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Physico-chemical characterization of modified poly(vinyl alcohol) based hydrogels

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The study reports the preparation and characterization of modified PVA based hydrogels with biomedical applications as carriers for drug delivery systems. PVA modified copolymers were previously synthesized by grafting with L-lactic acid, using manganese acetate as catalyst and different molar ratio of PVA/L(+)-lactic acid (1/1; 1.5/1; 2.2/1). The hydrogels were synthesized using sodium tetraborate ($Na_2B_4O_7 \cdot 10H_2O$) as crosslinking agent, triethylenetetramine as accelerator, in water system at room temperature. Crosslinking agent concentration varied between 5 and 12 wt. % depending on poly(vinyl alcohol) grafting degree. After crosslinking, the hydrogels were maintained 24 hours at room temperature, then were introduced in the freezer (-22 ^{0}C) for 6 h and subsequently were dried by lyophilization (-48 ^{0}C) to constant weight. The swelling properties of the synthesized hydrogels were investigated in phosphate buffer (pH 7.4) at 37 ^{0}C temperature. The hydrogels were characterized by infrared spectroscopy (IR), thermal analysis (DTG, DSC).

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1. Introduction

Hydrogel is a three-dimensional network of hydrophilic polymers in which a large amount of water is present. Hydrogels are multicomponent systems consisting of polymer and large amounts of water that present reversible deformation and do not flow. The elastic network can be permanent (vulcanized rubber) or temporary (gelatines). The quantity of water that is contained in certain hydrogel depends on the affinity between the network atoms and the solvent. For a good affinity the hydrogel size grows to maximize the number of interactions between the polymer segments and the solvent molecules. [1]. In general, the amount of water is at least 20 % of the total weight. If water is composed of more than 95 % of the total weight, the hydrogel is called superabsorbent. The most characteristic property of hydrogel is that it swells in the presence of water and shrinks in the absence water. The extent of swelling is determined by the nature (mainly hydrophilic) of polymer chains and the crosslinking density.

To maintain the three-dimensional structure, polymer chains of hydrogels are usually crosslinked either chemically or physically. In chemical gels polymer chains are connected by covalent bonds, and thus it is difficult to change the shape of chemical gels. The crosslinking agents are at least di-functional agents, the crosslinking is produced randomnly and the number of crosslinks depends on the crosslinking ratio. Covalent linkages between polymer chains can be established by the reaction of functional groups with complementary reactivity (amine–carboxylic acid, isocyanate-OH/NH_2 [2]. On the other hand, polymer chains of physical gels are connected through non-covalent bonds, such as van der Waals interactions, ionic interactions, hydrogen bonding, or hydrophobic interactions [3]. Chemically crosslinked gels can be obtained by radical polymerization of low molecular weight monomers in the presence of crosslinking agents. Poly(2-hydroxyethyl methacrylate) (pHEMA) is a well known and frequently studied hydrogel system. This hydrogel was first described by Wichterle and Lim [4] and is obtained by polymerization of HEMA in the presence of a suitable crosslinking agent (e.g. ethylene glycol dimethacrylate). Poly(vinyl alcohol) (PVA) is a polymer of great interest because of its many desirable characteristics specific for various pharmaceutical and biomedical applications. The crystalline nature of PVA has been of specific interest particularly for physically crosslinked hydrogels prepared by repeated cycles of freezing and thawing. The preparation of pure PVA hydrogels using freezing and thawing techniques was first reported by Peppas [5], aqueous solutions of PVA between 2.5 and 15 wt. % PVA were frozen at –20 ^{0}C and thawed back to room temperature resulting in the formation of crystallites. In preparing PVA gels by freezing and thawing techniques, the addition of solvents has also been investigated by Hyon and Ikada [6] that obtained porous and transparent hydrated gels from a PVA solution in a mixed solvent of water and water-miscible organic solvents. The concentration of PVA in solution was between 2 and 50 wt. %. The organic solvents examined included dimethyl sulfoxide, glycerine, ethylene glycol, propylene glycol. The method consisted of cooling the solution to below 0 ^{0}C for the crystallization of PVA followed by the subsequent exchange of the organic solvent in the gel with water. This process resulted in the formation of a hydrated gel of PVA with high tensile strength, high water content, and high light transmitance. High light transmitance is an important property of the material, especially when considering the material for contact lens applications.

