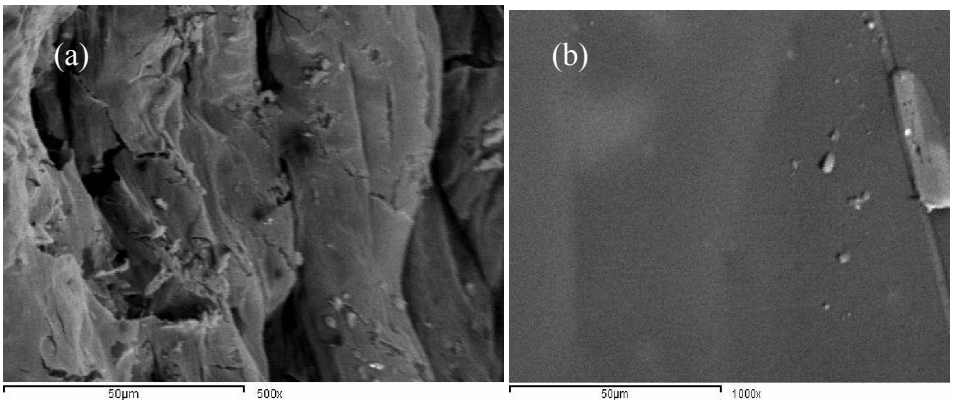
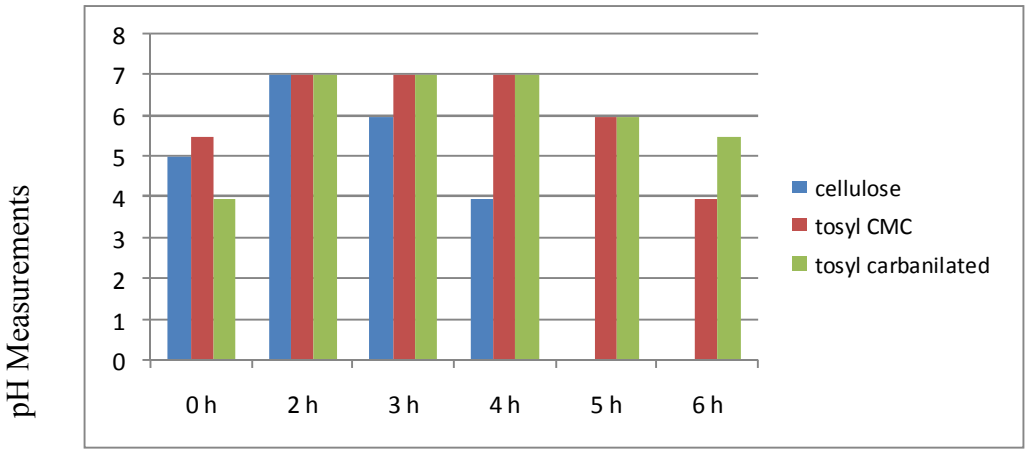


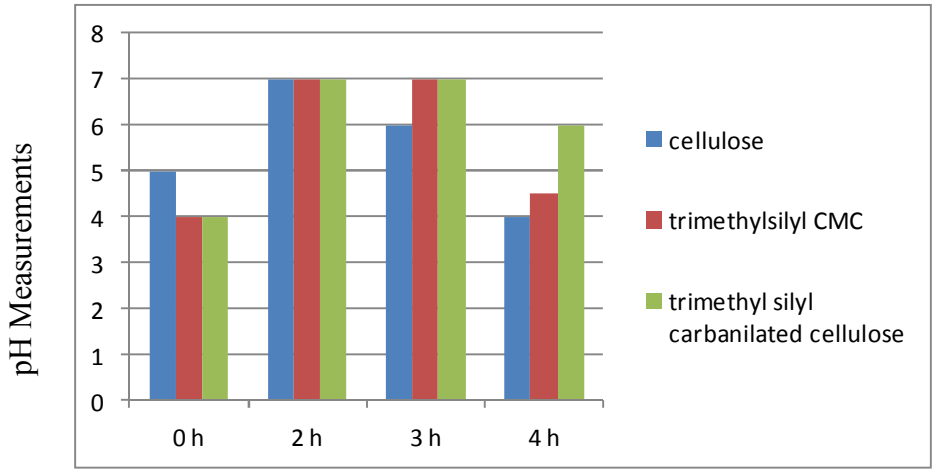

**Fig. 8. SEM of (a) trimethylsilylcarbanilated cellulose and (b) trimethylsilylcarboxymethyl cellulose**

(A)




Time of drug release, h

(B)




