



*Dedicated to Professor Bogdan C. Simionescu
on the occasion of his 65th anniversary*

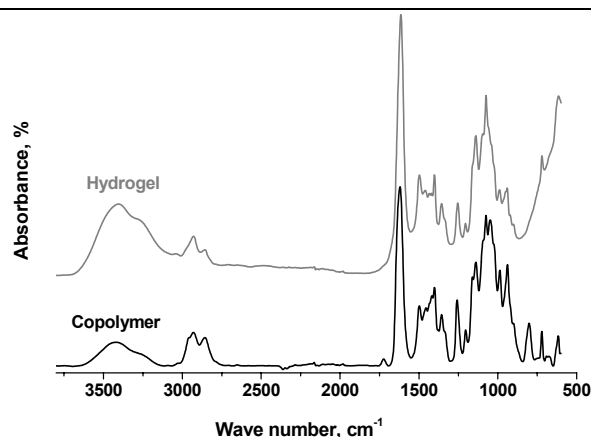
HYDROGEL BASED ON POLY(N, N-DIMETHYLACRYLAMIDE-co-3, 9-DIVINYL-2, 4, 8, 10-TETRAOXASPIRO (5.5) UNDECANE) WITH DUAL SENSITIVE BEHAVIOR. SYNTHESIS AND CHARACTERISATION

Loredana E. NITA, Aurica P. CHIRIAC,* Manuela T. NISTOR and Iordana NEAMTU

“Petru Poni” Institute of Macromolecular Chemistry, 41A Grigore Ghica Voda Alley, 700487 Iași, Roumania

Received September 19, 2012

The preparation of a new hydrogel based on poly(N,N-dimethylacrylamide-co-3, 9-divinyl-2, 4, 8, 10-tetraoxaspiro (5.5) undecane) crosslinked with N, N' – methylene-bis-acrylamide is presented. The hydrogel composition is proved by FTIR and ¹H-NMR spectra which include specific peaks of the comonomers as well as show the formation of the crosslinking bridges between copolymer and N, N' – methylene-bis-acrylamide. The morphology, water sorption capacity, and swelling kinetic were investigated by various techniques. The study demonstrates the superabsorbent character of the new hydrogel which as well presents higher hydrophilicity and sensibility at temperature and pH.



INTRODUCTION

Hydrogels based on synthetic biopolymers find numerous applications in the biomedical devices and tissue engineering due to their high water content and tissue like physical, bio-chemical and mechanical properties.^{1,2} The advantages of hydrogels based on synthetic polymers rely on the ability to adjust their properties through tailored polymer synthesis and choice of the crosslinking procedure. This allows the control over the swelling degree, stability and biodegradability, mechanical strength and enables the generation of responsive-

ness to external stimuli. Usually, hydrogels are used as injectable or preformed single phase materials for drug delivery or as matrix for the encapsulation of bacteria, cells or drugs.³

The hydrogels have numerous applications in drug delivery,^{4,5} tissue engineering,^{6,7} biocatalysis⁸ or food technology. In this study we point up the synthesis of a new hydrogel based on poly(N,N-dimethylacrylamide-co-3, 9-divinyl-2, 4, 8, 10-tetraoxaspiro (5.5) undecane) crosslinked with N, N' – methylene-bis-acrylamide. The novelty is given by the copolymer structure which has gel formation capacity, binding properties, amphiphilicity, good oxidative and thermal stability, biocompatibility,

* Corresponding author: achiriac1@yahoo.com

good films forming, and pH sensitive response.^{9,10} The thermosensitive character of this compound was already established. Taking this in the consideration, the synthesis of the new hydrogel based on poly(N,N-dimethylacrylamide-co-3, 9-divinyl-2, 4, 8, 10-tetraoxaspiro (5.5) undecane) can be of interest for the future biomedical applications.

RESULTS AND DISCUSSION

The **FTIR spectra** of both copolymer and hydrogel are illustrated in Fig. 1. The FTIR spectrum of the copolymer shows peaks at specific regions which are in agreement with the expected peaks for this copolymer. The presence of DMA is displayed by a strong absorption at about 1620 cm^{-1} attributed to the free amide carbonyl groups. The spiroacetal moiety's inclusion is also confirmed by the presence of strong bands in the region of $1000\text{--}1200\text{ cm}^{-1}$ and at 1720 cm^{-1} (due to ether C-O-C stretching).

