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Microporous thermally sensitive hydrogels based on hydroxypropyl cellulose crosslinked with poly-ethyleneglicol diglycidyl ether

E. Marsano*, E. Bianchi, L. Sciutto

Dipartimento di Chimica e Chimica Industriale, Università di Genova, Via Dodecaneso 31, Genova 16146, Italy

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Abstract

New microporous thermally sensitive hydrogels were prepared by crosslinking hydroxypropylcellulose (HPC) with poly-ethyleglicol diglycidyl ether. The crosslinking reaction was carried out in heterogeneous liquid crystalline phase. Phase separation was obtained at room temperature by using the mixed solvent water/dimethylsulfoxide (DMSO). A study of phase equilibrium for the ternary system HPC/water/DMSO is reported. Hydrogels obtained from heterogeneous conditions show a porous structure with interconnected channels characterized by high solvent adsorption rate, while gels obtained from homogeneous solutions show a compact structure. The hydrogels have thermally sensitive behaviour, swelling at low temperature and contracting at high temperature. A thermal cycle corresponding to a reversible process of solvent absorption and deabsorpion is illustrated.

Keywords: Hydrogel; Hydroxypropylcellulose; Thermally sensitive gels

1. Introduction

Hydrogels obtained by crosslinking hydrophilic polymers exhibit strong dependence of their swollen volume on the temperature. The volume change may develop gradually over a range of temperature or abruptly at a specific temperature. In the latter case gels are called 'responsive or environmental sensitive'. One of the more widely known examples are the gels derived from crosslinking reaction on poly(*N*-isopropylacrylamide) (NIPA) which undergo a discrete volume transition from a swollen to a shrunken state at 33.8 °C [1]. Similar transitions were interpreted in terms of 'phase transition' [2–8] and their mechanism was successively clarified [9]. These studies were the basis for developing new materials for applications as sensors, switches, artificial muscle responsive, and drug delivery systems [2–8,10–12].

An important factor for application is not only the maximum amount of water absorbed or released but also the rate of swelling and shrinking. As the response rate has been shown to be determined by the cooperative diffusion coefficient of the polymer chain in the solvent, (about 10^{-7} cm^2/s), the swelling–shrinking rate of a macroscopic sample is very low: a few mm thick gel may need minutes or hours before reaching equilibrium conditions after a change in temperature.

Reduction in the response time needs to decrease the characteristic diffusion path length as the time scales with the square of the dimensions in diffusion-limited process. However, reduction in dimension may not be appropriate for some applications where a certain degree of gel resistance is required. Reducing response time may also be obtained by microporous gels, i.e. gels with pore ranging in size from 0.01 to 100 μm. The swelling and shrinking of microporous gel can be seen as two distinct mass transfer steps: the first consists of the solvent convection through the pores and the second one in the diffusion of the solvent in the polymer struts. By this means the solvent can diffuse by convection at a high rate into or out of the gel through the interconnected pores, and the characteristic diffusional path length is half the thickness of the pore wall instead of the whole sample thickness.

Many researchers attained fast responsive NIPA gels by modifying the method of gel preparation [13–18]. In some cases the increase in the rate has been obtained by a polymerization-crosslink reaction in heterogeneous phase. The phase separation was obtained by conducting the

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* Corresponding author. Tel.: +39-10-3538727; fax: +39-10-3536199.
E-mail address: marsano@unige.it (E. Marsano).

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reaction at a temperature lower than the lower critical solution temperature (LCST).

This approach has been applied to other systems, for example to hydroxypropylcellulose (HPC), a hydrophilic derivative of cellulose that shows particular phase behaviour in aqueous solution. At relatively low polymer concentration, below 40% w/w, an isotropic phase at room temperature is stable. A phase transition to a cholesteric ordered phase occurs [19] by increasing concentration. As HCP aqueous solutions show LCST behaviour, an increase of temperature induces a demixing process in a rich and a lean HPC phase. Due to the high hydrophilicity and the presence of a high number of reactive OH groups and the LCST behaviour, HPC is an ideal polymer suited for hydrogel preparation.

Hu et al. [20] demonstrated, by investigation with laser light scattering, that HPC particles in water can self-associate at a slightly higher temperature than LCST and form metastable nanoparticle aggregates which remain the same size for a few days. A network formed by HPC nanoparticles using divinylsulfone [20,21] as a crosslinker, leads to the formation of microporous hydrogels that swell and shrink at temperatures below and above the LCST, respectively.

