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FLORY-HUGGINS INTERACTION PARAMETER FOR PVA-WATER IN HYDROGELS PREPARED BY TWO METHODS: FREEZING/THAWING AND CROSSLINKING WITH CITRIC ACID

M. I. Martinez [1], *E. Garzón* [2], *D. L. Pérez* [2], *C. Gartner*[3*]

1: Chemical Engineering Student. “Semillero de Polímeros de Ingeniería de Materiales”, University of Antioquia, Medellin, Colombia
2: Materials Engineering Student. “Semillero de Polímeros de Ingeniería de Materiales”, University of Antioquia, Medellin, Colombia
3: Materials Engineering Professor, University of Antioquia, Medellín, Colombia
* carmina.gartner@udea.edu.co

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ABSTRACT

PVA hydrogels are largely used for biomedical applications due to their biodegradability, biocompatibility, and suitable mechanical strength. These hydrogels can be synthetized by several methods. In this work hydrogels were obtained by two methods, freezing/thawing, and crosslinking with citric acid. The degree of swelling for both types of hydrogels was in the range of 60-70% which corresponds to a medium degree of swelling. Young’s modulus measurements gave values in the range of 0.20 to 4.00 MPa, which are proper values for tissue regeneration or wound healing applications. Crosslinking degree was found to be higher for the freezing/thawing hydrogels, in agreement with a lower degree of hydration and a higher modulus. By means of the Flory-Rehner model, the interaction parameter (χ) of PVA - water was calculated. This value depends on the availability of OH groups in the polymer. The highest value of χ was found for the hydrogels crosslinked with citric acid, revealing that their water-polymer interactions are weaker than those occurring in freezing/thawing hydrogels, which has more available OH groups. However, values higher than 0.5 were found for both types of hydrogels, indicating insolubility in water; therefore, these values imply mechanical stability in aqueous solutions. It is concluded that freezing/thawing is a more reproducible method, which allows the modulation of the crosslinking degree, perhaps, the most important parameter to be controlled.

PARÁMETRO DE INTERACCIÓN DE FLORY-HUGGINS PARA PVA-AGUA EN HIDROGELES PREPARADOS POR DOS MÉTODOS: FREEZING/THAWING Y ENTRECRUZAMIENTO CON ÁCIDO CITRICO

PALABRAS CLAVE

Hidrogeles
Alcohol polivinílico
Congelación - descongelación
Ácido cítrico
Parámetro de interacción de Flory-Huggins.

RESUMEN

Los hidrogeles de PVA se utilizan principalmente para aplicaciones biomédicas debido a su biodegradabilidad, biocompatibilidad y resistencia mecánica adecuada. Estos hidrogeles se pueden sintetizar mediante múltiples métodos. En este trabajo se obtuvieron hidrogeles por dos métodos: congelación/descongelación y reticulación con ácido cítrico. El grado de hinchamiento para ambos tipos de hidrogeles estuvo en el rango de 60-70% lo que corresponde a un grado medio de hinchamiento. Las mediciones del módulo de Young dieron valores en el rango de 0,20 a 4,00 MPa, que son adecuados para aplicaciones de regeneración tisular o cicatrización de heridas. Se encontró que el grado de reticulación era mayor para los hidrogeles de congelación/descongelación, mostrando un menor grado de hidratación y un módulo más alto. Mediante el modelo de Flory-Rehner, se calculó el parámetro de interacción (χ) de PVA-agua. Este valor depende de la disponibilidad de grupos OH en el polímero. El valor más alto de χ se encontró para los hidrogeles reticulados con ácido cítrico, revelando que sus interacciones agua-polímero son más débiles que las que ocurren en los hidrogeles obtenidos por congelación/descongelación, que tienen más grupos OH disponibles. Se encontraron valores superiores a 0,5 para ambos tipos de hidrogeles, lo que indica insolubilidad en agua; por tanto, estos valores implican estabilidad mecánica en soluciones acuosas. Se concluye que la congelación / descongelación es un método más reproducible, que permite modular el grado de reticulación, el cual es, tal vez, el parámetro más importante que debe ser controlado.

1. INTRODUCTION

Polyvinyl alcohol (PVA) is a synthetic polymer made from polyvinyl acetate through hydrolysis. It is of great interest for its potential use in many fields; since it is biodegradable, non-toxic, biocompatible and water soluble. Fully hydrolyzed forms of PVA yield hydrogels with tunable properties through crosslinking of the polymer [1], might make them useful for biomedical applications. Properties such as microstructure, Young's modulus, and deformability are comparable to those of biological tissues, meaning that these hydrogels are ideal for tissue substitutes and other biomedical applications including controlled drug delivery devices and wound dressing [2].