A considerable amount of research studies investigated the addition of other components notably other polymers with PVA to create materials with desirable characteristics and properties. The addition of poly(ethylene glycol) (PEG) into a PVA system reduced protein adsorption and pH-sensitive polymeric systems containing PVA and poly (acrylic acid) (PAA) were synthesized [7, 8]. A temperature- and pH-sensitive PVA/PAA interpenetrating polymer network was investigated for indomethacin drug release [9]. PVA hydrogels were used for numerous biomedical and pharmaceutical applications as biomaterials [10]. Some of these advantages include their non-toxic, non-carcinogenic, and bioadhesive characteristics, as well as their associated ease of processing. In addition, PVA gels exhibit a high degree of swelling in water or biological fluids and a rubbery and elastic nature. Because of these properties, PVA was capable of simulating natural tissue and could be readily accepted into the body. Tamura et al. [11] examined the use of PVA gels prepared by freezing/thawing processes as a material for medical use. The gel had a water content of 80 to 90 % by weight, high mechanical strength, and rubber-like elasticity. The characteristics of the gel, which resembled that of natural tissue, did not change after long-term implantation. In addition, gel samples that were implanted subcutaneously or intramuscularly into rabbits showed good bioinertness, and no adhesion to surrounding tissue was found. Although initially some infiltration of inflammatory cells was found, it disappeared during the second week after implantation.

The study reports the synthesis and characterization of modified PVA based hydrogels. The hydrogels were synthesized using sodium tetraborate decahydrate as crosslinking agent, triethylenetetramine as accelerator, in water system at room temperature. Crosslinking agent concentration varied between 5 and 12 wt. % depending on poly(vinyl alcohol) grafting degree.

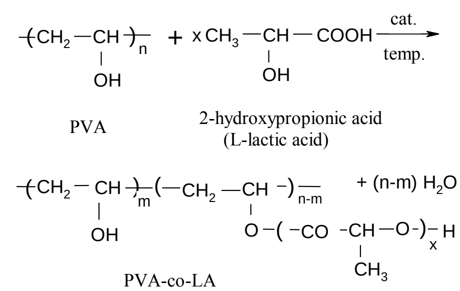
2. Experimental

2.1. Materials

The hydrogels were carried out with copolymers synthesized in the laboratory obtained by modification of PVA with L(+)-lactic acid. The average numeric molecular weights Mn determined by GPC varied between 25000 and 40000 (Table 1). The raw materials used in our experiments are available as commercial products and were analytical grade reagents. L(+)–lactic acid [(S)-2 hydroxipropionic acid] aqueous solution 90 wt.%, (Fluka, Switzerland) was used as received. PVA degree of hydrolysis 98 %, DP=400, saponification index 140 ± 30 mg KOH/g, was from Romacryl-Rasnov, Romania. Other chemical reagents utilized in the study were sodium tetraborate decahydrate ($Na_2B_4O_7 \cdot 10H_2O$), triethylenetetramine $NH_2CH_2CH_2(NHCH_2CH_2)_2NH_2$ (Fluka) and phosphate buffer solution pH=7.4.

2.2. Synthesis of hydrogels

The hydrogels were prepared from PVA-g-lactic acid modified copolymers. The copolymers were obtained in the laboratory modifying PVA by a polycondensation mechanism, using PVA/LA in different molar ratio (2.2/1; 1.5/1; 1/1), in the presence of manganese acetate $(CH_3COO)_2Mn \cdot 4H_2O$ as catalyst. The reaction mechanism is presented in scheme 1.



Scheme 1. Copolymer synthesis PVA-co LA.

PVA aqueous solutions of PVA-co-LA (c=13.4 %) were prepared by agitation at 40-50 ^{0}C. Also, a representative sample of PVA dissolved in water (c=8%) at 70-80 ^{0}C was prepared. The solutions were filtered, then were chemically crosslinked with a crosslinking system made of sodium tetraborate water solution (c=5%) and triethylenetetramine (activator), at laboratory temperature. The concentration of the crosslinking agent varied between 5-12 % (Table 1), and the obtained gels presented prolonged good time stability. After crosslinking the hydrogels were maintained 24 hours at laboratory temperature, then were introduced 6 hours in the freezer (–20 ^{0}C) to finalize the crosslinking process. The samples were then lyophilized 12 hours at –48 ^{0}C in order to remove mostly of the solvent. Afterwards, the hydrogels were dried to constant weight in a vacuum dryer at 45-50 ^{0}C. The swelling behavior was studied in phosphate buffer solution pH=7.4, at 37 ^{0}C temperature.

2.3. Methods of investigation

IR spectra of the PVA-co-LA copolymer and PVA polymer were recorded on spectrophotometer M80 type using KBr pellets for sample preparation.