The aim of this work is to obtain microporous thermally sensitive HPC hydrogels with a high swelling rate by using a new approach to the phase separation.

The formation of a heterogeneous phase was obtained at room temperature by using HPC in the mixed solvent water/dimethylsulfoxide (DMSO). The phase behaviour of HPC in water/DMSO was studied and the crosslinking process was performed both in heterogeneous and in homogeneous solution.

2. Experimental

2.1. Materials

The HPC sample was obtained from Hercules Inc. Its molecular weight is 80,000 g/mol and its molar substitution is 4. Purification of the polymer was performed by dissolving HPC in water at polymer concentration Cp = 25 wt%, centrifugating at 10,000 rpm for 30 min to eliminate suspended particles, and freeze drying.

DMSO, poly-ethyleneglicol diglycidyl ether (crosslinking agent) and reagent grade sodium hydroxide (crosslinking reaction catalyst) were purchased from Fluka.

2.2. Methods

2.2.1. Gel preparation

Master batches of 30 wt% HPC solution were prepared by dissolving dry frozen HPC in DMSO at room temperature. Some portions of these batches were put into a 40 mm diameter flask, first diluted with DMSO and then with water, slowly stirred for 24 h to ensure uniform mixing while avoiding bubble formation. Some solutions appear homogeneous while others cloudy (see below). A solution of NaOH in water, 10 wt%, was added and the mixture continuously stirred for 24 h. The crosslinker, polyethyleneglicol diglycidyl ether (PEGDE) was then added (wt HPC/wt PEGDE = 1), the stirring was stopped and the solution thermostated at a temperature of 35 or 70 °C for a time varying from 2 to 48 h.

After the crosslinking reaction had ended, the sample was removed from the flask and placed into a distilled water bath at room temperature to remove the unreacted HPC and crosslinker. The water was changed every 4 h over a period of 4 days, and then the crosslinked HPC was freeze dried.

2.2.2. Ternary phase diagram

Ternary mixtures were prepared by mixing known amounts of HPC–DMSO stock solutions with water or NaOH–water solutions. The solutions were stirred by slow rotation at 20 °C for a few days to achieve the phase equilibrium. The mixtures were examined with the polarizing microscope to determine the occurrence of one or more phases and their anisotropy.

2.2.3. Gel swelling

The weight swelling degree SWp of a gel is defined as the ratio between the weight Wg of the swollen gel, and the weight Wp of the dried polymer network (SWp = Wg/Wp). In order to measure SWp, a piece of previously dried and weighed gel, was located in a stainless steel basket and put into water at constant temperature. By measuring the weight of the gel at different times (*t*), it is possible to have a trend of SWp vs. *t*; the swelling generally increases to a plateau (SWeq equilibrium value) in 10–30 min, strictly depending on the crosslinking reaction condition used during gel preparation.

2.2.4. Micro structural characterization

Scanning electron microscopy of freeze-dried HPC hydrogel was performed to obtain information on the pore size and to correlate the porosity to crosslinking conditions. Small pieces of swelled gels were freeze-dried to maintain the porous structure without any collapse. The freeze-dried pieces were plunged in liquid nitrogen and the vitrified samples were cut whit a cold knife. Some freeze-dried samples were placed in to a metallic tube, diameter 2–5 mm, and cut by using a Leica ultramicrotome (ultracut R) with a low temperature Leica EM FCS accessory. No differences between the two method used to prepare the samples were observed. The samples were mounted on SEM stub using silver glue and sputter-coated with gold (20 μm). The microstructure of the HPC samples was imaged using a scanning electron microscope, Cambridge Stereoscan model 440 at 20 kV accelerate voltage.