PVA can be crosslinked physically, chemically, and radiation initiated. Physical crosslinking involves the formation of crystalline regions in the PVA solution through repeated freezing and thawing cycles; in this way, a tough, elastic gel can be formed avoiding toxic agents. The number and duration of cycles influences the crystallinity and the final properties of the gel [3]. In contrast, chemical crosslinking requires a crosslinker agent that can react with the available hydroxyl groups from the vinyl alcohol. The most common crosslinkers are bifunctional aldehydes such as glutaraldehyde and glyoxal, boric acid, and dicarboxylic acids such as citric, succinic, and tartaric acid [4]. Figure 1 exemplifies the esterification reaction between citric acid and PVA.

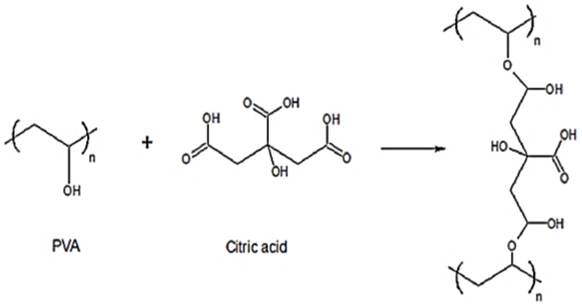

Figure 1. *Crosslinking reaction between citric acid and PVA.*
Adapted from Merck et al. 2020 [5].

Hydrogels are three-dimensional networks with the ability to absorb large amounts of water, increasing its volume by swelling without losing its shape. In the dry state, the gel is a solid and hard material (xerogel), but when immersed in an aqueous solution, it becomes softer due to the water that diffuses into the interior of the gel until reaching a physicochemical equilibrium. Diffusion includes the migration of water into the pre-existing spaces between the hydrogel's polymer chains. The number of these spaces, depend on the crosslinking degree. The amount of water absorbed in the equilibrium is the balance between the cohesive forces that prevent the expansion, and the osmotic forces originated by the entrance of water into the gel [6, 7].

The swelling behavior is crucial for explaining the physical properties of the hydrogels. The usual criterion for the theoretical description of swelling processes in gels is the Flory–Rehner theory. This is an extension of the Flory -Huggins phase theory based on a simple lattice model that can be used to understand the non-ideal nature of polymer solutions, analyzed in terms of the change of Gibbs free energy. This equation introduces the dimensionless Flory-Huggins interaction parameter (χ), which indicates the energy due to the molecular interactions when a polymer and a solvent are mixed [8].

The Flory – Rehner theory describes the contribution of the polymer - solvent mixture to the swelling of a gel. This theory does not require a great number of parameters and, despite its simplicity, encompasses a large variety of phenomena and situations. However, this theory has some weaknesses and limitations as assuming an ideal polymer network, and not considering the effects of loops, entanglements, free branches, finite length of the chains or their polydispersity [9]. The Flory - Rehner relates the interaction parameter (χ) between polymer and solvent and the crosslinking density (ν_e). The last is perhaps, the most influencing parameter. The higher the crosslinking, the shorter the chain length between crosslinking points, which lowers the elastic expansion of the hydrogel, decreasing the amount of water that can enter the network.

Other parameters that modulate the entrance of water in the network are the interactions between polar groups and the molecular structure of the polymer [7, 10]. In polymer–water systems, the higher the value of χ, the weaker is the interaction between polymer and water, and the stronger is the interaction between hydrophobic groups or between polymer chains. The arithmetic value of χ is relevant for the calculation of the crosslinking density via swelling methods, for the evaluation of the swelling behavior and, for the estimation of thermodynamic properties. The value can be calculated from the equation 1. It relates the volume fraction of the polymer in the hydrogel (ϕ_2), the molar volume of water (V_1), the functionality of the crosslinker (*f*) which measures the number of active bonds that the crosslinker possesses [11]. It also relates the crosslinking density (ν_e) which measures the crosslinking points per volumetric unit [10, 12]. ν_e is calculated from the equation 2 where E is the Young's modulus of hydrogel, R is the constant of the ideal gases and T is the absolute temperature.