Thermogravimetric analyses (TG and DTG) were carried out with a derivatograph Q-1500 D, MOM-Budapest (Hungary) type at the following conditions: the weight of the sample 50 mg, the heating rate 10 ^{0}C/min, the maximum heating limit 700 ^{0}C, reference material α-Al_2O_3.

Table 1. Hydrogel synthesis.

Sample[1]	Molar ratio PVA-co-LA[2] (mol)	Molecular weight M_n	Aqueous solution copolymer PVA-co-LA[3] (g)	Sodium tetraborate decahydrate (g)	Triethylene tetramine (ml)
A_5	2.2/1	34164	6	0.040	0.02
A_8	2.2/1		6	0.064	0.03
A_{10}	2.2/1		6	0.080	0.04
B_8	1.5/1	40145	6	0.064	0.03
B_{10}	1.5/1		6	0.080	0.04
B_{12}	1.5/1		6	0.096	0.05
C_8	1/1	25393	6	0.080	0.04
C_{10}	1/1		6	0.096	0.05
C_{12}	1/1		6	0.113	0.06
PVA_4	1/0	18000	5	0.016	0.01
PVA_5	1/0		5	0.020	0.01
PVA_{10}	1/0		5	0.040	0.02

[1] index indicates the percent of the crosslinking agent
[2] - molar ratio of components in copolymer synthesis.
[3]- PVA-co-LA solution c =13.40 wt.%; PVA solution c=8 wt.%.

The molecular weight of PVA-co-LA copolymer was determined by the gel permeation chromatography (GPC) technique at ambient temperature. The system was equipped with an adjustable flow capacity and constant rate pump LC 1120 and an evaporative mass detector PL–EMD 950 type. It was fitted out also with columns PL-gel 5 μm MIXED-D and PL-gel 5 μm MIXED-C packed with polystyrene/divinylbenzene copolymer. PL-polymer, polystyrene standards (580÷316500) were employed. Dimethylformamide was used as the mobile phase at a flow rate of 0.7 ml/min.

The thermal DSC analyses were carried out by means of a Mettler 12E type differential scanning calorimeter (Switzerland) with a heating rate of 10^0C/min in nitrogen atmosphere. The first heating run was carried out with a 10-12 mg sample in the temperature range between room temperature and 300^0C. The second heating run was performed with samples, which were suddenly cooled to room temperature. Pure indium was used as a standard for calorimetric calibration.

The swelling ratio of the gels in phosphate buffer solution pH=7.4 were studied at 37 ^{0}C temperature.

3. Results and discussion

Aqueous solutions of some copolymers obtained by chemical modification of poly(vinyl alcohol) with L(+)-lactic acid by polycondensation mechanism were used to prepare the hydrogels. The IR spectra of PVA and copolymer obtained are presented in figure 1. In the case of PVA as well as of copoolymer PVA-co-LA the presence of some very wide absorption bands are observed at 3400 cm^{-1} characteristic to νOH group. This band has a more reduced intensity in the case of the copolymer, as some of the OH groups from PVA were estherified in the presence of L(+)-lactic acid. Also in the case of PVA some absorption bands δOH at 1320-1376 cm^{-1} can be noticed, and in the case of the copolymer these bands are missing or much decreased. The ester group at 1735 cm^{-1} present in the synthesized copolymers (νC=O) of great intensity confirms the grafting reaction of (L+)-lactic acid with PVA.

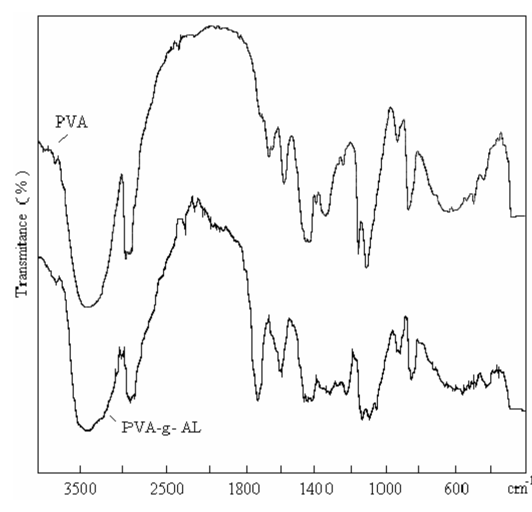


Fig. 1. IR spectra of PVA and PVA-co-LA.

