

HYDROGELS OF CELLULOSE ACETATE CROSSLINKED WITH PYROMELLITIC DIANHYDRIDE – PART I: SYNTHESIS AND SWELLING KINETICS**Víctor A. Oliveira***, Tácia C. Veloso e Versiane A. Leão

Departamento de Engenharia Metalúrgica, Universidade Federal de Ouro Preto, Campus Morro do Cruzeiro, 35400-000 Ouro Preto – MG, Brasil

Cláudio G. dos Santos

Departamento de Química, Universidade Federal de Ouro Preto, Campus Morro do Cruzeiro, 35400-000 Ouro Preto – MG, Brasil

Vagner R. Botaro

Departamento de Química, Universidade Federal de São Carlos, Rodovia João Leme dos Santos, km 110, 18052-780 Sorocaba – SP, Brasil

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This work describes the synthesis of hydrogels of cellulose acetate (AC) crosslinked with 1,2,4,5-benzenotetracarboxylic dianhydride (PMDA). The crosslinking reaction was monitored by FTIR. Analysis of aromatic fragments from the alkaline hydrolysis of the gels by UV spectroscopy indicated that an increase in the stoichiometric ratio of dianhydride resulted in higher degrees of crosslinking. The non-porous nature of the gels was confirmed by analysis of nitrogen adsorption. Water absorption isotherms showed that as the temperature and degree of crosslinking increased, the percentage of water absorbed at equilibrium (%S_{eq}) also increased. The hydrogels presented second order swelling kinetics.

Keywords: cellulose acetate; hydrogel; PMDA.

INTRODUCTION

Hydrogels are tridimensional polymer networks capable of absorbing large amounts of water or biological fluids without dissolving, due to chemical or physical crosslinking. As a result of their swelling ability, these materials have received increased attention because of their potential application in bioengineering, biomedicine, food industries, separation processes, water purification, chromatography and controlled drug delivery systems.¹⁻¹⁰

The great capacity of water absorption by these materials is particularly important in the biomaterials field, given the relatively high water content of body tissues. Hydrogels can be referred to as physical, when the crosslinks result from electrostatic forces, hydrogen bonds, hydrophobic interactions or chain entanglements, or as chemical, when covalent bonds are responsible for the crosslinking.¹⁰ Depending on the nature of the hydrophilic groups, which account for their water absorption capacity, hydrogels can be also classified as ionic or neutral.

From thermodynamics of neutral polymer networks, it is known that degree of swelling is driven by two opposing factors: one involves the solvent-polymer interaction which results in changes in the mixing free energy of the system, and another factor is due to elastic forces within the polymeric network, caused by increasing water content within it. In the case of ionic hydrogels, the osmotic pressure caused by the presence of ions inside the polymeric network must also be considered.^{9,11}

Some studies show that the percentage of water absorbed by hydrogels at equilibrium (%S_{eq}) can vary with the gel history, changes in the hydrophilic character of the network or in temperature, pH and radiation dosages (during synthesis), structural changes of the polymeric network, type and amount of solvent used for the synthesis as well as degree of crosslinking.^{2,3,5-8,10,12-15} By determining %S_{eq}, important parameters such as diffusion coefficient, relaxation

mechanism, swelling kinetics, mixing enthalpy and the molar mass between network points can be obtained.^{3,5,6,10}

Water molecules are known to act as plasticizers and, in fact, during water absorption, a glass-rubber transition is observed in the hydrogel which results in a decreasing glass transition temperature of the material. For some hydrogels, the swelling process causes erosion of the material.^{8,9,16,17}

Hydrogels can also be classified as ionic or neutral, depending on whether ions are present or not. The presence of ionic groups within the polymeric network renders the hydrogel rather sensitive to changes in pH and the ionic force of the medium.⁹ Because of this sensitivity, ionic hydrogels can be used in controlled delivery systems, since variations in pH and ionic force can trigger the swelling process and, thus, promote the release of some agent eluted through the gel.