$$\chi = -\frac{ln(1-\phi_2)+\phi_2+\nu_e V_1\left(\phi_2^{1/3}-2\phi_2 f^{-1}\right)}{\phi_2^2} \quad [1]$$

$$\nu_e = \frac{E\emptyset_2^{-\frac{1}{3}}}{3\mathrm{RT}} \quad [2]$$

Using this theory, it is also possible to describe the average molecular weight of the polymer chains between two consecutive bonds (Mc). These bonds can be chemical cross-links, physical entanglements, crystalline regions, or even polymeric complexes [13]. The equation 3 relates the density of the xerogel and the cross-link density (ν_e).

$$M_c = \frac{\rho_d}{\nu_e} \quad [3]$$

Applying this model, this paper aims to show a simple experimental method to calculate χ for PVA – water. Thus, PVA hydrogels were prepared by two methods. The first one is the freezing / thawing method, well-known and widely reported, which results in physical crosslinking [3]. The second one is a newer chemical method, using citric acid as a crosslinking agent. Citric acid is chosen because of its non-toxicity, as it is usually used as food additive, which makes it suitable for the preparation of possibly biocompatible PVA hydrogels.

2. MATERIALS AND METHODS

2.1. Materials

Analytical grade poly vinyl alcohol (PVA), molecular weight (Mw) 89,000-98,000 and 99% hydrolyzed, was purchased from Sigma-Aldrich. Citric acid 99.5% pure was purchased from Merck. Both reagents were used without further purification.

2.2. Preparation of hydrogels

Hydrogels were prepared by two methods: freezing/thawing (FT) and crosslinking with citric acid (CAC). For the FT method, a 6% (W/V) PVA solution in distilled water was poured into 9 cm diameter petri dishes and frozen at -12 °C for 24 hours, and then thawed at 36 °C for other 24 hours, performing one only cycle. This method was used as a reference and is broadly reported [14, 15]. For CAC, a method was adapted from the one reported by C. Birck, *et al*. [4]. It can be describe as following: 2 cm^3 of 15% (W/V) citric acid solution were slowly dropped into 10 cm^3 of 6 wt.% PVA solution, under constant stirring of 180 rpm at room temperature. This citric acid concentration was chosen after scanning concentrations between 10 and 25 wt.% PVA-citric acid solution was then poured into 9 cm diameter petri dishes, letting stand at 60 °C for six hours. Both types of hydrogels were dried, cut into rectangular shapes, measured with a micrometer, and weighed. Six replicates wereperformed for each method.

2.3. Characterization

2.3.1 Density measurements

Density for FT hydrogels were measured by displacement under method ASTM D-792-20

[16]. Density for CAC hydrogels was calculated by the ratio W/V, using an average of three measurements of weight and dimensions. Xerogel weights were used for density measurements.

2.3.2 Swelling kinetics

Samples in the form of sheets with dimensions in a range of 18-20 mm wide, 80-100 mm long and 0.5-0.7 mm thick were cut from each xerogel. These sheets were weighed and immersed in distilled water at ambient temperature (22-23 °C). Weight measurements were done for 40 minutes, which is the time, experimentally found, when the absorption equilibrium is reached. Weight measurements were performed at given times, every 3 minutes during the first 15 minutes, and every 5 minutes for the remaining time. The excess of superficial water was removed and then weighed.
Using equations 4, 5 and 6 the water fraction (W_f), percentage of hydration (H_p) and degree of swelling (D_s) were determined, where m_e is the hydrogel equilibrium weight and m_d is the xerogel weight. The polymer fraction in the hydrogel ($\emptyset_2$) is calculated from equation 7, where ρ_d is the xerogel density as was described in the density measurements. ρ_{H_2O} is the water density [7, 17].

$$W_f = \frac{m_e - m_d}{m_e} \quad [4]$$

$$H_p = 100 \cdot \left(\frac{m_e - m_d}{m_d}\right) \quad [5]$$

$$D_s = \frac{m_e}{m_d} \quad [6]$$

$$\emptyset_2 = \frac{\frac{m_d}{\rho_d}}{\frac{m_d}{\rho_d} + \frac{m_e - m_d}{\rho_{H_2O}}} \quad [7]$$

2.3.3 Young's modulus measurements under uniaxial tension

These tests were performed at room temperature for the same gels used for swelling measurements, measured in the elastic zone before yielding. Six replicates were performed for each type of hydrogel. It was used a Shimadzu AGS-X 50 KN double column, universal testing machine, with a resolution of 0.01 Newton and 0.0001 millimeters, a speed of 5 mm / minute and a preload force in a range between 0.10-0.20 N. The water content of the hydrogels samples was measured before the mechanical test by relating the hydrogel weight right before the measurement, to a water content using the swelling curve.