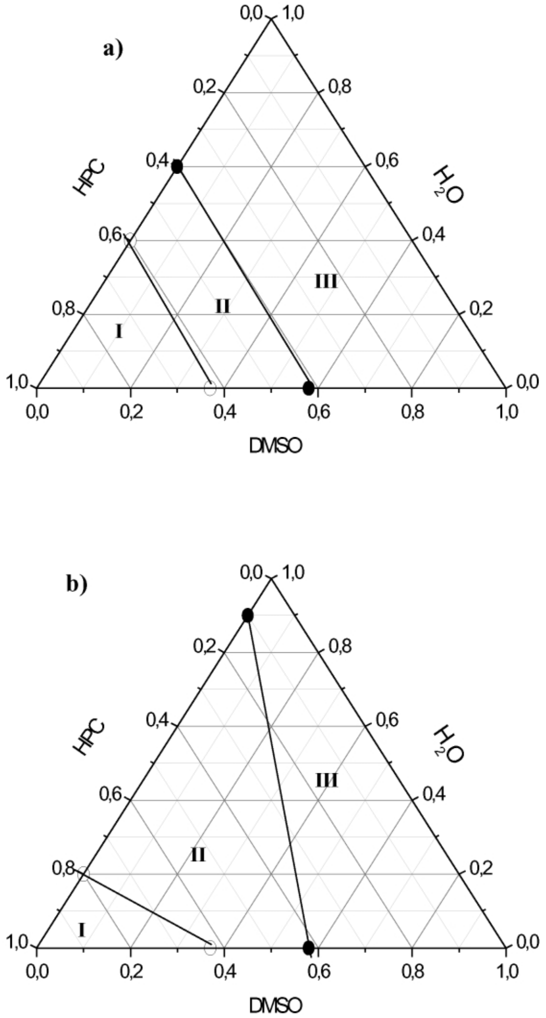

Fig. 1. Hypothetical phase diagrams for HPC in non-interacting water-organic binary solvent. (a) Temperature <40 °C; (b) temperature >40 °C. (I) Anisotropic solution; (II) biphasic gap; (III) isotropic solution.

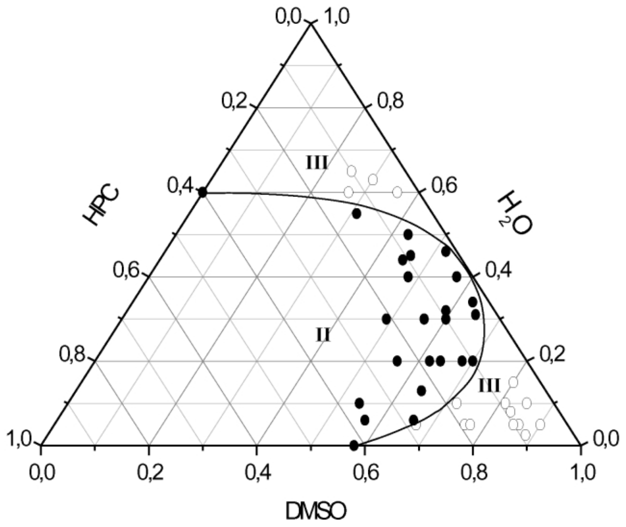

Fig. 2. Phase diagram HPC/H_2O/DMSO at room temperature.

2.2.5. *Effective porosity*

The effective hydrogels porosity was defined by Kabra et al. [21] as the fraction of gel volume occupied by interconnected holes. It can be determined by measuring the weight decreasing, due to the out flow of water, when a mechanical pressure is applied to the swollen gel. Samples of about 0.5 g (W_0) were placed between two absorbent ceramic disk and repeated pressed, pressure 30–50 MPa, up to constant weight (W_f). The effective porosity γ is obtained by the ratio: $\gamma = (W_o - W_i)/W_o$.

3. Results and discussion

A few hydrogel samples, based on HPC crosslinked with poly-ethyleneglicol diglycidyl ether ($M_w = 526$), were prepared according to the procedure described in the experimental part. The crosslinker, selected among hydrophilic compounds to improve the swelling behaviour of HPC networks in water, may not simply be used in aqueous solution as a competing reaction between epoxy groups and water molecules prevails on the crosslinking process. However, the addition of suitable amount of a polar organic solvent, like DMSO, allows gels to synthesize, as explained in the following. It is useful to remember a few general points: DMSO is a good HPC solvent, which forms monophasic isotropic solutions up to 42 % (Cp') polymer concentration. At Cp' an HPC anisotropic liquid crystalline (LC) phase starts to form: a narrow biphasic gap containing both iso and aniso phases may be observed and, if we further increase the polymer concentration, only the LC phase will be stable. This behaviour is absolutely similar to the one we observed in other organic solvents [22,23] and in water [19] at room temperature. The narrow biphasic gap moves towards higher Cp by increasing the temperature for all the

