THERMO-SENSITIVITY OF N-VINYL PYRROLODONE-CO-2-HYDROXYETHYLMETHACRYLATE HYDROGELS

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Abstract— **The copolymerization of HEMA with different hydrophilic and hydrophobic co-monomers allows for the manipulation of their intrinsic properties. 2-Hydroxyethylmethacrylate (HEMA)-based hydrogels thus are of great interest due to their outstanding physico-mechanical properties and chemical stability. The idea to use HEMA in order to create thermo-sensitive polymers was based on our assumption that thermal-sensitivity comes from a suitable hydrophilic-hydrophobic balance of macromolecules. In this work we have chosen N-vinyl pyrrolidone as a hydrophilic co-monomer with the relatively hydrophobic HEMA due to its good polymerizing properties as well as its non-toxicity in a polymer state and deserved recognition as a biocompatible material. As a result, copolymerization of NVP and HEMA was successful in obtaining new types of thermo-sensitive polymers composed of hydrophilic and hydrophobic monomers.**

I. INTRODUCTION

2-Hydroxyethylmethacrylate (HEMA)-based hydrogels are of great interest due to their outstanding physico-mechanical properties and chemical stability. Biocompatibility, oxygen permeability and transparency of the hydrogels cause their wide application in medicine as contact lens materials [1]. Their unique swelling behavior, easy diffusion of solvents and low molecular weight compounds in, through and out of the HEMA-based materials have stimulated an extensive interest in their application as a controlled drug delivery system [2, 3] and implant materials [4, 5].

The copolymerization of HEMA with different hydrophilic and hydrophobic co-monomers allows for the manipulation of their intrinsic properties, such as water uptake, swelling kinetics and permeability, etc in resulting materials. Alkyl methacrylates are frequently used as hydrophobic co-monomers. These include acrylic [2] and methacrylic [4, 6] acids, acrylamide [7] and specific co-monomer N, N'-dimethyl-(acrylamido-propyl) ammonium propane sulfonate [8] among the hydrophilic species copolymerized with HEMA. Copolymers of HEMA with N-vinyl pyrrolidone (NVP) are well known as much-used biomaterials, mostly in a hydrogel state [2, 5, 9-11]. Recently Gallardo A. with coworkers issued a series of papers on linear bioresorbal copolymers of NVP and HEMA [12-15].

The development of drug delivery systems with site targeting effects and controlled sustained release is extremely desirable nowadays. In that regard, so-called thermo-sensitive polymers are very promising since many illnesses usually induce fever. The localized increase of temperature in the vicinity of a sick organ can utilize different physical properties of the polymers. The solubility and swelling capacity of such polymers deteriorate under higher temperatures; and this property can then be used to program drug release at a certain site and at a required rate.

The most famous thermo-sensitive polymers are presented by poly (N-isopropylacrylacmide) (NIPAAm) [15, 16], poly (vinylmethyl ether) [18], poly (vinyl-caprolactam) [19], and some other synthetic thermo-sensitive polymers described in the literature [20, 21]. HEMA was used for modification of known thermo-sensitive polymers such as poly (NIPAAm) [23, 24] and poly (acryloil-L-proline methyl ether) [9]. However, thermal sensitivity of the above-mentioned modified polymers was due to the main component, while HEMA was chosen for the purpose of adding mechanical strength and integrity to the hydrogels [24] and was not considered to contribute to thermo-sensitivity. Taken in large amounts, HEMA even deteriorates the swelling response of poly (acryloil-L-proline methyl ether) because it lowers the initial degree of swelling at low temperatures [9].

The fact that the water uptake of poly (HEMA) hydrogels increases at lower temperatures is well known [25]. Recently, the influence of temperature on the degree of swelling of HEMA-based hydrogels was studied in ref. [8]. The swelling degree of the hydrogels showed an extreme level of dependence on temperature with a minimum at 55°C. In the cited work, the phenomenon was related to the reduction of hydrogen binding force in the vicinity of the macromolecules. Thus, bound water becomes non-binding water and may rapidly move out of the polymeric network. The re-increase of their swelling above the minimum temperature was explained by mixing forces between water and polymer that exceeded the self-attraction forces. However, detailed investigation of HEMA-based polymers' thermo-sensitivity has not yet been performed.