The physical integrity of the hydrogels was qualitatively examined for two months by keeping the hydrogels immersed in water and examining their physical integrity and degree of swelling.

3. RESULTS AND DISCUSSION

Two types of hydrogels, obtained by two different methods, were analyzed. One by the freezing-thawing (FT) method and the other by the citric acid cross-linking method. For the first case, preliminary tests were carried out using several freeze-thawing cycles and it was found that a single cycle originated hydrogels with the required physical integrity. This property did not differ significantly from those hydrogels obtained through several cycles and therefore this single-cycle method was selected for the present study. As for the hydrogels prepared from citric acid, 15 wt.% citric acid was chosen as the optimal concentration because the prepared hydrogels showed good properties, swelled correctly and were flexible, when compared to the FT hydrogels, which was used as the reference method.

The results obtained from the swelling measurements for the two types of hydrogels are shown in Figure 2. It is seen that swelling is faster for the first 15 minutes. This is the starting time of the swelling equilibrium until it reaches the maximum degree. The behavior of both types of hydrogels is very similar, although the water fraction absorbed for citric acid hydrogels is higher.

From the swelling curves, many parameters can be obtained, such as the degree of swelling, water fraction and the percentage of hydration. The latter measures the amount of fluid that the hydrogel can absorb, allowing the hydrogel to be classified qualitatively between low, medium, and high swelling [7].

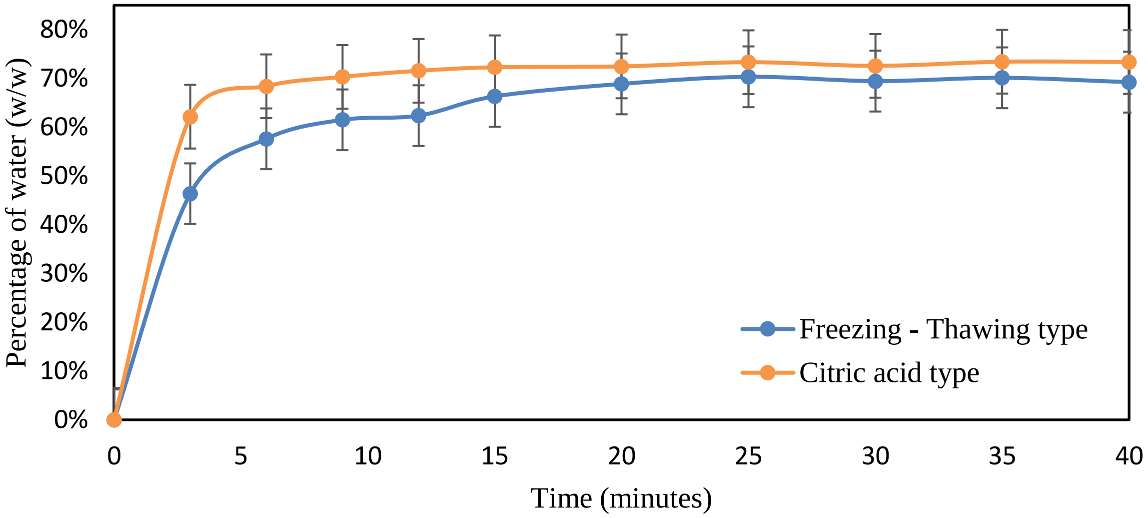

Figure 2. *Swelling kinetics plots for hydrogels obtained by the methods of FT and CAC*

Table 1 summarizes the information obtained from swelling measurements. The two types of hydrogels indicated medium swelling [7]. The degree of swelling (D_s) or swelling index, percentage of hydration (H_p) and water fraction in the equilibrium (W_f), were lower for the hydrogels obtained by freezing/thawing than for those obtained by citric acid (Table 1). These results reveal a higher degree of crosslinking for the hydrogels obtained by FT as was further verified by the Young's modulus measurements.

Young's modulus of hydrogels (E) with a moisture content between 63 and 73% (Table 2) were measured. The probes for Young's modulus were measured with a certain moisture content, because xerogels were very fragile and brittle.