The use of cellulose esters and ethers as drug carriers has become very common in the pharmaceutical industry and the development of new cellulosic materials, capable of carrying and responding to environmental stimuli, has received increasing attention and shown very promising results.^{18,19} These controlled release systems are usually designed to protect patients from unfavourable environments, provide them with more comfort, prevent side effects and improve efficiency through structural modifications of the drug carrier system. The present paper describes part of a larger study aimed at modifying polymeric materials from renewable resources, which are biodegradable and biocompatible, and to assess their application as biomaterials.

EXPERIMENTAL**Starting materials**

The cellulose acetate (AC) [CAS:9004-35-7] employed was a commercial product purchased under the trade name Acetol Flakes® and had a nominal degree of acetate substitution (DS) 2.5. The crosslinking agent 1,2,4,5-benzenotetracarboxylic acid dianhydride

*e-mail: victor@demet.em.ufop.br

[CAS: 89-32-7], also referred to as pyromellitic dianhydride (PMDA), was kindly donated by Degussa GmbH and had 97% purity. Avicel [CAS: 9004-34-6] was supplied by Merck. Acetone (99.5%) was used as the solvent and was purchased from Proquimios; the catalyst triethylamine (99%) was purchased from Vetec Química Fina. AC was treated with ethyl ether for 30 min, ethanol for 1 h and subsequently washed with distilled water. The samples were immersed in water at 80 °C for 3 h and then dried at the same temperature under vacuum (600 mmHg) for 24 h²⁰ PMDA was dried under vacuum (600 mmHg) at 105 °C for 2 h and kept in a desiccator. Acetone and triethylamine were used as received.

Degree of acetylation

20 mL of 75% v/v aqueous ethanol were added to dried samples of AC (0.5 g); the flasks were covered and heated at 60 °C for 30 min, followed by addition of 25 mL standard 0.5 mol L⁻¹ NaOH solution. The mixture was kept at 60 °C for a further 15 min and allowed to react for 72 h at room temperature; the excess NaOH was titrated with standard HCl solution. The same procedure was carried out using Avicel, taken as 100% cellulose, instead of AC, and this blank was used as a reference to estimate DS according to Equations 1 and 2:²¹

$$\%Acetyl = \frac{\{(V_{NaOH} \times A) - (V_{HCl} \times B)\} - \{(V'_{NaOH} \times A) - (V'_{HCl} \times B)\}}{w} \times 4.3 \quad (1)$$

$$DS = \frac{3.86 \times (\%Acetyl)}{102.4 - (\%Acetyl)} \quad (2)$$

where % Acetyl is the percentage of acetyl groups in the sample, *A* and *B* are the concentrations of NaOH and HCl solutions, respectively, *V*_{NaOH} and *V*'_{NaOH} are the volumes of NaOH solution added to the sample and the blank, respectively; *V*_{HCl} and *V*'_{HCl} are the volumes of HCl solution added to the sample and the blank, respectively, *w* is the mass of the sample, in grams, and *DS* is the degree of acetyl substitution.^{21,22} All the measurements were carried out in triplicate.

Gel synthesis

In a conical flask, a saturated solution was prepared by dissolving AC (2.0 g) in acetone (50 mL) and the solution was filtered under atmospheric pressure and transferred to a beaker, equipped with a magnetic bar, before addition of PMDA. The amounts of PMDA were calculated considering that each dianhydride molecule must react with two anhydroglucose units from different cellulose acetate chains in order to cause crosslinking. Thus, hydrogels were prepared with stoichiometric ratios 0.1, 0.25, 0.5, 0.75 and 1.0 mol of PMDA per mol AC. As the dianhydride was dissolved, the transparent mixture was kept under continuous stirring at room temperature and gradually changed from translucent to a yellowish color. Upon complete dissolution of PMDA, triethylamine was added and, after a few minutes, a sudden change in viscosity was observed and the mixture eventually turned into a hydrogel.

Hydrogels were removed from the flask, chopped into approximately 1 cm³-pieces and treated with 20% v/v aqueous ethanol for 5 days at room temperature. The ethanol solution was eventually replaced by distilled water and the mixture was kept under continuous stirring at 70 °C. When no absorption related to PMDA could be detected in UV-vis analysis of an aliquot, the hydrogels were dried at 40 °C for 72 h in a conventional oven, 48 h in a vacuum oven and then placed in a desiccator. The hydrogels were then labelled according to the amount of PMDA used. Thus, 0.1P refers to a gel prepared with 0.1 mol PMDA per mol AC, and so on.