The idea to use HEMA in order to create thermo-sensitive polymers was based on our assumption that thermal-sensitivity comes from a suitable hydrophilic-hydrophobic balance of macromolecules. And this property can be governed by copolymerization of hydrophilic and hydrophobic co-monomers. Indeed, a new kind of thermo-sensitive polymers of vinyl ether, ethylene glycol-co-vinyl butyl ether and vinyl ether of diethylene glycol-co-vinyl butyl ether was reported in [26-28]. Homo-polymers of vinyl ethers of glycols are hydrophilic, and polyvinyl alkyl ethers are hydrophobic and both of them do not exhibit thermal sensitivity. Unlike all the above-mentioned thermo-sensitive polymers which are based on single amphiphilic monomers, the authors utilized a new approach, which is the combination of hydrophilic and hydrophobic monomers at mutual copolymerization.

In the present work we have chosen N-vinyl pyrrolidone as a hydrophilic co-monomer with the relatively hydrophobic HEMA due to its good polymerizing properties as well as its non-toxicity in a polymer state and deserved recognition as a biocompatible material.

II. EXPERIMANTAL

2.1. Materials

N-vinyl pyrrolidone (NVP) was purchased from Aldrich with a declared purity of 99+%. 2-Hydroxyethylmethacrylate (HEMA) was supplied by Acros Organics with a purity of 96% stabilized by methacrylsaeure-2-hydroxyethylester. Initiator 2,2-Azobisisobutyronitryl (AIBN) of 98%-grade purity was supplied by Janssen Chimica. All materials were stored at low temperature and used as received. Sodium chloride and sodium dodecyl sulfate (Aldrich) were of analytical grade and used without further purification.

2.2. Synthesis of polymers

The monomer mixtures were prepared in 50 vol.% ethanol solutions. The amount of initiator was $5 \cdot 10^{-3}$ mol/l of total monomer. The mixtures of 15 ml volume were poured into glass vials and bubbled with nitrogen for 15 minutes to remove oxygen. The vials were then tightly covered and sealed with Teflon film. Copolymerization reaction was performed at 60°C. Two series of NVP-HEMA copolymers were synthesized using varied feed compositions and duration of copolymerization. All other conditions were kept constant. After synthesis, the copolymers were twice precipitated in diethyl ether from dilute ethanol solutions and dried until constant weight under vacuum.

2.3. Polymer characterization

The copolymer compositions were determined by elemental analysis.

Glass transition temperatures of the copolymers were determined using a DSC 2010 TA Instrument. Prior to the experiments, the copolymers were dried under vacuum at 50°C overnight. Three runs were performed under 25 mm/min nitrogen gas flow. The samples of 10-12 mg were equilibrated at 25°C and heated to 230°C with the rate 5°C min^{-1}. After the first and second runs the samples were left to cool inside the device.

The molecular weight of the copolymers was determined by gel permeation chromatography (GPC) of 0.5 wt.% solutions in dimethyl formamide using a Millipore Walter GPC Instrument.

Thermo-sensitivity of the copolymers was observed on a UV-vis spectrophotometer (Shimadzu). Aqueous solutions of certain concentrations were prepared. The solutions were poured into 1 ml UV cells and sealed with Teflon film. The temperature was increased at increments of 1°C, and at increments of 0.2°C in the vicinity of cloud point. The cell in the solution was kept at each experimental point for 30 min to reach equilibrium state. The transmittance was measured at 450 nm wavelength and taken as an average of 3 measurements. Cloud point was taken as a temperature; at that point the solution has a half-valued transmittance of its initial level at the lowest temperature.

III. RESULTS AND DISCUSSION

3.1. Synthesis of NVP-HEMA copolymers

Synthesis of N-vinyl pyrrolidone-co-2-Hydroxyethyl-methacrylate (NVP-HEMA) was carried out by the regular procedure of radical copolymerization in alcohol solutions initiated by 2,2-Azobisisobutyronitryl (AIBN). Two series of copolymers in a wide range of feed compositions were obtained for 50 and 80 minutes of polymerization time τ (table 1).