Figure 3 is the plot of the stress-strain curve in the elastic zone for both type of hydrogels. Results are reported in Table 2.

Modulus for FT hydrogels is almost 10 times higher than modulus for CAC, which reflects a higher degree of crosslinking for the former, in agreement with the results obtained from swelling kinetics. FT xerogels showed higher density than CAC which is consistent with a higher degree of crosslinking [6]. These results are comparable with those obtained by J. Wang, *et al.* [12], who measured Young's modulus of 2-hydroxyethyl methacrylate (HEMA) hydrogels. Furthermore, the modulus obtained by Y. L. Contreras-Marín and R. M. Quispe-Siccha [18] are considerably higher for a PVA system, considering that their hydrogels were obtained by FT after 4 cycles of freeze and thaw.

Table 1. *Data from swelling kinetics. Reported data is an average of all the measurements.*

Hydrogel type	m_d (g)	m_e (g)	W_f (g/g)	H_p (%)	D_s (g/g)
Freezing – Thawing	0.2177±0.0454	0.7056±0.1070	69.24±1.77	225.59%±18.75%	325.59 ±18.18
Citric acid	0.3920±0.0105	1.4739±0.0911	73.37±1.06	275.85%±14.97%	375.85±14.97

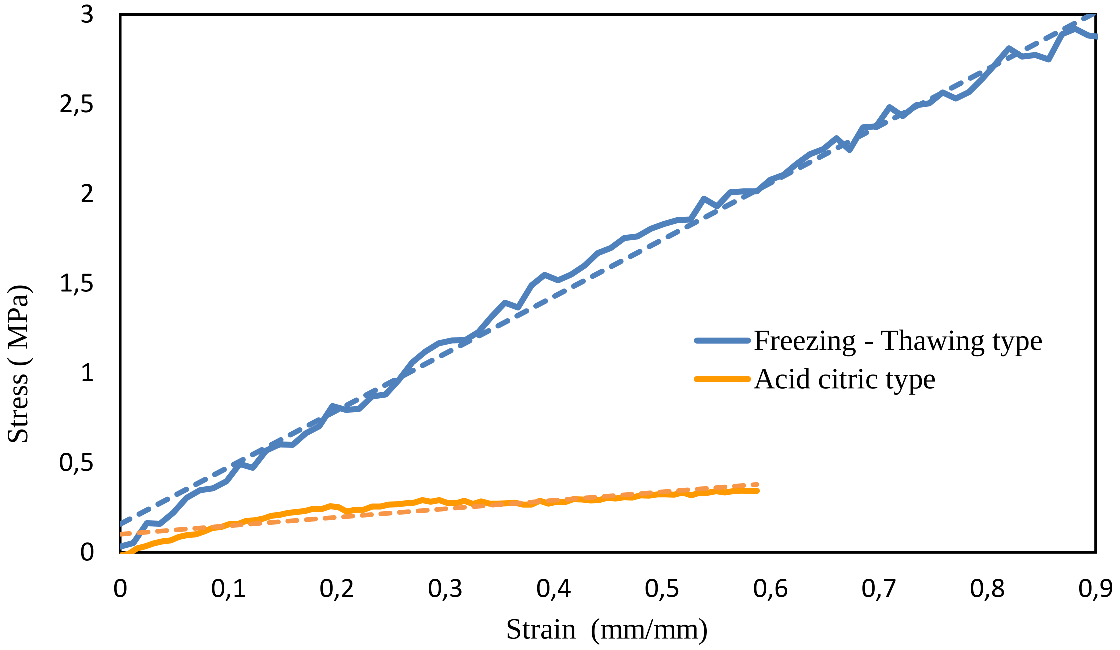

Figure 3. *Stress-strain curves before the yield point of hydrogels obtained by FT and CAC.*

Table 2. *Summary of the average results for weight, density, and Young's modulus for both types of hydrogels.*

Hydrogel type	ρ_d (g·cm^{-3})	Water percentage for modulus measurements	E (MPa)
Freezing – Thawing	1.4683±0.0611	63.51%±0.48%	2.9024±1.0472
Citric acid	1.1122±0.0767	73.11%±2.16%	0.3290±0.0694

It was assumed that a single cycle of FT would give a low crosslinking degree as reported in the literature, but it was found to be higher than the crosslinking degree obtained by the CAC method [19]. It can be deduced that the esterification reaction of the acid groups of citric acid with the OH groups of PVA chains is less effective due to the steric hindrance of water and a slow esterification kinetics [11]. Even though an optimal concentration of citric acid was found experimentally, some hydrogels had an excess of salt on the surface after drying, and the pH of the solution was acid (around 5.0), indicating that the reaction was incomplete.