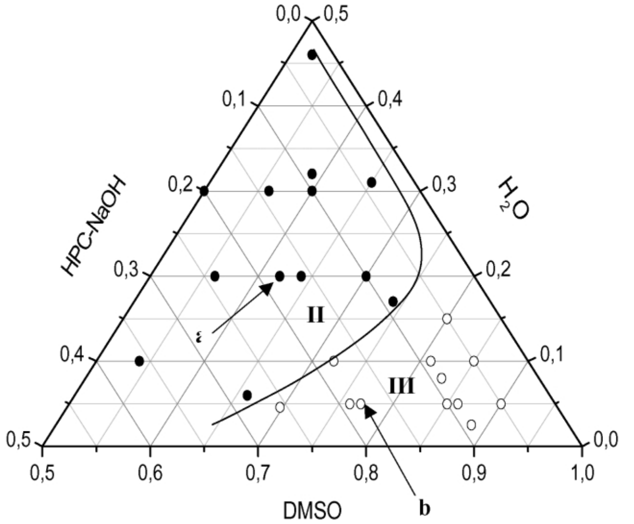

Fig. 3. Phase diagram HPC-NaOH/H_2O/DMSO at room temperature. HPC/NaOH = 7.14 (w/w). (a) Heterogeneous and (b) homogeneous mixtures selected to perform the crosslink.

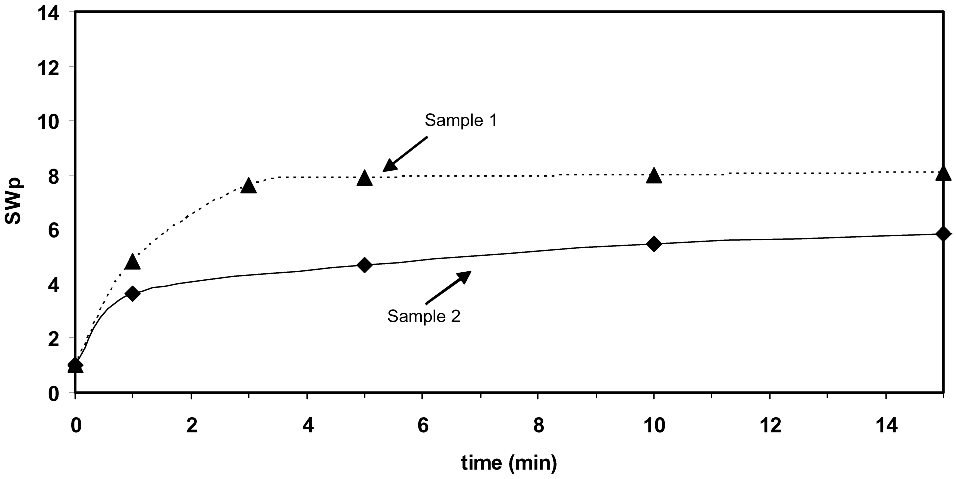

Fig. 4. Swelling degree (SWp) vs. time for gels obtained from homogeneous solution (full-line) and heterogeneous solution (dotted line).

Table 1
Composition of the solutions subjected to crosslinking reaction with poly-ethyleneglicol diglycidyl ether, microstructural characterization and swelling behaviour

Sample	HPC/NaOH[a] (w/w, %)	DMSO (w/w, %)	H_2O (w/w, %)	Temperature (°C)	Reaction time (h)	Phase	Effective porosity (γ)	Pore size diameter (μm)	SWeq.
1	18	62	20	35	48	Heterogeneous	0.3	3–10	8
2	18	77	5	35	48	Homogeneous	n.d.	No pore	5
3	18	62	20	70	2	Heterogeneous	0.7	0.5–3	12

n.d. = not detectable
[a] Ratio HPC/NaOH equal to 7.14.

systems, probably due to the increase of polymeric chain flexibility [24]. When the temperature is higher than about 40 °C [25] a wide miscibility gap forms in water at any polymer concentration so that a very diluted isotropic phase and a very concentrated anisotropic one are in equilibrium. This behaviour has never been observed in organic solvent. So, when HPC is dissolved in a mixed water/organic solvent, two hypothetical phase diagrams (Fig. 1a and b) may be anticipated.