The hydrogel spectrum confirms the crosslinking reaction presenting a new peak at 3334 cm^{-1} corresponding to -NH stretching of the N, N' - methylene-bis-acrylamide unit. Also, the bands from 1722 cm^{-1} (C=O carbonyl), 1433 cm^{-1} (CH_3 bending vibrations), 1160 cm^{-1} and 1048 cm^{-1} (C-O vibrations) disappear, being involved in the crosslinked bridges.

In **$^1\text{H-NMR}$ spectrum** of the copolymer (Fig. 2) the proton peaks corresponding both to 3, 9- divinyl-2,4,8,10-tetraoxaspiro[5.5]undecane and N,N-dimethylacrylamide are: δ (ppm) = 7.26 (CDCl_3), 7.56 (OH), 7.3-7.34 ($\text{CH}_2=\text{CH}_2$), 4.663 ($-\text{CH}_2=\text{C}-$), 3.264 ($-\text{CH}_2\text{O}-$), – characteristics for U and at 3.087 ppm ($-\text{N}-\text{CH}_3$) and 3 ppm (CH) – characteristics for DMA. The hydrogel $^1\text{H-NMR}$ spectrum presents significant differences. Thus, the peaks from 7.56 ppm and 7.3-7.34 ppm disappear and the new peaks are registered between 4 ppm to 6 ppm which sustain the new bridges formed during the crosslinking process between N, N' - methylene-bis-acrylamide and the copolymer.

Scanning electron microscope (SEM) microphotograph for longitudinal cross-section of hydrogel is presented in Fig. 3. The sample cross-section revealed the homogeneous porous structure of the gel which was attributed to the preformed 3D macroporous network.

Water vapors sorption capacity for the samples at 37°C in the 0-90 % relative humidity range (RH) was investigated by using the IGAsorp equipment. The vapors pressure was increased step by step with 10% humidity, every step having a pre-established equilibrium time between 10 to 20 minutes. The registered sorption/ desorption isotherms are presented in Fig. 4.

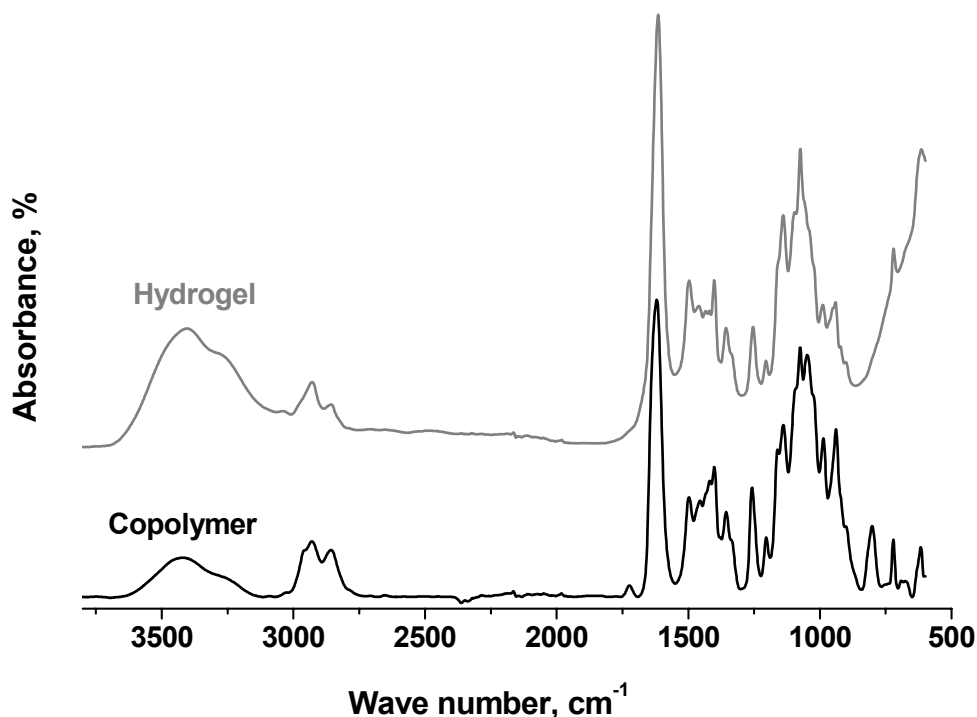


Fig. 1 – FTIR spectra of the hydrogels synthesized in comparison with the copolymer spectra.