Characterization

FTIR spectra were run on a Nicolet spectrometer mod. Impact 410 in the range 4000-500 cm⁻¹, after 32 scans. Samples were prepared by homogenizing 10 parts KBr with 1 part hydrogel in achate mortar and pressing the mixture into pellets.

Surface modification of AC structure after the crosslinking reaction was analysed by SEM on a JEOL - 5SM-5510 microscope coupled with an energy dispersive spectrometer (EDS). Micrographs of secondary and back-scattered electrons were obtained with an acceleration potential of 20 kV, spot size 35. Samples were covered with a fine layer of graphite.

Density and porosity of the hydrogels were determined in a gas (He) multipycnometer QuantaChrome, mod. Nova 1000.

Samples weighing about 0.5 g for each hydrogel, and one sample of AC subjected to the same procedures of synthesis and purification as the hydrogels, were submitted to alkaline hydrolysis (0.5 mol L⁻¹ NaOH) at 70 °C for 1 week. Total hydrolysis of ester groups was confirmed by FTIR of the residue after filtration. A qualitative analysis by UV-Vis spectroscopy was carried out in the filtrate, using an HP UV-Vis spectrometer Mod. 8453, working in the range 240-310 nm. In these analyses, the hydrolysate of pure AC was used as the background.

Water absorption isotherms

Dry hydrogels having a cylindrical shape 1.0 cm thick and 4.5 cm diameter were immersed in distilled water at 20, 30 and 40 °C. The amount of absorbed water was determined gravimetrically at various time intervals. The surface of each sample was quickly dried with tissue paper before the weighing process.

Absorption isotherms were obtained by plotting swelling percent (%S) as a function of time. %S was calculated by Equation 3:

$$\%S = \frac{M_t - M_0}{M_0} \times 100 \quad (3)$$

where *M_t* is the mass of the swollen gel at time *t*, *M₀* is the mass of dry gel and %S is the percentage of absorbed water. The percentage of water absorbed at equilibrium (%S_{eq}) can be related to the amount of water absorbed after the diffusion process showing that polymeric chain relaxation had occurred. This parameter reflects the maximum capacity of water absorption by the gel.

Swelling kinetics

A kinetic study of the swelling process was carried out considering the integrated form of a second-order kinetic approach as demonstrated by Schott^{3,5,23} through Equation 4:

$$\frac{t}{M_t} = A + Bt \quad (4)$$

where *M_t* is the mass of water absorbed at time *t*, and *A* and *B* are physical coefficients which can be evaluated in the following way: for longer swelling times, the term *Bt* >> *A*, so that *B* = 1/*M_{eq}*, which is the reciprocal of the amount of absorbed water at equilibrium. It follows that a theoretical amount of absorbed water at equilibrium, *M_{eq}*, can be estimated from the reciprocal of the angular coefficient, 1/*B*. At the beginning of the experiment, when *t* values are shorter, *A* >> *Bt* and Equation 4 can be rewritten as:

$$\lim_{t \rightarrow 0} \frac{\partial M_t}{\partial t} = \frac{1}{A} \quad (5)$$

Thus, the linear coefficient of the line obtained by plotting Equation 4 corresponds to the reciprocal of the initial rate of swelling.

RESULTS AND DISCUSSION

Fourier transform infrared spectroscopy – FTIR

The average degree of substitution for AC as determined by Equation 2 was found to be 2.53 with a standard deviation of 0.12. Based on this result, all the work was carried out considering the presence of one free hydroxyl per two anhydroglucose units.

FTIR analysis of gel 0.5P (Figure 1) showed important differences between the hydrogels before and after washing, in comparison with the AC starting material. The main differences included out of plane angular vibrations of aromatic C–H bonds at 817 cm^{-1} , axial bending vibrations of C–O from cyclic anhydrides at 949 cm^{-1} , in plane angular deformation of aromatic C–H at 3070 cm^{-1} and the axial bending vibration of the C–O bond from aromatic carboxylic acid esters at 1299 cm^{-1} . The broadening as well as the splitting of the carbonyl band at about 1750 cm^{-1} were caused by the incorporation of ester groups into the chains and also the ketone and carboxyl moieties present in the crosslinking agent structure. Another important feature of the spectra is the broadening of the absorption at 3480 cm^{-1} , resulting from the increase in hydroxyl groups of the carboxylic acids in the crosslinked structure.