Fig. 1a refers to the room temperature and Fig. 1b to the temperature over 40 °C. It is evident that the heterogeneous area II increases with the rise in temperature. These hypothetical phase diagrams have been designed supposing that the polymer–solvent interactions were the same for both solvents and that the mixture of water/organic solvent was considered athermal. Anyway these hypotheses rarely occur.

Nowadays various physico-chemical behaviours related to organic/aqueous binary systems are known [26]. Viscosity of DMSO/water mixtures shows a maximum at

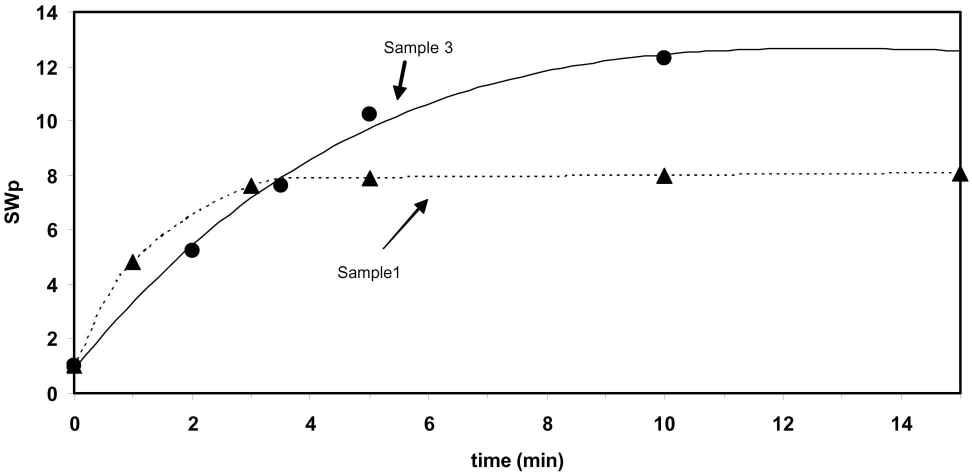

Fig. 5. SWp vs. time for gels crosslinked from heterogeneous solution at 35 °C (dotted line) and 70 °C (full line).