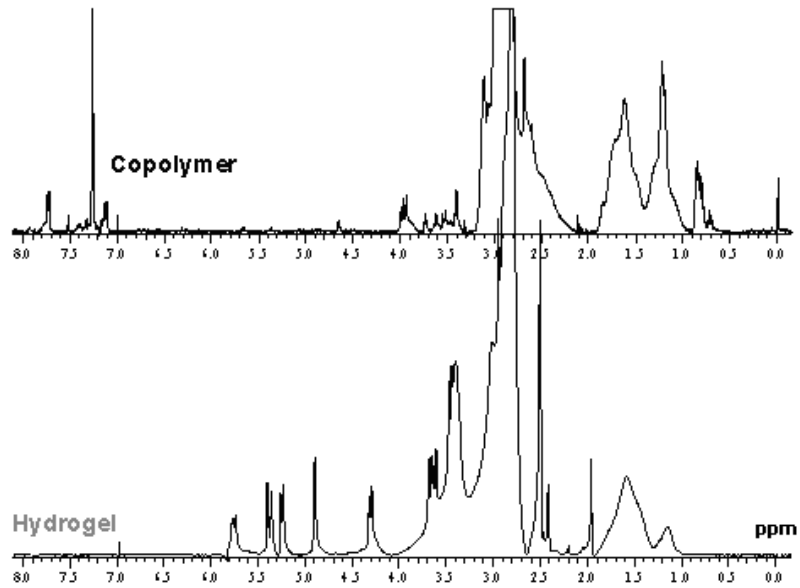


Fig. 2 – $^1\text{H-NMR}$ spectra of the hydrogels synthesized in comparison with the copolymer spectra.

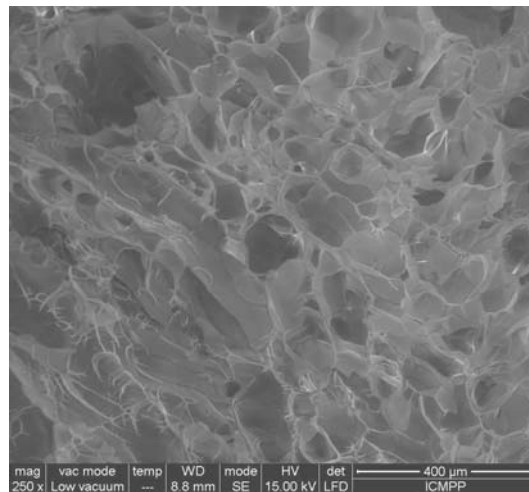


Fig. 3 – SEM microscopy of the hydrogel.

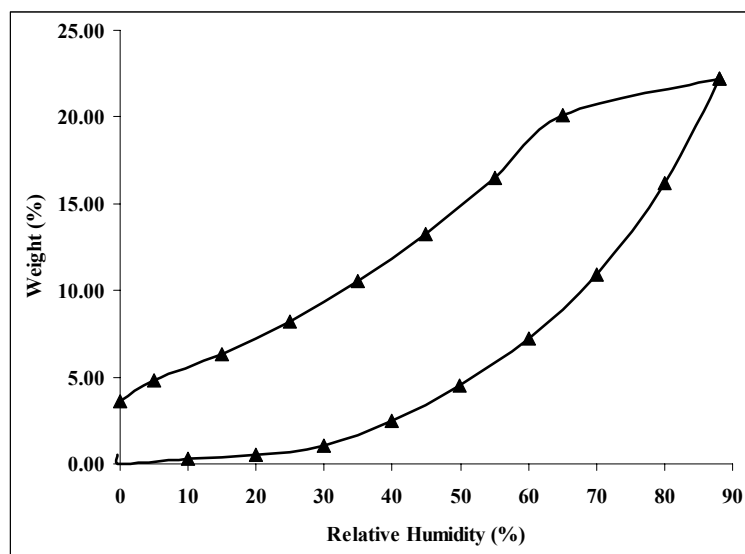


Fig. 4 – The sorption/desorption isotherms.