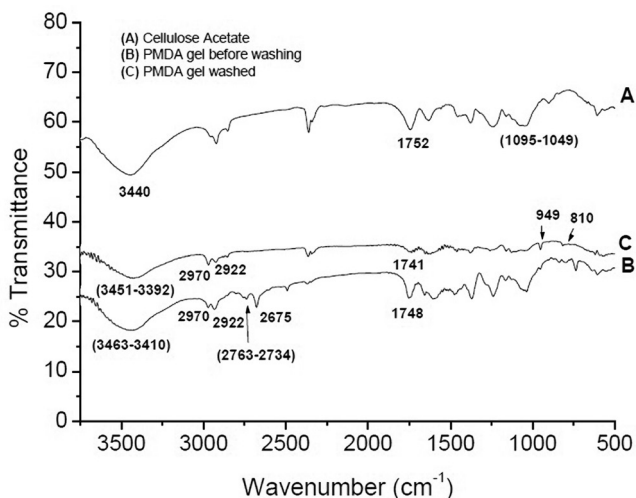


Figure 1. FTIR of cellulose acetate (A) and its gel with PMDA at a molar ratio 0.5 before (B) and after (C) washing

Scanning electron microscopy and UV-vis spectroscopy

Micrographs of cellulose acetate and gel 0.5P are shown in Figure 2. These micrographs indicate a higher rugosity of AC surface as compared to its gel with PMDA evidencing the surface modification

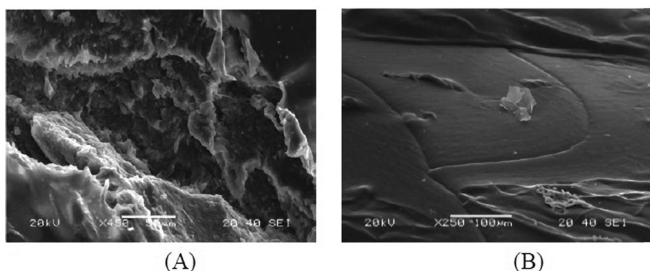


Figure 2. SEM images of cellulose acetate (A) and its gel with PMDA (B) at a molar ratio 0.5

caused by the crosslinking reaction. Density for this gel was found to be 1.42 g cm^{-3} and the average pore diameter 41.6 \AA . According to the classification proposed by Peppas and Meadows²⁴ this hydrogel can be referred to as nonporous.

Figure 3 shows the UV-vis spectra of the hydrolysates of gels prepared with different amounts of PMDA, showing absorption maxima at around 295 nm , assigned to the aromatic moieties in the crosslinking agent. As expected, the results confirm that the degree of crosslinking increases with increasing concentration of the dianhydride.

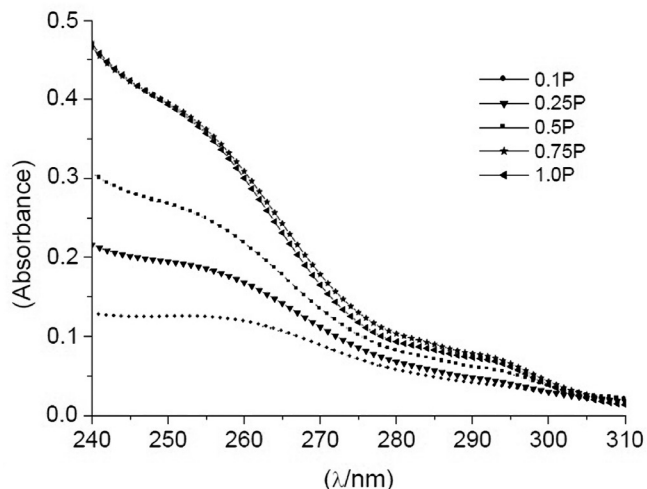


Figure 3. UV-vis spectra of the hydrolysates of gels prepared with different amounts of PMDA

Absorption isotherms

Swelling tests carried out with AC resulted in average $\%S_{eq}$ of 28.68% with a standard deviation of 1.73. The absorption isotherms of water by the gels were investigated at 20, 30 and $40\text{ }^{\circ}\text{C}$ and Figure 4 shows the isotherms obtained at $40\text{ }^{\circ}\text{C}$. For all temperatures, it was found that the higher the degree of crosslinking, the higher the percentage of water absorbed at equilibrium ($\%S_{eq}$). It was also observed that an increase in temperature caused an increase in $\%S_{eq}$ of the gels, regardless of the degree of crosslinking.