Time of drug release, h

**Fig. 9.** (A) Comparison between cellulose, tocylcarboxymethyl cellulose and tocylcarbanilated cellulose in solution of pH = 2.0 and (B) Comparison between cellulose, trimethylsilylcarboxymethyl cellulose and trimethylsilylcarbanilated cellulose in solution of pH = 2.0

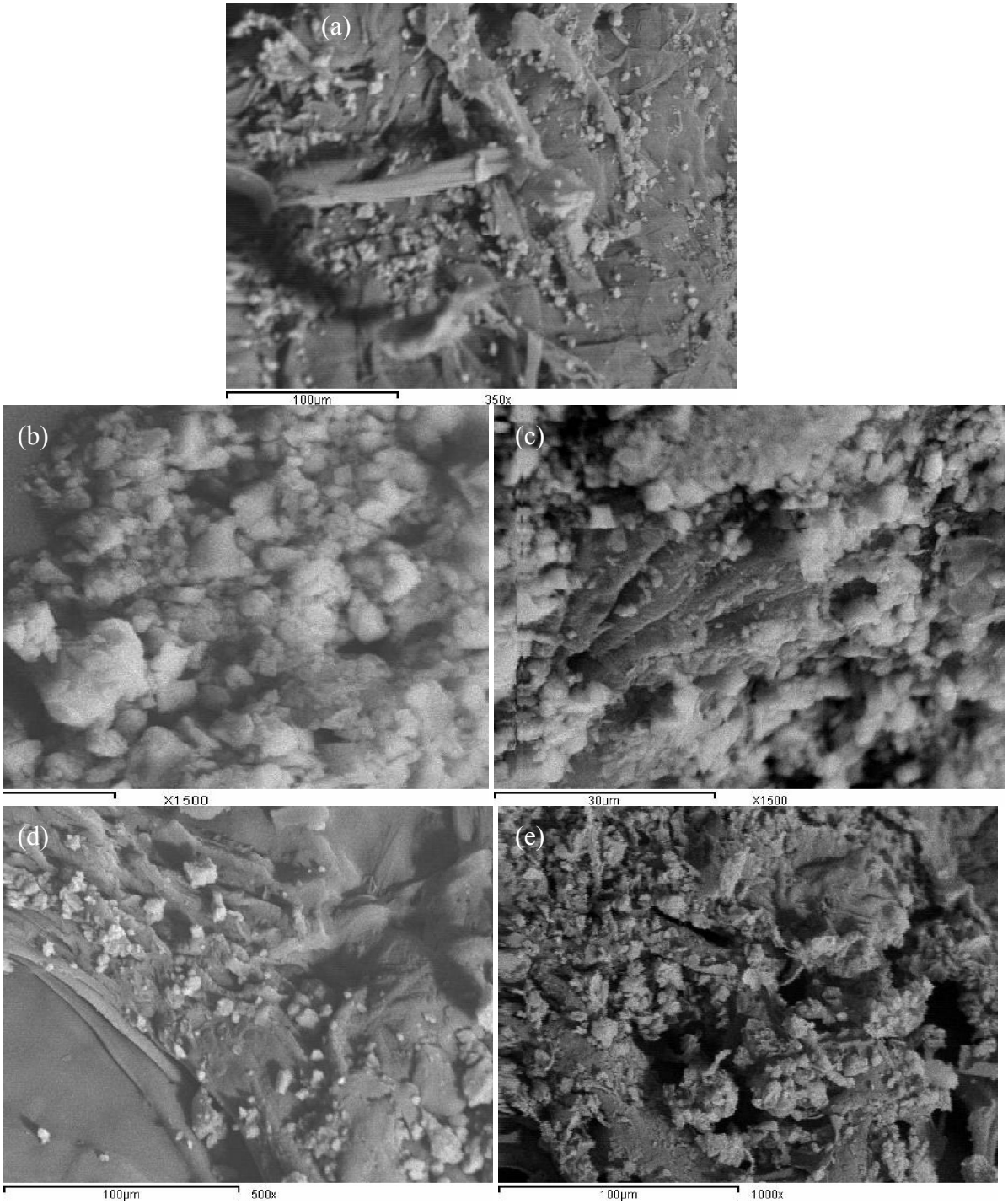
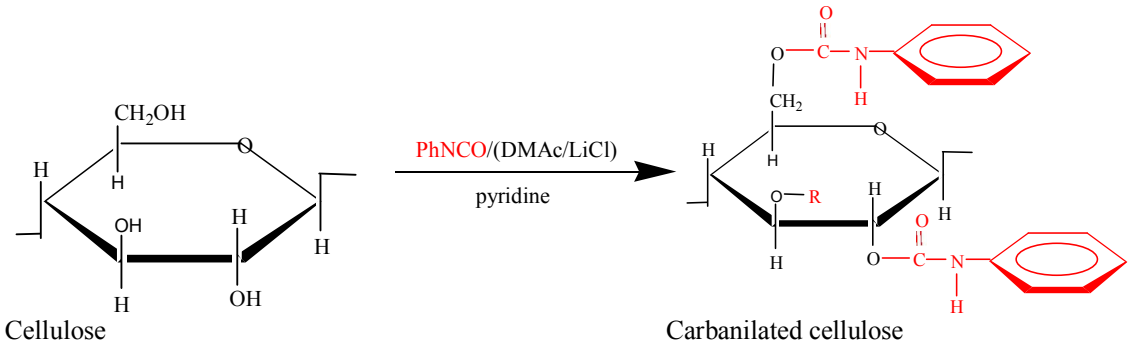
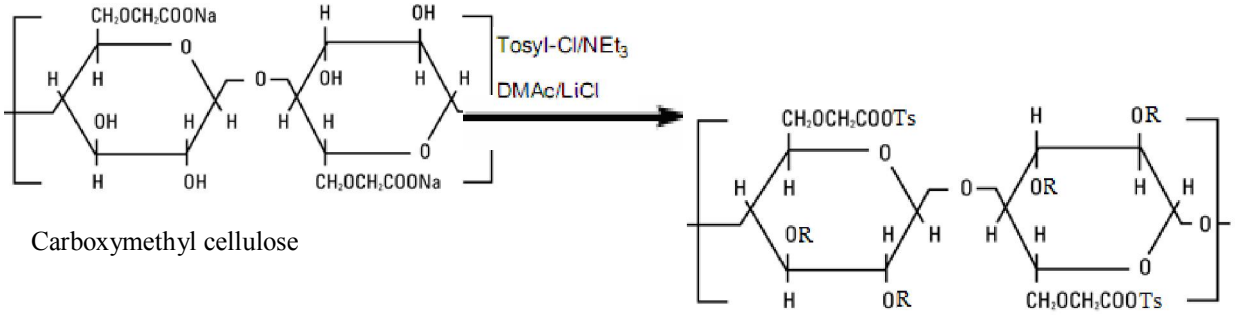



