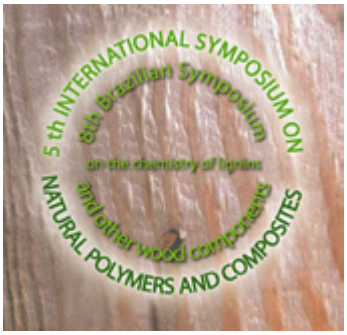

Production and Characterization of Cellulose Acetate Gels: Application in Drug Delivery Sistems

Vagner Roberto Botaro*, Priscila de Freitas Siqueira e Cláudio Gouvêa dos Santos

* Departamento de Química da UFOP – botaro@iceb.ufop.br
Universidade Federal de Ouro Preto - LAMP: Laboratório de Materiais Poliméricos
Campus – Morro do Cruzeiro – CEP 35400-000 – Ouro Preto - MG

Abstract: *Cellulose acetate chains with degree of substitution lower than 3 can be cross-linked to give the so-called cellulose acetate gel. In our studies, the modification of cellulose acetate was carried out in homogeneous medium employing tetrahydrofurane or acetone as solvents and two different dianhydrides, pyromellitic (PMDA) and benzophenone dicarboxylic (BTDA), as cross-linking agents. The products were characterized by FTIR and thermal analysis, in order to evaluate the success of gelation process. The observed affinity of the gel towards diclofenac sodium and the controlled release obtained in this work open new perspectives for its use as support for drug delivery systems.*

Keywords: *cellulose acetate, drug delivery, gel, cross-linking*

Introduction

Most reports about modification of lignocellulosics are mainly based on chemical modifications such as specific reactions on hydroxyl groups of cellulose [1]. Cellulose acetate is a polymer of great industrial importance, with applications in photographic, film and filters industries[3]. The cellulose acetate chains with degree of substitution lower than 3 can be crosslinked to give the so-called gel of cellulose acetate. These linkings cause an intensification of certain properties of cellulose acetate such as an increase of its rigidity. These gels present important properties as specific degrees of swelling in different solvents and applications as supports in chromatographic processes of size exclusion and drug release systems [4]. The gelation has been equally used in a great variety of cellulosic materials, such as cotton, rayon, cellophane, paper and pulps of different vegetal sources [5]. The use of the gelation process of unmodified cellulose in a homogeneous medium demands its solubilization in very specific and non-conventional solvents. In our studies, the modification of cellulose acetate was easily accomplished in homogeneous organic media using tetrahydrofurane or acetone, and the reactivity of two different dianhydrides, PMDA and BTDA, were investigated. Figure 1 shows a sketch of the partial structures expected to be formed after the modification reactions.

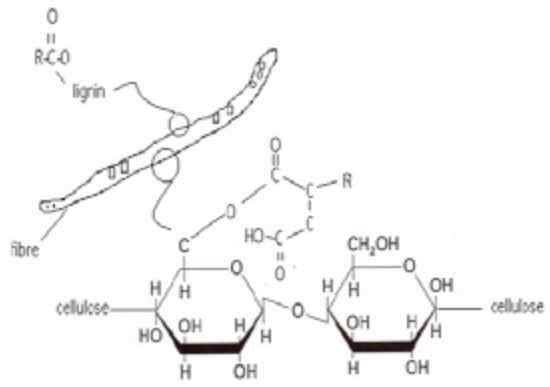

Figure 1: Partial structures expected to be obtained by the reactions between cellulose and dianhydrides.

Experimental

Gel preparation: Cellulose acetate used in this work presents a degree of substitution equal to 2,3 and was kindly donated by QUIMPETROL Company Ltd. Typical modification reactions were carried out under homogeneous conditions employing 0.500 g of cellulose acetate in 25 mL of acetone. After complete dissolution, BTDA or PMDA were added at equimolar amounts in relation to the available free number of hydroxyl cellulose groups. Triethylamine was added in catalytic amounts, about 1 % in relation to the cellulose acetate mass. The temperature during gelation was kept constant at 25 ^{o}C, using thermostatic bath. The reactional system was kept closed under inert nitrogen atmosphere, for about 24

hour. The products had a gel consistency, but could be filtered and were washed exhaustively with THF and acetone. The product was, finally dried at 105 °C and kept in a desiccator.

Gel Swelling in different solvents: Gels were swelled in different solvent, according to Table 1. About 0.300 grams of gel were added to 100 mL of each solvent and after 30 minutes the gel was carefully removed, superficially dried with an absorbent paper and weighed. The degree of swelling were estimated on the basis of the percentage of mass increase.

Capacity of the gel in absorbing drugs – swelling studies:

The gel was cut in small cubes with 1.0 cm edges. Then it was added to a solution of diclofenac of sodium (0.5 grams in 1 L) and allowed to swell for 48 hours. Finally, the gel was filtered and washed exhaustively with water, in order to eliminate all the superficial diclofenac.

Controlled release: the loaded gel was immersed in 200 mL of water with pH 6.0. Samples of 1,0 mL were periodically removed at 2-hour intervals and immediatelly submitted to U.V. analyses in the range of 200 the 400 nm. The amounts of diclofenac realeased during the process (g/L) were calculated by comparing the results to a calibration curve obtained by analysis of diclofenac standards solutions (0,01 to 0,25 g/L).