Table 1. Composition of NVP-HEMA in feed and in copolymers

N	Code	[NVP]:[HEMA], mol% in feed	[NVP]:[HEMA], mol% in copolymer	Synthesis conditions
a				
N	Code	[NVP]:[HEMA], *mol% in feed*	[NVP]:[HEMA], mol% in copolymer	Synthesis conditions
1	H1	90:10	62.88:37.12	[AIBN]=$5 \cdot 10^{-3}$ mol/l; [C_2H_5OH]=50 vol.%; T=60°C; τ=50 min
2	H2	80:20	46.49:53.51	
3	H3	80:25	37.34:62.66	
4	H4	70:30	29.25:70.75	
b				
5	H5	80:20	62.15:37.85	[AIBN]=$5 \cdot 10^{-3}$ mol/l; [C_2H_5OH]=50 vol.%; T=60°C; τ=80 min
6	H6	70:30	34.83:65.17	
7	H7	60:40	22.46:77.54	

The regularities of the synthesis in the system are well described in the literature [12, 13, 29-31] and are found to be similar in bulk and water/alcohol solutions. Reactivity ratios differ significantly for the comonomers, namely HEMA is very reactive (r_{HEMA}=3.12÷8.18, as reported), while the reactivity of NVP equals virtually zero [12, 13, 29-31]. That explains a noticeable enrich-

ment of copolymer composition by more active HEMA in comparison with its content in the initial monomer mixtures, since it polymerizes first. The copolymers of the second series are characterized by the higher content of NVP units. For example, the samples coded as H2 and H5 were synthesized at the same feed composition, but the latter proceeded for 30 minutes longer. Co-polymerization of H2 was ceased at an early stage, when 46.49 mol% of NVP was transformed into a polymer state. Continuation of the reaction resulted in 62.15 mol% of NVP in the copolymer H5, because the monomer intensively participates in macromolecule formation in the later stages. This is due to the monomer mixture becoming more and more depleted in HEMA as the more active co-monomer is consumed in the early stages of the reaction.

Thus, knowing the above-described regularities of NVP-HEMA synthesis, one may obtain a copolymer of any required composition by choosing a suitable feed composition and alteration of the reaction duration.

3.2. Copolymer characterization

Copolymerization of NVP and HEMA in alcohol media is yielded in 17÷24 wt.% depending on feed composition. Higher values could not be achieved due to the strong tendency to form cross-linked structures. As expected, yield is a function of feed within one series as well as duration of copolymerization: its magnitude is increased with HEMA content in feed and τ.

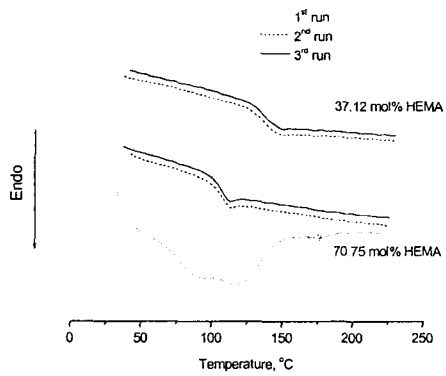

Fig. 1. DSC determination of glass temperatures for NVP-HEMA copolymers.

Thermal properties of the copolymers were specified by DSC determined glass transition temperatures (T_g). The measurements were supported by three runs (fig.1); after each run the samples were allowed to cool down slowly to accept original conformation. The first run was performed in order to eliminate the plasticizing effect of water residuals absorbed from the humidity of the laboratory. Second and third runs provided more or less true results, and the average value was considered (see table 2). Glass transition temperature of 163.4°C was determined for the homo-polymer poly(NVP) (Fluka, M_r~40.000) by DSC technique in ref. [32], while for poly(HEMA) T_g, it was 105.8°C as reported in [33]. The co-polymers exhibited one glass transition in the studied temperature range, and is evidence of their amorphous nature. The existence of long blocks was not observed implying a statistic distribution of monomer units along polymeric chains. Taking into account the reactivity ratios reported for this copolymerizing system, one might assume that the structure of the copolymers synthesized from HEMA-rich monomer mixtures at a low conversion degree and this is presented by sequences of HEMA units separated by one NVP unit. At high conversion, the formation of longer NVP sequences is possible since its concentration in copolymerizing mixture increases. This results in the existence of two well-defined types of the respective homo-polymers, poly(HEMA) and poly(NVP). However at high levels of NVP in the feed the tendency to alteration might take place during the final stages of copolymerization when almost the whole amount of HEMA is involved into macromolecules, longer sequences of NVP could be formed. This was proved by micellar electro-kinetic capillary chromatography (MEKC) allowing differentiation of macromolecules of different hydrophobicity in ref. [13]. Quantitative analysis of the copolymer structure was studied in detail in other investigations cited above [12, 13 , 29-31].