Table 1

The Main Parameters from Water Sorption–Desorption Isotherms

Sample	Weight (%d.b.)	BET analysis	
		A _{BET} (m ² /g)	Monolayer (g/g)
	22.2100	251.539	0.0716

It is known that the sorption/desorption isotherms are the result of the complex processes arisen in interdependence with the material type, size, shape and electronic structure. The difference of the equilibrium properties between water sorption and desorption is not unusual for polymer systems or other materials and has been reflected in hysteresis. There may be different causes for the hysteresis, like shrinkage of the materials, sorption sites that may resist to water vapor when they are filled with gas after drying. The explanation for hysteresis is based on a change of geometry during the adsorption and desorption process.¹¹

Fig. 4 shows water sorption at 37 °C, expressed as the total water uptake per sample mass, as a function of the environmental relative humidity (sorption isotherms) for the prepared hydrogel. The shape of water vapor sorption isotherms and the amount of adsorbed water are dependent on the characteristics of the studied sample. Thus, physically bound water can be adsorbed onto the surface or inside the material structure or could be capillary condensed in pores. The BET surface area analysis kinetic models applied to determine the specific surface area of powders, solids and granules (the values are expressed in meter square per gram) gave values depicted in Table 1.

This model is very often used for modeling the sorption isotherms and is based on the following BET equation:

$$W = \frac{W_m \cdot C \cdot RH}{(1 - RH) \cdot (1 - RH + C \cdot RH)} \quad (1)$$

where: W is the weight of the adsorbed water; W_m is the weight of the water forming a monolayer; C is the sorption constant; RH – relative humidity. BET model describes the sorption isotherms up to a RH of 40%, depending on the type of sorption isotherm and on the type of material. This method is limited mainly to isotherms of type II but can also describe the isotherms of types I, III, and IV.¹² According to the values presented in Table 1 and as can be seen from Fig. 4, the prepared hydrogel based on poly(N,N-dimethylacrylamide-co-3, 9-divinyl-2,4,8,10-tetraoxaspiro (5.5) undecane) has higher water sorption capacity owing to the

increase in hydrophilicity, property which improves the biocompatibility of the copolymer.

The Swelling studies for the samples in buffer solution (at pH = 7.4) and at the two temperatures: 25°C and 37°C – illustrated in Fig. 5 – reflect the subsequent applications for this type of hydrogels. The swelling degree behavior shows the dependence of this characteristic on the temperature and evidences the superabsorbent character of the synthesized hydrogel. Thus, the hydrogel swelling degree increases from about 2400% at 25°C to 3200% at 37°C.

The swelling kinetic of the analyzed hydrogel sample is presented in Table 2. To elucidate the mechanism of swelling, the equation proposed by Korsmeyer and Pepas (2)¹³ was used:

$$F = \frac{W_t}{W_{eq}} = kt^n \quad (2)$$

where: F – is the fractional uptake at predetermined time t ; k – is the swelling characteristic constant; W_t and W_{eq} – are the amount of buffer solution absorbed by the polymeric network at the predetermined t time and at equilibrium; n – is the diffusion exponent, which is indicative for the swelling mechanism. The diffusion exponent (n), resulted from the kinetic studies, was obtained by fitting the fractional change mass (M_t / M_∞) for $W_t / W_{eq} \leq 0.6$. From the experimental data result the strong dependence of the swelling kinetic on temperature. Thus, at 25°C the hydrogel presents a Fickian diffusion of the buffer in the polymeric network. The temperature increase to 37°C determines a non Fickian diffusion. This behavior suggests the thermo-responsive character of synthesized hydrogel.