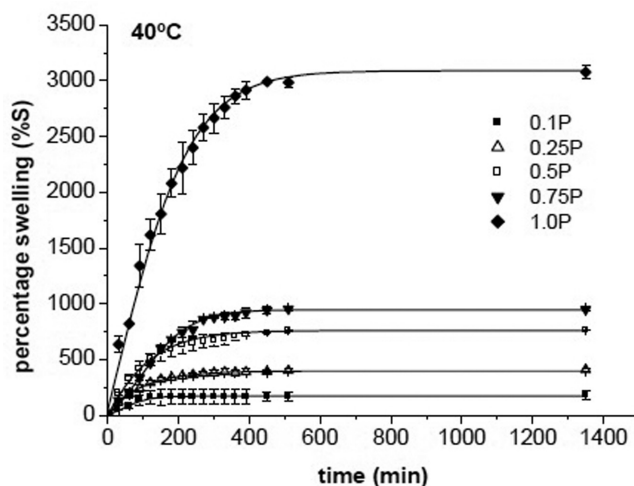


Figure 4. Water absorption isotherms of the gels with PMDA at $40\text{ }^{\circ}\text{C}$

Although the increase in crosslinks causes a reduction in mobility of the polymeric chains, the presence of ionic groups and polar

organic functions introduced in the network during the crosslinking reaction promote hydrogen bonding between the hydrogel and water. In this case, the increase in $\%S_{eq}$ is a consequence of the greater hydrophilic characteristics caused by the crosslinking. On the other hand, the increase in $\%S_{eq}$ with higher temperatures is related to the augmented chain mobility, which makes it easier for water molecules to migrate towards the gel interior; to the increase in thermal energy of water molecules, which results in more molecules having sufficient energy to engage in the diffusion process and, finally, to the higher amount of deprotonated carboxylic groups which renders the gel more hydrophilic.

Swelling kinetics

The considerable number of organic functions present in the hydrogels opens up the possibility of various polymer-solvent interactions. It follows that any type of kinetics proposed on the basis of swelling data is bound to relate to the global process, which, for practical purposes, is acceptable.

Application of the data obtained from the swelling tests to Equation 4 resulted in a series of plots as shown in Figure 5 for tests at

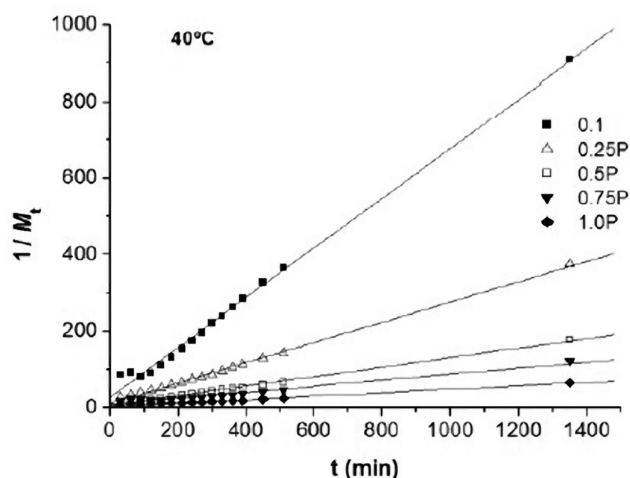


Figure 5. Plots of $1/M_t$ as a function of t for the gels with PMDA at 40 °C

40 °C with the results showing that the initial rate of water absorption varied randomly for the hydrogels. The lines presented correlation coefficient > 0.98 (Table 1) for all temperatures, confirming that the global process of swelling follows second-order kinetics.