On the other hand, the FT method is very effective because it allows the formation of very strong intra molecular hydrogen bonds between the PVA chains when the water freezes. Then on thawing, very stable crystals are formed, even at room temperature [4]. As the latter method is more efficient, it gives a higher degree of crosslinking.

Table 3 reports the calculated parameters of the effective crosslinking density (v_e), the volumetric fraction of polymer in the hydrogel ($\emptyset_2$), the molar mass per crosslinking (M_c) and the PVA-water interaction parameter (χ).

Table 3. *Effective cross-link density (v_e), Molar mass per cross-link (M_c) and polymer-water interaction parameter (χ) for both types of hydrogels at a specific temperature.*

Hydrogel type	**T (K)**	$\emptyset_2$	v_e **(mol·m^{-3})**	M_c **(g·mol^{-1})**	χ
Freezing – Thawing	296.15	0.2321±0.0222	639.33±210.47	2457.77±908.88	0.5143±0.0001
Citric acid	295.15	0.2460±0.0179	71.18 ±13.80	16102.92±3956.77	0.5930±0.0090

The effective crosslinking density (v_e) is much higher for the FT hydrogels as it was concluded by swelling kinetics and Young's modulus measurements.

On the other hand, the volumetric polymeric fraction in the hydrogels ($\emptyset_2$) is slightly smaller for FT hydrogels, which argue with a higher effective crosslinking density. $\emptyset_2$ indicates the proportion of polymer in the hydrogel with respect to the water absorbed during swelling; this is directly proportional to the modulus of elasticity and the effective crosslinking density [7]. The higher $\emptyset_2$ for citric acid hydrogels with a lower effective crosslinking density can be due to a weight overestimation, because they also have ester groups and non-reacted citric acid, besides the polymer PVA. In contrast FT hydrogels only have PVA.

The crosslinking density (v_e) is the variable that most influences the swelling behavior of the hydrogel since a lower crosslinking density means a greater distance between the crosslinking points. This leads to a greater resistance to elongation and a higher amount of water that enters the hydrogel network [8]. It is stated by I. Katime [7] that the favorable osmotic force of the swelling of an enthalpic nature is opposed by another unfavorable force, the result of the tensions of the macromolecules of an entropic nature [7].

The molar mass per crosslinking (M_c) is higher for less crosslinked polymers since there is a greater distance between network points. This statement agrees with the experimental data since the molar mass for the CAC hydrogels was eight times higher than that obtained for the FT hydrogels.

The interaction parameter χ indicates the change of interaction energy when a solvent and a polymer are mixed. In polymer-water systems, the higher the value of χ, the lower the hydrophilic interactions [8]. Values of χ were found by means of the referenced model (Equation 1) and shown in Table 3. A higher value was obtained for citric acid hydrogels, which is explained by the presence of crosslinks as interchain ester groups, created from the chemical reaction between PVA hydroxyl groups and the acid groups of citric acid, as illustrated in Figure 1 [5]. The smaller number of OH groups, decreases the probability of interactions between PVA and water, and simultaneously the overall hydrophilicity of the gel. Consequently, the interaction between polymer chains or hydrophobic interactions is increased.

On the other hand, the higher availability of OH groups for FT hydrogels increases hydrophilic interactions lowering the value of the interaction parameter [7, 8, 20]. Nevertheless, a χ value greater than 0.5, were found for both types of hydrogels, indicating insolubility. Therefore, the calculated values imply stability of hydrogels in aqueous solutions. Experimentally it was found that these hydrogels immersed in water kept their physical integrity for as long as two months.

4. CONCLUSIONS

Finding χ is important because it enables the thermodynamic modeling of PVA hydrogels in aqueous solutions from accessible experimental data as density, swelling kinetics and Young's modulus. It should be noted that these values can only be used for a specific system of PVA and crosslinking agent at a given temperature and concentration conditions.

Although crosslinking with citric acid is a promising method, freezing/thawing has proven to be more efficient, allows for better modulation of the degree of crosslinking, does not have external agents that could contaminate the hydrogel, and involves fewer experimental errors.

5. ACKNOWLEDGEMENTS

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