The influence of the pH upon the physical-chemical properties of the hydrogel is essentially for its future biomedical applications. In this context the swelling tests in the range between 4 to 11 pH, were made. The swelling capacity of the hydrogel depends as well on the pH as it is illustrated in Fig. 6. Thus, the swelling degree is growing when the buffer pH increases from 4 to 7, but it decreases considerable at pH=8. This abrupt

change into the swelling degree when pH is switched from 7 to 8 is an important fact by

allowing the obtainment of pulsatile drug delivery systems.

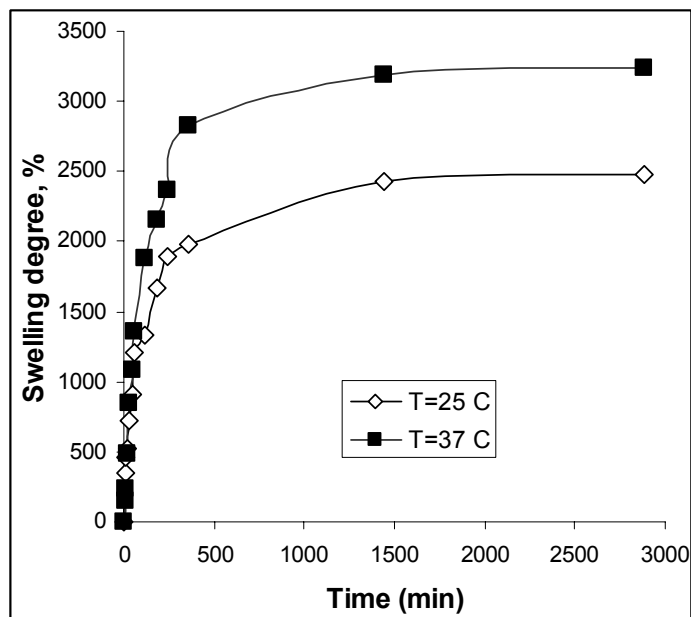


Fig. 5 – The swelling behavior of the hydrogel at two different temperatures: 25°C and 37°C.

Table 2

The kinetic parameters of swelling according to Korsmeyer-Pepas kinetic based model

Swelling kinetic at 25°C			Swelling kinetic at 37°C		
n	k	R ²	n	k	R ²
0.4226	0.3246	0.9971	0.9444	0.8773	0.9911

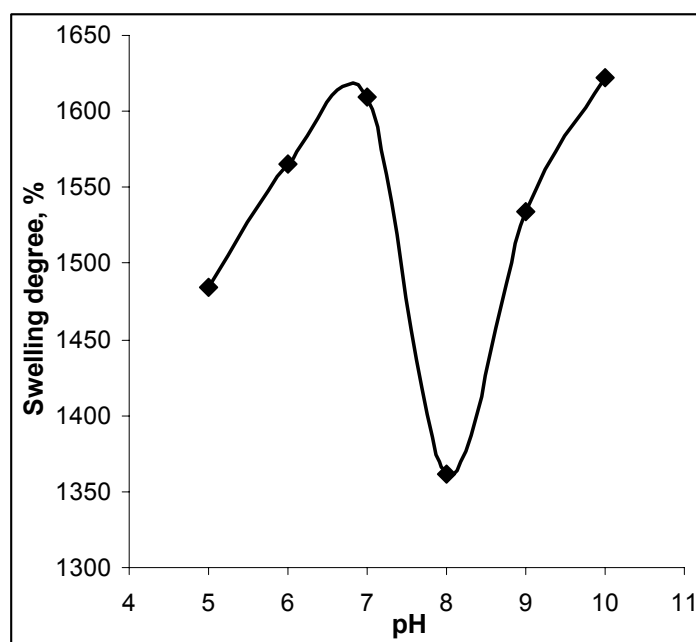


Fig. 6 – The swelling behavior of the hydrogel at different pH values.