The dependence of molecular weight of the copolymers correlates data on composition and yield, and the same explanation might be given (table 2).

Table 2. NVP-HEMA copolymers characterization

N	Code	Yield, wt.%	T_g	M_w	PD	Cloud point of 5wt% solutions, °C
			A			
1	H1	17.03	138.33	161.000	1.043	48.3
2	H2	18.16	123.44	163.000	1.042	36.4
3	H3	19.67	113.62	170.000	1.038	14.8
4	H4	20.66	107.34	178.000	1.035	<0.6
			B			
5	H5	19.88	139.98	182.000	1.035	14.2
6	H6	22.79	111.57	190.000	1.027	7.2
7	H7	24.44	106.26	196.000	1.025	<0.6

As shown in the table, there is little difference between the molecular weights of the copolymer, however a slight increase was observed with an increase in HEMA content in feed, obviously due to its greater activity. The copolymers of series *b*, which were polymerized for 30 minutes longer, are of higher molecular weights compared with the analogues of series *a*. A narrow distribution of molecular weight (PD) was observed for all copolymers.

3.3. Thermo-sensitive behavior of NVP-HEMA copolymers in water

Thermo-sensitivity is a property of some amphiphilic polymers with a certain hydrophilic-hydrophobic balance of macromolecules which simultaneously contain a hydrophilic part, responsible for solubilization in an aqueous environment, and a hydrophobic part, which provides the ability to self-associate at increasing temperatures through hydrophobic interactions, whilst existing in a water medium. At that point, a coil-globule conformational transition of macromolecules occurs

caused by the deterioration of polymer solubility in water and is expressed in the appearance of cloudiness of the solutions and precipitation of a polymer [34, 35]. Indeed, hydrogen bonds between polymer and water molecules, which are responsible for solubilization, are weakened at higher temperatures. At the same time hydrophobic interaction between non-polar groups strengthens. Both effects force macromolecules to accept compact globular conformation and result in their collapse. At that point, the solution becomes cloudy or opaque, and under further heating, the polymer precipitates.

As mentioned in the introduction, the NVP-HEMA copolymers were expected to exhibit thermo-sensitive properties assuming different hydrophilic-hydrophobic qualities of their components. HEMA was taken as the hydrophobic co-monomer and NVP as the hydrophilic co-monomer.

In this research, the thermo-sensitivity of NVP-HEMA copolymers was investigated by the measurement of transmittance of their aqueous solutions using a UV-vis spectrophotometer. 5 wt.% water solutions of the copolymers with different compositions were prepared. The data are presented in fig. 2. As shown, at low temperatures the solutions are transparent. As temperature increases, they become cloudy and their transmittance is drastically reduced and approaches zero.

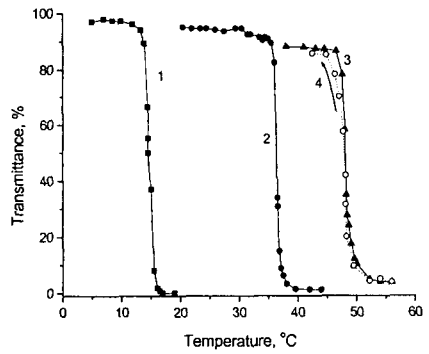

Fig. 2. Transmittance of 5wt.% water solutions of NVP-HEMA copolymers as a function of temperature. [NVP]:[HEMA], mol.%: 1 – 37.34:62.66; 2 - 47.79:52.51; 3,4 - 62.88:37.12.

The curves in fig. 3 describe cloud point behavior for three copolymers of different compositions. Highly hydrophilic copolymers, containing just 37.12 mol% of HEMA, exhibits the highest cloud point value. In our previous work on the study of states of water in NVP-HEMA hydrogels, performed by DSC analysis, we have found that the presence of hydrophobes in the polymer structure induces noticeable water structuring in their vicinity [36]. In other words, hydrophobic interactions in the hydrogels play a significant role in polymer-water relations. Indeed, to convert it into a collapsed state requires raising the temperature to strengthen the hydrophobic interactions between rare hydrophobic moieties, as well as to destruct H-bonds with water. More hydrophobic copolymers are characterized by easier coil-globule transition, which occurs at mild conditions close to human body temperature (curve 2). The copolymer composed of the highest amount of HEMA among others presented in fig. 3, undergoes the phase transition at the lowest temperature. It requires little heating in order to accept compact conformation due to the high content of hydrophobic groups in its structure. The observed behavior is practically reversible, as demonstrated by curve 4, obtained by cooling the sample after heating beyond cloud point. Three cycles were carried out to prove the reversibility of the phase transition and the same results were obtained.