**Fig. 10.** SEM for the drug loading with (a) cellulose, (b) tosylcarboxymethyl cellulose, (c) tosylcarbanilated cellulose, (d) trimethylsilylcarboxylmethyl cellulose and (e) trimethylsilylcarbanilated cellulose



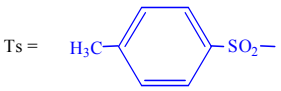

Cellulose Carbanilated cellulose

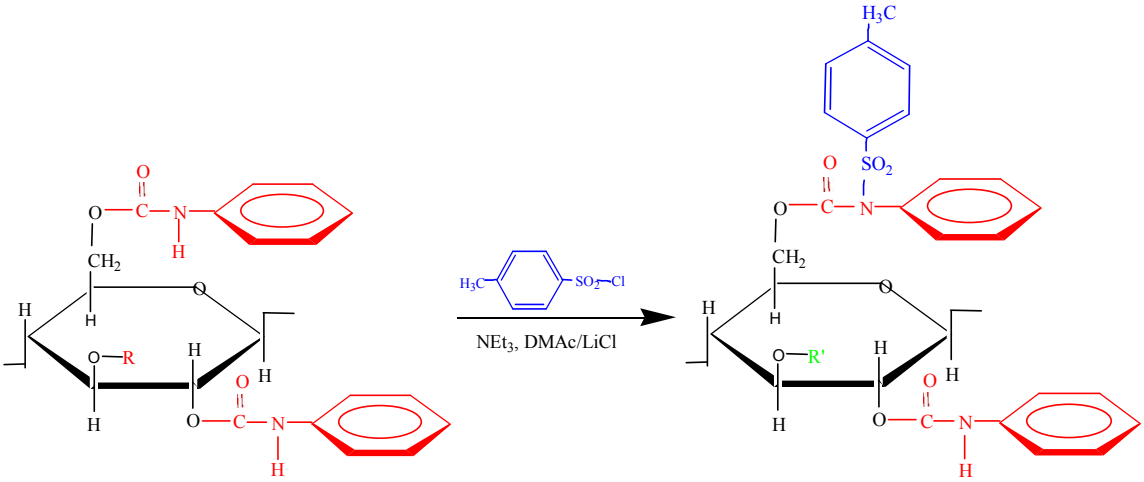
**Scheme 1.** Synthesis of carbanilated cellulose