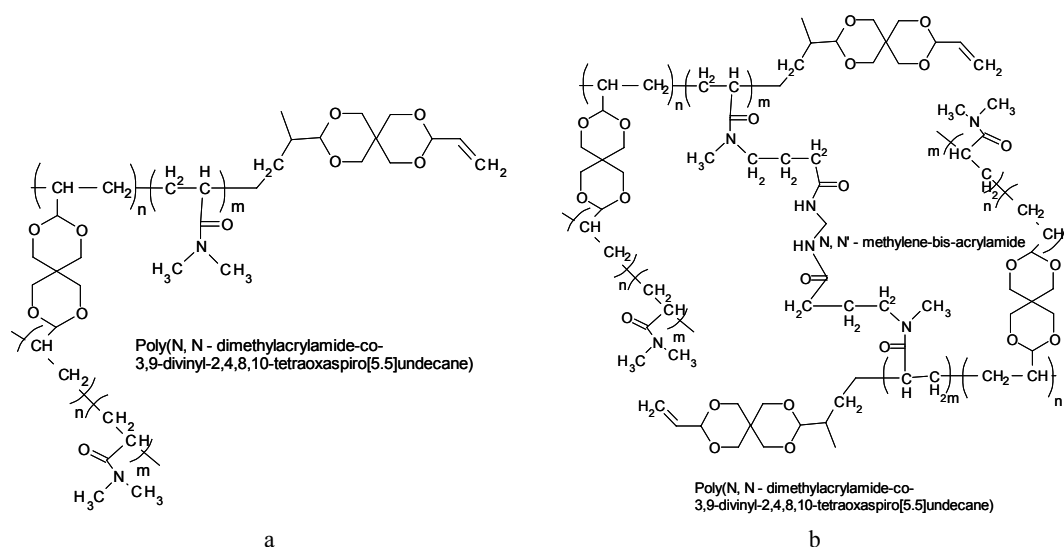


Fig. 7 – The idealized structure: poly(N,N-dimethylacrylamide-co-3, 9-divinyl-2, 4, 8, 10-tetraoxaspiro (5.5) undecane) (a) and gel based on the copolymer crosslinked with N, N' – methylene-bis-acrylamide (b).

EXPERIMENTAL

Materials and synthesis

The synthesis procedure of the copolymer based on N,N-dimethylacrylamide (DMA) (from Sigma – Aldrich, used without purification), and 3, 9-divinyl-2, 4, 8, 10-tetraoxaspiro (5.5) undecane (U) (from Sigma-Aldrich, used without purification), was presented before.^{9,10} Shortly the synthesis was performed through radical polymerization in N, N-dimethylacetamide solution in the presence of dibenzoyl peroxide (BPO) as initiator.

The hydrogel was then obtained by crosslinking poly(N, N-dimethylacrylamide-co-3, 9-divinyl-2, 4, 8, 10-tetraoxaspiro (5.5) undecane) with N, N' – methylene-bis-acrylamide in the presence of ammonium persulfate (initiator from Sigma) and N, N', N'-tetra-methyl-ethylene-diamine (reaction accelerator from Sigma). The copolymer and gel idealized structures are presented in the Fig. 7.

The water used in all experiments was purified using an Ultra Clear TWF UV System.

Characterization

FTIR spectra of the polymers were recorded on a Vertex Bruker Spectrometer in an absorption mode ranging from 400 to 4000 cm^{-1} . The polymeric sample was grounded with potassium bromide (KBr) powder and compressed onto a disc for analysis. Spectra were acquired at 4 cm^{-1} resolution as an average of 64 scans.

¹H-NMR experiments were performed with a Bruker Avance DRX 400 spectrometer equipped with a 5-mm broad band probe. ¹H-NMR spectra were recorded at a frequency of 400 MHz in CDCl_3 .

SEM studies were performed on samples (previously dried by lyophilization), fixed by means of colloidal copper supports. The samples were covered by sputtering with a thin layer of gold (EMITECH K 550x). The coated surface was examined by using an environmental scanning electron microscope type Quanta 200 operating at 30 kV with secondary electrons in high vacuum mode.

Water vapors sorption capacity of the samples was measured by using the fully automated gravimetric analyzer IGAsorp supplied by Hiden Analytical, Warrington (UK). An ultrasensitive microbalance measures the weight change as the humidity is modified in the sample chamber at a constant regulated temperature. The measurement system is controlled by a user-friendly software package. The drying of the samples before sorption measurements was carried out at 37°C in flowing nitrogen (250 mL/min) until the weight of the sample was in equilibrium at RH<1 %.