When the temperature increased from 20 to 30 °C, the initial rate of swelling did not present a linear behavior, that is, for some hydrogels it increased, while for others it decreased. However, comparison with the results obtained at 40 °C shows that the initial rate of swelling increased for all the gels. As discussed above, this was accounted for by the greater mobility of the chains, the increased thermal energy of water molecules and the considerable number of deprotonated carboxyl groups.

Table 2 lists the experimental values of the amount of absorbed water at equilibrium (M_{eq}) at different temperatures and the ratio between the experimental and theoretical values shown in Table 1. As the results show, the experimental values are in close agreement with the theoretical values, with the differences ranging from a maximum of 19% to a minimum of 1%. The model does not take into account the change in surface area caused by swelling, therefore M_{eq}^*/M_{eq} ratios are lower than unity and higher deviation from unity occurs at higher crosslinking degrees, because swelling is more pronounced for these hydrogels. Despite these deviations, the results strongly support our assumption that the swelling process obeys second-order kinetics.

CONCLUSIONS

Hydrogels of cellulose acetate, having a degree of acetylation of 2.5, were prepared using PMDA as the crosslinking agent in stoichiometric proportions of 0.1, 0.25, 0.5, 0.75 and 1.0. FTIR proved to be a suitable method to follow the course of reactions and progress of purification. The rugosity of cellulose acetate is greater than that of its gel and this surface modification was evidenced by scanning electron microscopy. Hydrogels presented an average pore diameter of 4.16 Å, and were classified as nonporous. UV-vis spectroscopy of the gel hydrolysates confirmed that gels prepared with more dianhydrides presented higher degrees of crosslinking.

Swelling isotherms indicated that the more crosslinked the hydrogel, the higher the amount of water absorbed at equilibrium ($\%S_{eq}$), due to the greater hydrophilic characteristic of the polymeric network. $\%S_{eq}$ also increased with temperature and this was explained

Table 1. Amount of (theoretical) absorbed water at equilibrium (M_{eq}^*), initial swelling rates and correlation coefficients of absorption isotherms of gels of PMDA

Temp. / gel	0.1P	0.25P	0.5P	0.75P	1.0P	
$M_{eq}^* = 1/B$ (g)	20 °C	0.85	2.07	4.41	6.11	11.73
	30 °C	1.34	3.66	4.97	9.59	14.48
	40 °C	1.54	3.8	8.13	12.75	22.57
1/A (g/min)	20 °C	0.017	0.043	0.034	0.067	0.085
	30 °C	0.068	0.035	0.035	0.103	0.096
	40 °C	0.035	0.074	0.119	0.098	0.203
R^2	20 °C	0.999	0.999	0.999	0.998	0.987
	30 °C	0.999	0.995	0.995	0.986	0.987
	40 °C	0.997	0.999	0.999	0.980	0.993

Table 2. Experimental values of the amount of absorbed water at equilibrium (M_{eq}) and the ratio between experimental and theoretical values

Temp. / gel	0.1P	0.25P	0.5P	0.75P	1.0P	
M_{eq} (g)	20 °C	0.817	1.966	4.004	5.608	10.152
	30 °C	1.311	3.281	4.35	8.553	12.426
	40 °C	1.483	3.600	7.594	10.963	20.123
M_{eq}^* / M_{eq}	20 °C	0.96	0.95	0.91	0.92	0.87
	30 °C	0.98	0.90	0.88	0.89	0.86
	40 °C	0.96	0.95	0.93	0.86	0.89

on the basis of higher thermal energy of water molecules, increased mobility of the polymeric chains and the presence of ionic groups within the network.

Kinetics studies of the swelling process showed that the initial rate of water absorption increases when the temperature increases from 20 to 40 °C and the process follows second-order kinetics.

Hydrogels investigated in this work could be prepared with PMDA content as low as 0.1 mol/mol and showed substantial capacity for water absorption. The low energetic demand of the raw materials used in their preparation, the renewable character of cellulose acetate and the simplicity of the gel formation process must also be highlighted. All things considered, hydrogels of cellulose acetate crosslinked with PMDA emerge as an interesting alternative for materials used in controlled drug delivery systems, water treatment schemes and separation processes, such as chromatography.

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