In Fig. 2 IR spectra of hydrogels prepared by chemical crosslinking of PVA-co-LA with a crosslinking system: aqueous solution of sodium tetraborate (c=5 %) and triethylenetetramine as activator is presented. In both cases the crosslinking is confirmed by the presence of the absorption bands at 1310-1380 cm^{-1} of medium intensity, specific to νB-O linkages. Moreover, in the crosslinked PVA-co-LA copolymer the presence of some absorption bands at 1650 cm^{-1} can be noticed characteristic to alchil–NH_2 group and at 2350 cm^{-1} characteristic to νNH_2^+ groups.

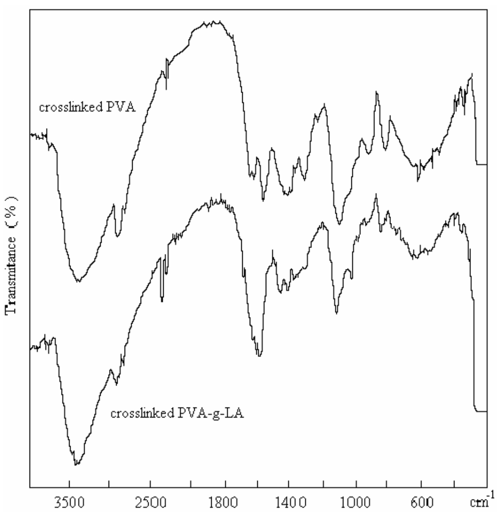
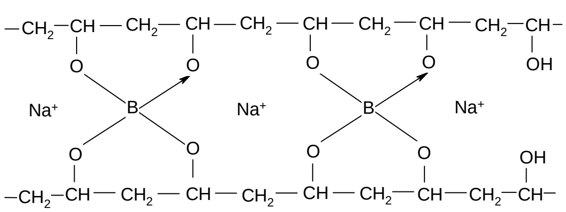


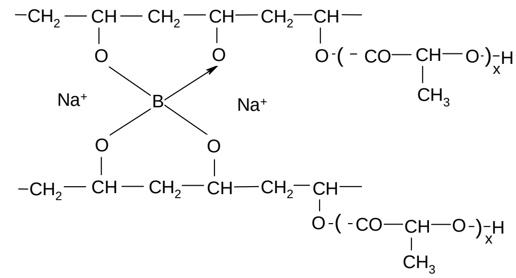
Fig. 2. IR spectra of crosslinked PVA and PVA-co-LA .

PVA crosslinking with sodium tetraborate and triethylenetetramine as activator was achieved at 25 ^0C when thickening and gelation of the polymer by chemically bonding a didiol-type (Scheme 2) could be noticed.



Scheme 2. Crosslinking of PVA with $Na_2B_4O_7$ 10 H_2O.

In the case of copolymer PVA-co-lactic acid (with probable structure presented in scheme 1), the mechanism of crosslinking with sodium tetraborate and triethylenetetramine as activator was achieved at the unesterified OH groups. The greater the molar ratio PVA/LA in the copolymer, it presented more OH free groups that could participate at crosslinking reaction with sodium tetraborate. The possible crosslinking mechanism is presented in scheme 3.



Scheme 3. Crosslinking of PVA-co-LA with $Na_2B_4O_7{\cdot}10\ H_2O$.

The thermal behaviour of the crosslinked copolymers was considered by thermogravimetric analyses (DTG) and differential scanning calorimetry (DSC). The weight losses obtained by oxidative thermal decomposition (TG) of the copolymers are presented in Figs. 3, 4 and the data concerning the thermal stability and the activation energy (E_a) in Table 2.

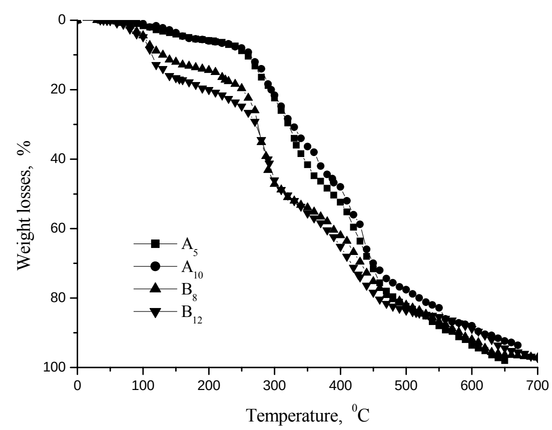


Fig. 3. TG diagrams of crosslinked copolymers PVA-co-LA (molar ratio PVA/LA: 2.2/1 and 1.5/1).