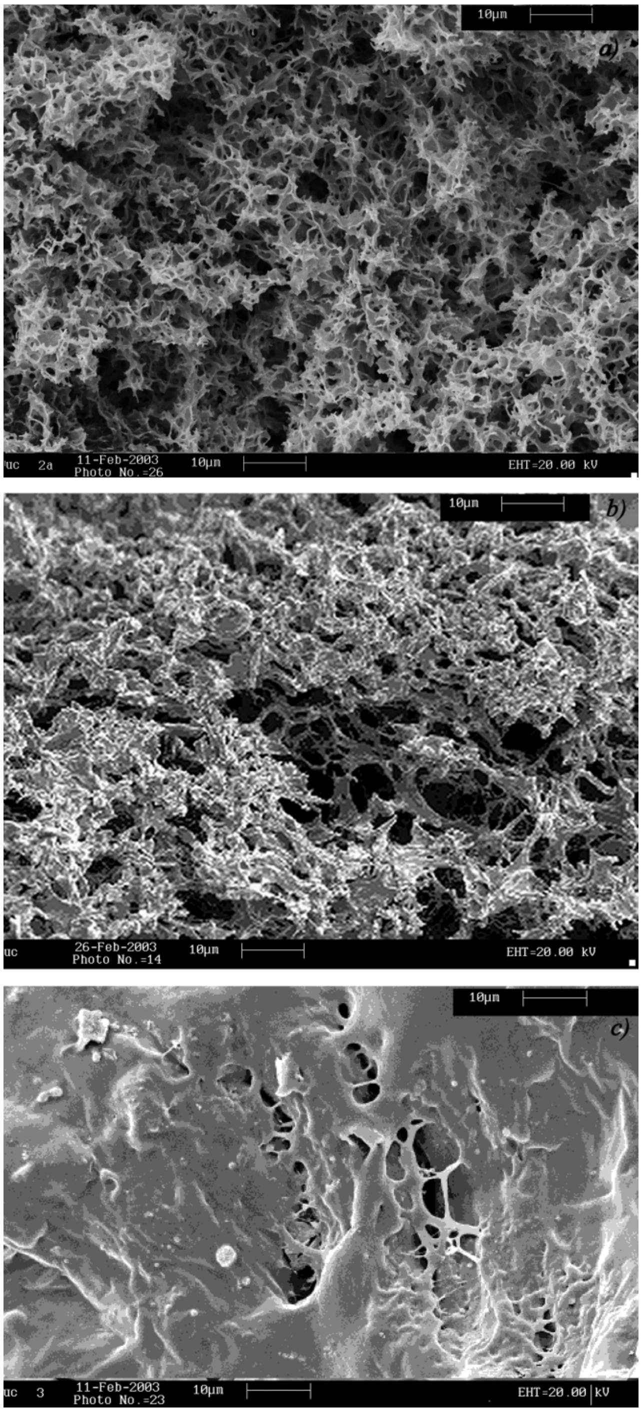

Fig. 6. SEM micrographs of freeze-dried gels. Gel crosslinked in heterogeneous phase (a) sample 3; (b) sample 1 crosslinked in homogeneous phase; (c) sample 2.

DMSO mass fraction $\cong 0.7$ and it has been interpreted as a self association of the small organic solvents in aqueous media [26]. Segregation of chemically distinct environments, which do not necessarily affect the macroscopic homogeneity are considered responsible for the phenomenon. On this basis, we expect a noticeable effect of the mixed solvent on the phase diagram. Fig. 2 shows the experimental diagram HPC/H_2O/DMSO at room temperature. A wide heterogeneous biphasic region, area II, is delimited from the curve which goes from Cp' in water to Cp' in DMSO. Observation under optical microscope confirms the presence of a liquid crystalline phase within this area. Area III is related to homogeneous isotropic solutions and tends to contract as temperature increases. Concerning the gels, areas II and III were selected to make a comparison among gels obtained by crosslinking HPC in heterogeneous and homogeneous conditions.

Another problem concerned the choice of crosslinking conditions since epoxy groups need basic solutions and a suitable temperature to react. This may be overcome by adding NaOH to the ternary mixture HPC/H_2O/DMSO, but does not have a negligible influence on the phase diagram. After some attempts, the weight ratio HPC/NaOH = 7.14 appeared to be the optimum one and a new ternary diagram, whose components are H_2O, DMSO and HPC/NaOH instead of neat HPC, was determined. The result is shown in Fig. 3, where only the left portion of the ternary diagram is quoted. A comparison with Fig. 2 shows that area III is narrower in this case. On this basis we have selected the mixtures (a) homogeneous and (b) heterogeneous to perform the crosslink.

The process was performed at a temperature of 35 or 70 °C, as described in Section 2. Three gel samples were prepared starting from solutions of areas II and III (Fig. 3). Table 1 gives the composition of the initial solution (columns 2, 3, 4, 5), the synthesis temperature (column 6), the crosslinking time (column 7), the phase composition at room temperature (column 8) and the maximum gel swelling in water at room temperature (column 9). HPC concentration was kept constant to decrease the number of variables; moreover, significant higher concentration gave too rigid gels, while significant lower concentration gave non self-supporting gels. Fig. 4 makes a comparison between SWp of samples obtained from a homogeneous solution (5% H_2O) and heterogeneous solution (20% H_2O) crosslinked at 35 °C. The equilibrium swelling is higher in the second case, as expected on the basis of previous works [13–18], where the usefulness of crosslinking heterogeneous systems was clearly demonstrated. However, it

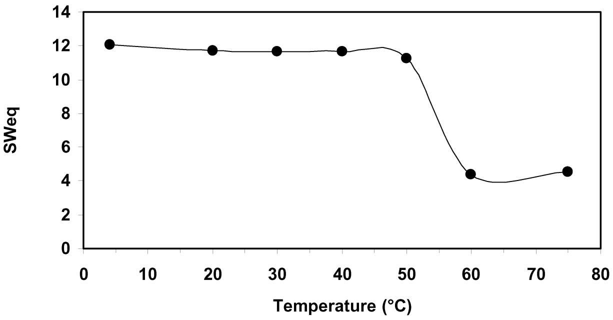

Fig. 7. Equilibrium swelling degree (SWeq) vs. temperature of a gel prepared from heterogeneous solution at 70 °C.