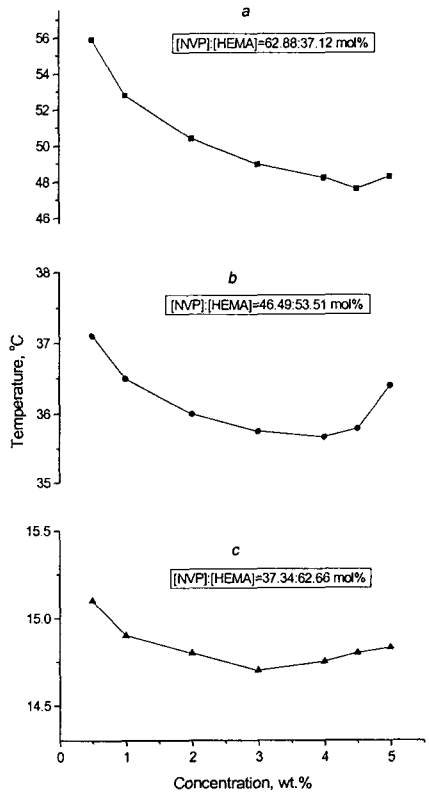

Fig. 3. Phase diagram of NVP-HEMA copolymers of different compositions in water.

The same procedure was performed for the solutions of lowered concentrations to construct the phase diagram for the NVP-HEMA system (fig. 3). The curve connecting the cloud points passes a minimum, which is a lower critical solution temperature; lower that temperature the copolymer is soluble at any concentration.

A noticeable result was that the dilution of hydrophilic samples (a) has a stronger effect on cloud point than changes by 10°C between LCST and cloud point for 0.5wt.% solutions (fig.3*a*), while for HEMA-rich copolymer cloud points of solutions of various

concentrations differ within 1 degree C (Fig.3*c*). Obviously, the diluted solutions of the hydrophilic copolymer must be heated to a higher temperature in order to induce sufficient compaction of macromolecules, than that of the hydrophobic macromolecule. The right coexistence curve after the LCST describes the behavior of semi-concentrated and concentrated solutions where macromolecules interconnected with each other, so that some heat is consumed to destroy intermolecular binding and then to cause the contraction of each single macromolecule. Intermolecular binding is stronger for the copolymer with a greater content of HEMA, meaning that it occurs mostly between hydrophobes. That is why the position of LCST is shifted to lower concentrations for HEMA-rich copolymers from 4.5 to 3 wt.% as HEMA content increases from 37.12 to 62.66 mol% respectively.

3.4. Influence of NaCl on cloud point

In the presence of a low molecular weight salt such as NaCl, the phase transition of NVP-HEMA copolymers occurs more easily at lower temperatures (fig. 4). The higher the ionic strength, the lower the cloud point. As shown in figure 4, an ionic strength lower by 0.1M has little effect on transmittance-temperature dependence; even the curves at 0.001 (not shown) and 0.01 mol/l of NaCl almost coincide. The increase of ionic strength from 0.2 to 0.5 results in an expressive (about 6°C) reduction of temperature range whereas phase transition takes place. The reason for that is the so-called salting-out effect, typical for non-ionic polymers. It is related to competition between polymer and salt ions for the solvation by water molecules and consequently deterioration of the dynamic quality of the solvent in the presence of inorganic salt.

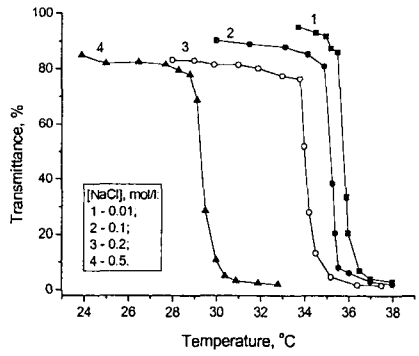

Fig. 4. Transmittance of NVP-HEMA copolymers solutions (5 wt.%) as a function of temperature in the presence of NaCl. [NVP]:[HEMA]=46.49: 53.51 mol%.