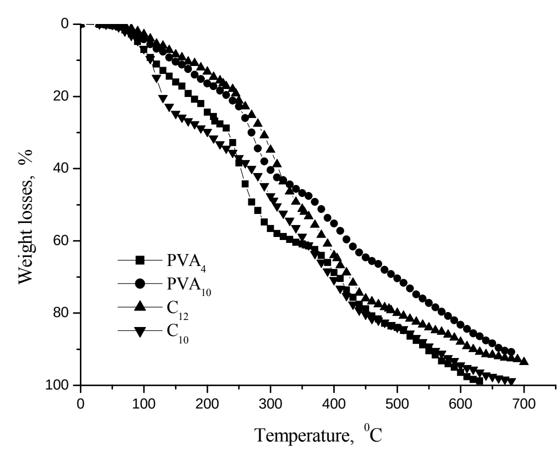


Fig. 4. TG diagrams of crosslinked copolymer PVA-co-LA (PVA/LA: 1/1) and crosslinked PVA.

From the data presented in the table and the TG diagrams can be noticed that the hydrogel obtained with the crosslinked copolymer that has in its structure a molar ratio PVA/LA (2.2/1) is thermally more stable comparative with the hydrogels prepared with PVA/LA copolymers (the molar ratio 1.5/1 and 1/1), or crosslinked PVA. Generally, the thermal stability lowers with PVA ratio decrease and lactic acid ratio increase in the structure. It can be explained as by the increase of lactic acid ratio in the copolymer synthesis, the number of unesterified OH groups is more reduced and sodium tetraborate cross-linking less efficient. The weight losses of 50 % by oxidative thermal decomposition were recorded on temperature intervals 310-410 ^{0}C for crosslinked copolymers and 275-375 ^{0}C for crosslinked PVA.

Table 2. Thermal behaviour data.

Sample	T_{10} (^{0}C)	T_{50} (^{0}C)	T_i (^{0}C)	T_f (^{0}C)	$W_{Ti\text{-}Tf}$ (%)	E_a (kJ/mol)	n	T_g (^{0}C)
A_5	250	385	207	390	38.50	105.30	1.8	90
A_{10}	258	400	200	388	32.50	95.50	1.5	99
B_8	130	315	225	340	36.50	195.80	2.1	75
B_{12}	165	310	155	330	40.40	53.20	0.4	89
C_{10}	110	310	230	345	42,50	103.30	1.6	-
C_{12}	173	340	225	353	35.50	101.50	1.3	41
PVA_4	115	275	212	355	41.20	163.50	2.4	65
PVA_{10}	150	375	210	350	32.00	114.80	1.9	112

The activation energy and the reaction order (n) were determined by Coats-Redfern method [12-14] on the main decomposition process (T_i-T_f). The activation energy as a function of the conversion of the thermal decomposition processes (Figs. 5 and 6), presents a quick lowering to a conversion of 0.20 wt %, then its variation is almost linear. The sudden lowering of Ea observed on the first part of the interval, suggests that at the beginning the decomposition reaction has an autocatalytic behaviour, due to oxygen traces in the copolymers that act as catalyst of the thermal decomposition processes.

The glass transition temperature (T_g) of the crosslinked copolymers and crosslinked PVA was determined by differential scanning calorimetry (Fig. 7). The glass transition temperature depends of the structure of the copolymers used to prepare the hydrogels (the molar ratio PVA/LA), and the degree of crosslinking (Table 2). It can be noticed a T_g lowering with lactic acid molar ratio increase in the hydrogel structure and a T_g increase when the degree of crosslinking raises.

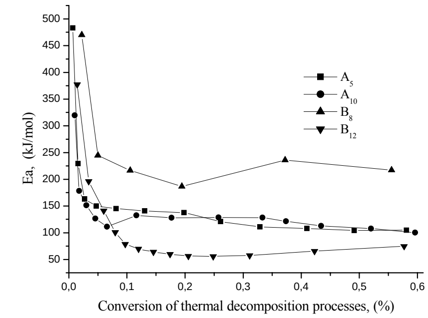


Fig. 5. Dependence of Ea on conversion degree of thermal decomposition processes.