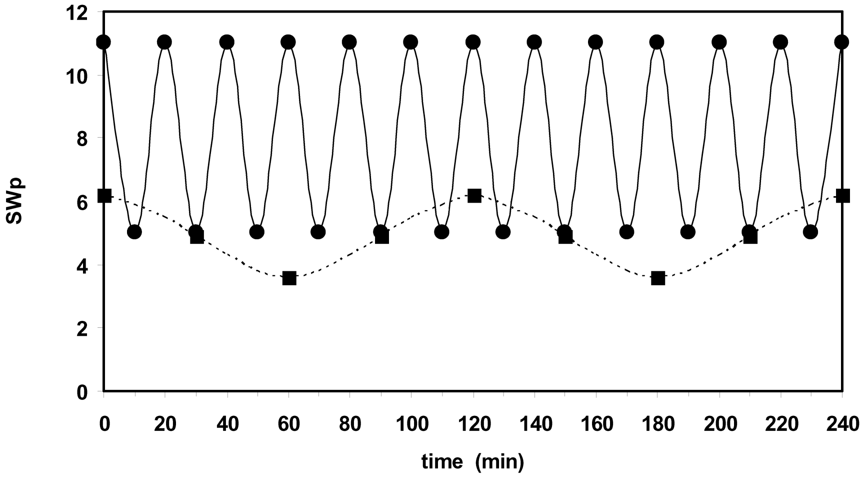

Fig. 8. Trend of SWp as a function of time by varying the temperature from 60 to 20 °C (full-line; sample 3) and from 50 and 11 °C (dotted line; copolymer HPC-polyvinylpyrrolidone [28]).

may be useful to observe that in this case the crosslinking time only takes a few days, allowing a progressive phase separation during the crosslinking process which reduces the likelihood of obtaining large swelling values. Fig. 5 supports the previous conclusion, showing that the same heterogeneous solution (sample 1–3, Table 1) crosslinked at 35 and 70 °C, gives gels with different swelling behaviours. The crosslinking time decreases to 2 h at 70 °C, resulting in the synthesis of a more swellable system. The SEM micrograph of sample 3 (Fig. 6a) shows a porous structure with interconnected channels (pore cross section 0.5–3 μm). The effective porosity, $\gamma = 0.7$, confirms the interconnected pore morphology, which justifies the high and quick solvent absorption. Sample 1 obtained in heterogeneous phase but with longer reaction time shows a different morphology, (SEM micrograph figure Fig. 6b), the pores are fewer, pore size are 3–10 μm, and seem to be dispersed in a continuous phase. The lower value of the effective porosity, $\gamma = 0.3$, confirms the lower porosity, associated to lower swelling rate of the sample. These results can be due to a progressive phase separation and to a degree of crosslinking in the homogenous concentrated phase higher with formation of a less microporous structure, Samples 2 obtained by crosslinking homogeneous solutions are completely different: a compact structure without evident pore but only some large channel, as shown in Fig. 6c and not detectable effective porosity confirms the formation of a non porous gels.

Environmental behaviour concerning temperature variation were tested with sample 3. Fig. 7 gives SWeq. vs. temperature between 5 and 75 °C. A sharp jump from SWeq. 12 to SWeq. 4 at a temperature of 55 °C was observed. Similar behaviour has previously been observed by some of us for HPC methacrylate [27]. However, the jump occurs at lower temperature, in the 37–43 °C range depending on the amount of the methacrylic component, and it is never very sharp. The difference in the jump temperature can be correlated to the type and to the extent of modification of HPC polymer. While methacrylic substituents decrease, the hydrophylicity of HPC derivatives, with consequent decreases of LCST [25] polyethyleneglicol diglycidyl ether being hydrophilic, could have an opposite effect. Finally, we would like to note the interesting characteristics of the swelling and deswelling cycle induced by a variation in temperature. When a piece of gel (sample 3) is put in contact with water at 20 °C, it swells and if temperature is increased to 60 °C, it deswells. It takes about 10 min for swelling, until 12, and deswelling, until 4. This process may be repeated many times, with excellent reproducibility of the degree of swelling and with a fast response. Fig. 8 shows a comparison of the cycle of our gel with that of HPC/PVP copolymer [28]. In a period of 240 min 12 swelling–deswelling cycles of our gel are compared to the two cycles of HPC/PVP copolymers: this behaviour highlights the efficacy of a microporous structure with respect to a compact one.

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