Dynamic swelling measurements were performed in buffer solutions at two temperatures, 24°C and 37°C. The amount of the adsorbed solution was monitored gravimetrically: swollen particles were regularly extracted from the swelling medium, wetted on the surface, weighed and placed again in the same bath. The measurements were continued until constant weight was reached for each studied sample. The degree of swelling (q) was calculated as follows:

$$Q, \% = [(M(t) - M_0) / M_0] * 100\% \quad (3)$$

where M(t) is the weight of the swollen particles at time t and M₀ is the weight of the sample before swelling. All the swelling experiments were performed in triplicate.

CONCLUSIONS

A new hydrogel based on poly(N,N-dimethylacrylamide-co-3, 9-divinyl-2, 4, 8, 10-tetraoxaspiro (5.5) undecane) crosslinked with N, N' – methylene-bis-acrylamide it was prepared. Both monomers bring for copolymer especially attributes as for example network formation, biodegradability and biocompatibility, gel formation capacity, binding properties, amphiphilicity, good oxidative and thermal stability, good films formers, acid pH sensitivity. The formation of the hydrogels was evidenced by FTIR and ¹H-NMR spectra

which show the formation of the crosslinking bridges between copolymer and crosslinker agent. Morphology, water sorption, and swelling behavior were investigated by various techniques. SEM micrograph confirms a homogeneous porous structure attributed to the formation of 3D macroporous network. The behavior during sorption/ desorption of water evidences the hydrophilicity of the polymeric system. The variation of the swelling degree shows the dependence of this parameter on temperature evidencing as well the superabsorbent character of the synthesized hydrogel. Thus, the swelling degree increases from about 2200% corresponding to the hydrogel swelled at 25°C to about 3200% in case of the hydrogel swelled at 37°C. At the same time, the swelling tests in the range of 4 – 11 pH evidence an abrupt change in the swelling degree at switching the pH from 7 to 8. This behavior is important in recommending the polymeric network for pulsatile drug delivery systems.

Acknowledgements: This work was financially supported by the grant of the Roumanian National Authority for Scientific Research, CNCS-UEFISCDI, project number PN-II-

211/2012 “Interdisciplinary research on multifunctional hybrid particles for bio-requirements”.

REFERENCES

1. A. S. Hoffman, *Adv. Drug Delivery Rev.*, **2002**, *43*, 3.
2. W. Pilnik and F. M. Rombouts, *Carbohydr. Res.*, **1985**, *142*, 93.
3. A. Dhanasingha and J. Groll, *Soft Matter.*, **2012**, *8*, 1643.
4. K. Y. Lee and S. H. Yuk, *Prog. Polym. Sci.*, **2007**, *32*, 669.
5. P. B. Malafaya, G. A. Silva and R. L. Reis, *Adv. Drug Deliv. Rev.*, **2007**, *59*, 207.
6. A. Montembault, C. Viton and A. Domard, *Biomaterials*, **2005**, *26*, 933.
7. T. Jiang, S. G. Kumbar, L. S. Nair and C. T. Laurencin, *Curr. Top. Med. Chem.*, **2008**, *8*, 354.
8. F. Van de Velde, N. D. Lourenco, H. M. Pinheiro and M. Bakker, *Adv. Synth. Catal.*, **2002**, *344*, 815.
9. A. P. Chiriac, L. E. Nita, I. Neamtu and M. Nistor, OSIM Patent Application A/00371/24.05.2012.
10. A. P. Chiriac, M. T. Nistor, L. E. Nita and I. Neamtu. Submitted for publication to *Rev. Roum. Chimie*.
11. A. Nistor, G. Stiubianu and C. Racles, M. Cazacu, *Materiale Plastice*, **2011**, *48*, 33.
12. M. Alexandru, M. Cazacu, M. Cristea, A. Nistor, C. Grigoras and B. C. Simionescu, *J. Pol. Sci. Part A: Polymer Chemistry*, **2011**, *49*, 1708.
13. N. A. Peppas and N. M. Franson, *J. Pol. Sci. Polym. Phys. Ed.*, **1983**, *21(6)*, 987.