Data on the effect of salt on the cloud point of 5 wt.% solutions of NVP-HEMA copolymers are summarized in table 3. As shown in the table, the most hydrophilic polymer, H1, is more sensitive to the addition of salt. It changes the value of the cloud point by 9 degrees while the hydrophobic analogue H3 is characterized by about 3 degrees difference in the same range of ionic strength. Probably, there is a tiny balance between hydrogel bonds with water promoting swelling, and hydrophobic attraction between hydrophobes in the first case. The addition of even a small amount of salt disturbs the fine equilibrium significantly, and macromolecules accept more compact conformations. As to the HEMA-enriched copolymer, it already has quite a compact conformation via strong hydrogen bindings between polar carbonyl and OH- groups as well as hydrophobic interactions so the addition of salt has less effect on its coil-globule transition.

Table 3. Cloud point of 5 wt./% water solutions of NVP-HEMA copolymers in the presence of NaCl.

[NaCl], mol/l	Cloud point, °C		
	[NVP]:[HEMA]= 62.88:37.12 mol% H1	[NVP]:[HEMA]= 46.49:53.51mol% H2	[NVP]:[HEMA]= 37.34:62.66 mol% H3
0.001	48.2	36.1	14.5
0.01	47.7	35.8	14.1
0.1	47.0	35.2	13.5
0.2	44.5	34.1	12.7
0.5	39.5	29.4	11.8

3.5. Influence of charged surfactant on cloud point

Essential hydrophobic interactions in HEMA-enriched copolymers induce their self-association even in cold water. Thus, critical phenomena could not be observed: the cloud point of the polymers containing HEMA over 70 mol% are located lower that 0.6°C. Increasing the cloud point was achieved by the addition of ionic surfactant sodium dodecyl sulfate (SDS) into the copolymer solutions. Interaction between those two is realized via hydrophobic attraction between HEMA's methyl group and the hydrophobic tail of the surfactant. Negatively charged heads of the surfactant attach along the polymer chains and provide electrostatic repulsion and enhanced solubilization. This phenomenon was investigated in detail in ref. [37] for poly (NIPAAm) hydrogels and a number of surfactants of different electrostatic origin. It was found that hydrophobic interaction occurs between the species. A rise in the phase transition temperature with high amplitude was observed in the case of charged surfactants. More recently, a number of papers regarding the modification of the thermo-sensitivity of polymers in the presence of ionic surfactants have been published [see for exp. 38-40].

The investigation of the thermal-sensitivity of NVP-HEMA copolymers, which are insoluble in distilled water due to their highly hydrophobic nature, was possible due to the enhanced solubility in the presence of surfactant. Experimental data on cloud point values as a function of the surfactant concentration in a logarithmic scale is presented in fig.5 for the copolymers with high HEMA content.

As shown, the temperature of phase transition increases according to exponential law and, once surfactant concentration exceeds a critical value, the

copolymers lose their thermo-sensitive behavior. In other words, at that concentration the electrostatic repulsion of the surfactant heads is stronger than the hydrophobic interactions at any temperature. Thus, the contraction of macromolecules is impossible, and they remain soluble even at high temperatures.

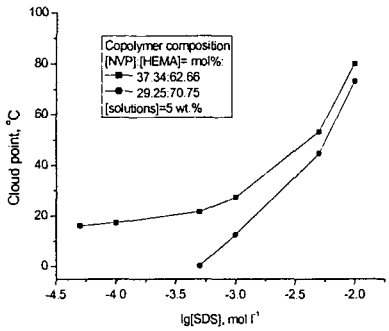

Fig. 5. Increase of cloud point of NVP-HEMA copolymers solutions (5 wt.%) in the presence of the ionic surfactant SDS.

IV. CONCLUSIONS

Copolymerization of NVP and HEMA was successful in obtaining new types of thermo-sensitive polymers composed of hydrophilic and hydrophobic monomers, whose homo-polymers do not exhibit critical phase transition in response to temperature. Thus, the copolymers were investigated for the purpose of evaluating their behavior in aqueous solutions at different temperatures. The thermo-sensitivity of the copolymers was revealed and is expressed in the existence of LCST. The critical temperature value is governed by the hydrophilic-hydrophobic balance of the copolymers, and shows lower values for the copolymers with greater HEMA content. Furthermore, the LCST is influenced by ionic strength and ionic surfactant that reduces or increases the parameter respectively. The copolymers of certain composition exhibit phase transition at human body temperature and are very promising for further investigation as a drug delivery system due to their accepted biocompatibility.

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