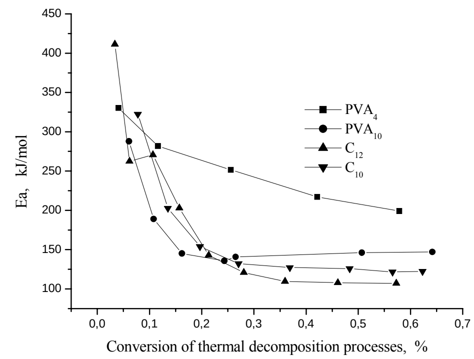


Fig. 6. Dependence of Ea on conversion degree of thermal decomposition processes.

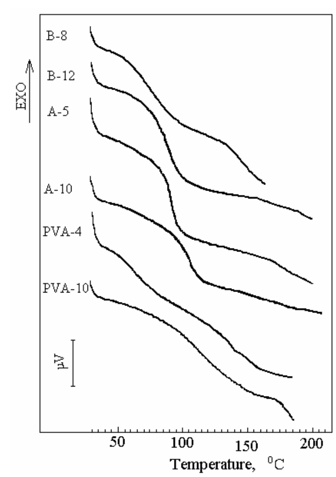


Fig. 7. DSC curves of crosslinked copolymers.

The swelling ratio in phosphate buffer solution (pH=7.4, T=37 ^{0}C) of the synthesized hydrogels are presented in Figs. 8 and 9. The hydrogels were brought to constant weight by vacuum drying at 50-60 ^{0}C, then were immersed in phosphate buffer solution (50 ml). The swelling behaviour was studied for 15 hours, the samples were taken at determined time intervals. Then, the samples were blotted with filter paper to remove the traces of the solution adherent to the surface and weighed at the analytical balance. The buffer solution was replaced after each determination. The swelling ratio (Q) is defined as:

$$Q= (Ws-Wd)/ Wd \quad (1)$$

Ws is the weight of the swollen sample and Wd is the weight of the dried sample.

The swelling behaviour of the copolymers is different and it depends of the copolymer structure (the molar ratio PVA/LA) and crosslinking agent concentration. It was found out that the hydrogels prepared from the copolymer with PVA/LA molar ratio 1.5/1 reach the equilibrium after a longer period of swelling than the hydrogels prepared from the copolymer PVA/LA (2.2/1) and PVA comparatively, and the quantity of water retained has a more raised value (Table 3).

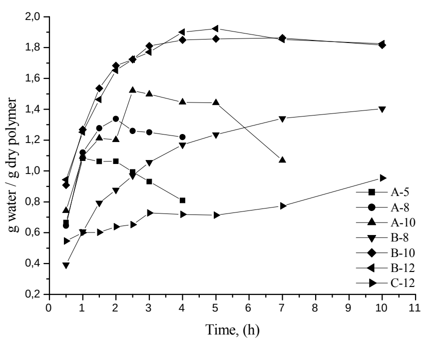


Fig. 8. Swelling ratio of PVA-co-LA copolymers.

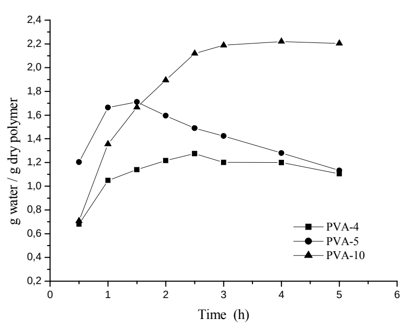


Fig. 9. Swelling ratio of crosslinked PVA.

Table 3. Equilibrium water content.

Sample	Swelling time (h)	water/dry polymer (g/g)
A_5	2	1.063
A_8	2	1.338
A_{10}	2.5	1.522
B_8	10	1.405
B_{10}	10	1.815
B_{12}	5	1.923
C_{12}	10	0.954
PVA_4	2.5	1.275
PVA_5	1.5	1.711
PVA_{10}	4	2.219

4. Conclusions

The copolymers synthesized by grafting reaction of PVA with lactic acid aqueous solution (c=90 %) in different molar ratio PVA/LA, were utilized to obtain hydrogels by crosslinking with sodium tetraborate and triethylenetetramine system. The obtained hydrogels behaved differently by swelling in phosphate buffer solution pH=7.4. This behaviour is determined by the reason that in the copolymers syntheses due to different PVA/LA delivery molar ratio the number of OH unestherified groups that participate at the crosslinking reaction is different and consequently the crosslinking density is different for each copolymer.

The hydrogels obtained from the copolymer PVA/LA (molar ratio 1.5/1) and crosslinking agent concentration 8-12 % presented a better swelling behaviour.

As the raw materials utilized in the copolymer syntheses are biodegradable and biocompatible, the hydrogels will be tested as matrices for achievement of drug delivery systems.

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