Results and Discussion

PMDA did not prove to be an efficient cross-linking agent under the reaction conditions used. On the other hand, the use of BTDA resulted in gel formation with 95 % yield. Both the chain size of the cross-linking agent and its reactivity seem to be essential for the success of these modification reactions. The increase in mass percentage of the BTDA gel in different solvent are listed in Table 1.

Table 1: Weight gain of the gel in different solvents

Solvent	Weight gain (%)	Dielectrical Constant
hexane	1,37	1,9
carbon tetrachloride	5,80	2,2
dicloromethane	38,9	8,9
ethyl acetate	3,67	6,0
acetone	28,0	20,7
methanol	10,7	32,7

The results show that the solvent employed present significantly different affinities towards the gel. Non-polar solvents such as hexane and carbon tetrachloride bring about low swelling, while very polar ones such as dichloromethane and acetone causes a greater swelling in contact with the gel. The highly polar acetate groups in the chains of cellulose seems to play an important role in the swelling process.

The thermogravimetrical analysis (Figure 2) shows different behaviors for cellulose acetate and BTDA-gel.

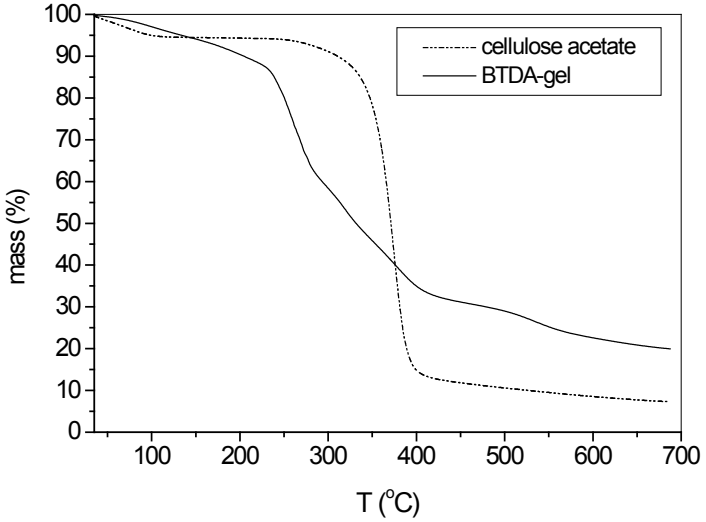

Figure 2: Thermogravimetrical analysis of cellulose acetate and BTDA-gel.

While the cellulose acetate presents a significant weight loss around 375 °C, the BTDA-gel present a less significant loss between 250 and 450 °C. This behavior is associated to the cross-linking between the cellulose acetate chains and the three-dimensional structures generated in the BTDA-gel.

After absorption of the diclofenac sodium and immersion in water, the gel showed the controlled release of the drug in water with pH 6. Figure 3 shows the U.V. spectra obtained during the release process of the diclofenac.

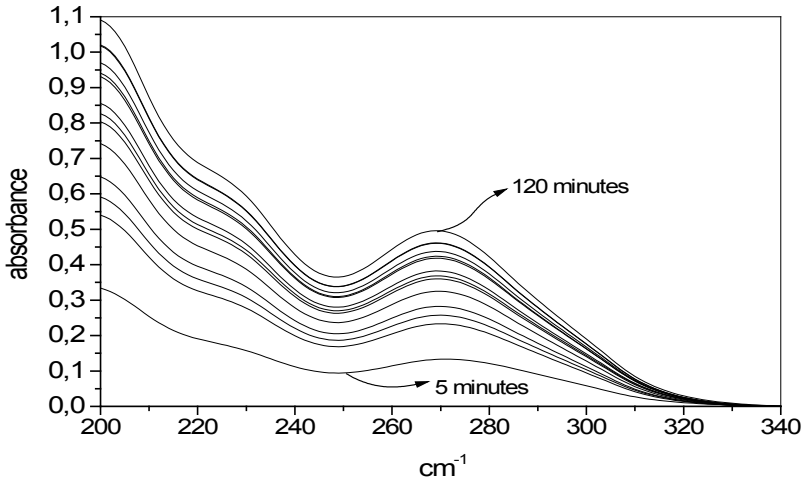

Figure 3: Controlled release of diclofenac sodium by U.V. analysis

Conclusions

The synthesized gel showed different interesting properties of swelling in solvent and the results obtained in the drug release studies are very encouraging. Theses results showed a first order kinetics during the time interval analyzed. The structural characteristics of the cellulose acetate polymer and drug affinities of the gel obtained suggest a potential application in the biomedical and pharmaceutical fields.

Acknowledgements

The PROPP/ UFOP and FAPEMIG

References

[1] V.R. Botaro, Gandini A., Chemical Modification of surface of Cellulosic fibers. Cellulose 5 (1998) 65-78.

[3]. Sang Ho Ye, J. Watanabe, Y. Iwasaki, K. Ishihara, Antifouling blood purification membrane composed of cellulose acetate and phospholipid polymer, Biomaterials, 24(23) (2003) 4143-4152.

[4]. R. Rodríguez, C. Alvarez-Lorenzo, A. Concheiro, Cationic cellulose hydrogels: kinetics of the cross-linking process and characterization as pH-/ion-sensitive drug delivery systems, Journal of Controlled Release, 86(2-3) (2003) 253-265. .

[5]. Z. Yue, I. J. McEwen, J. M. G. Cowie, Novel gel polymer electrolytes based on a cellulose ester with PEO side chains, Solid State Ionics, 156(1-2) (2003) 155-162.