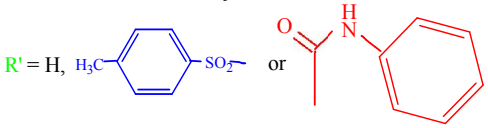

Carboxymethyl cellulose Tosylcarboxymethyl cellulose

**(a)**

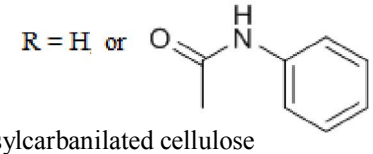



Carbanilated cellulose Tosylcarbanilated cellulose



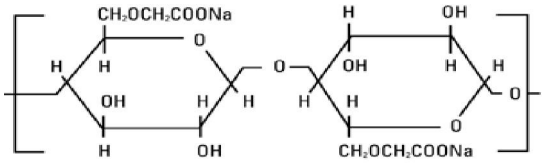

**(b)**



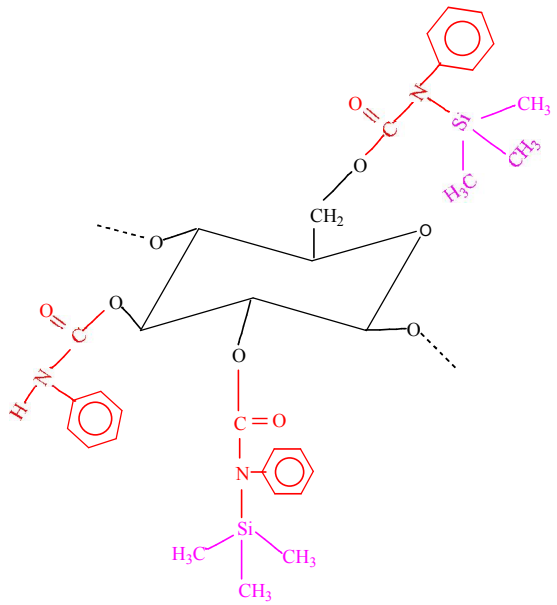

**Scheme 2.** Synthesis of (a) tosylcarboxymethyl cellulose and (b) tosylcarbanilated cellulose

**Table 2:** pH variations of cellulose and modified cellulose derivatives for drug release

| Weight of the anti-acid drug (g) | Cellulose-drug loading | Measurements | First Solution with pH = 2.0 | | | | Second Solution with pH = 3.5 | | | | Third Solution with pH = 5.0 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Time of release (h) | | | | Time of release (h) | | | | Time of release (h) | | | |
| | | | 0 | 2 | 3 | 4 | 0 | 2 | 3 | 4 | 0 | 2 | 3 | 4 |
| 0.014 | Cellulose | pH measurements | 5 | 7 | 6 | 4 | 6 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| 0.012 | Tosylcarboxymethyl cellulose | | 5.5 | 7 | 7 | 7 | 5 | 7 | 7 | 7 | 6 | 7 | 7 | 7 |
| 0.011 | Tosylcarbanilated cellulose | | 4 | 7 | 7 | 7 | 5 | 7 | 7 | 7 | 6 | 7 | 7 | 7 |
| 0.012 | Trimethylsilylcarboxymethyl cellulose | | 4 | 7 | 7 | 4.5 | 6 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| 0.012 | Trimethylsilylcarbanilated cellulose | | 4 | 7 | 7 | 6 | 4.5 | 7 | 7 | 7 | 6 | 7 | 7 | 7 |




**Structure 1.** CMC structure



**Structure 2.** Proposed structure of TMS-carbanilated cellulose

## 4. Conclusions

Carboxymethyl cellulose and carbanilated cellulose reacted with tosyl group forming tosylcellulose derivatives, as well as carbanilated cellulose reacted with trimethylsilyl group forming trimethylsilylcarbanilated cellulose showed controlled anti-acid release behaviour due to their morphological structures that contains porous structure that can absorb the drug inside to be released for long time. It has been observed also that both cellulose and trimethylsilylcarboxymethyl cellulose have an effect on drug release for a period of time. The different morphological structure implies the sustained release behaviour. Further, the release rate of anti-acid drug is faster in the different acidic solutions in absence of the cellulose or modified cellulose derivatives, which means the important for the cellulose and modified cellulose derivatives as drug loading and raises the possibility for further investigations in future.

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