Upon Synthesis of Poly(N-isopropylacrylamide-co-2-dimethylaminoethyl methacrylate-co-itaconic acid) Copolymers as Matrix Ensuring Intramolecular Strategies for Further Coupling Applications

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Abstract: The study presents a set of copolymers synthesis based on N-isopropylacrylamide, 2-dimethylaminoethyl methacrylate and itaconic acid comonomers found in different gravimetric ratio, acquired through polymerization in water in the presence of ammonium persulfate as radical initiator. The purpose was to prepare polymeric structure with dual sensitivity to temperature and pH respectively, and able as well to ensure intramolecular strategies for coupling applications of inorganic or bioactive compounds. The polymers composition was confirmed by FTIR and ^{1}H-NMR spectra. The thermal stability of the polymeric compounds was evaluated, and SEM investigations of the polymer morphology are also presented. The polymers dispersions were characterized from the viewpoint of their hydrodynamic radius, zeta potential and conductivity.

Keywords: N-isopropylacrylamide, 2-dimethylaminoethyl methacrylate, itaconic acid, radical polymerization, dispersion.

INTRODUCTION

Up to now a wide range of poly(N-substituted acrylamide)s, such as poly(N-isopropyl-acrylamide) (poly(NIPAM)) have been investigated [1].

The interest in poly(NIPAM) derives from its hydration–dehydration changes in water in response to changes in temperature, resulting in a lower critical solution temperature (LCST). The solubility of most polymers increases with the increase of temperature, but polymers exhibiting LCST present decreases of water solubility with the increase in temperature due to predominating hydrophobic interactions. LCST is defined as the temperature at which the polymer solution undergoes a phase transition from a soluble state (i.e., random coil form) to an insoluble state (i.e., collapsed or globule form) on elevating the temperature.

Poly(NIPAM) presents inversely LCST characteristic of thermo-responsive polymers, respectively a sharpness LCST of about 32°C, which is close to the physiological temperature. Thus, poly(NIPAM) when is heated above 32°C, the polymer becomes hydrophobic and precipitates out from solution and below LCST it becomes completely soluble because of hydrophilic state and forms a clear solution. Poly(NIPAM) is also able to vary its phase separation temperature by co-polymerization, addition of salts, or addition of surfactants to the polymer solution [2-7].

Growing interest was as well conducted for research directed toward molecules and macromolecules with branched structures and presenting functional groups. This interest is primarily related on the presence of high content of functional groups, which may lead to the widening range of applications along with improved possibilities of realizing special chemical architecture and supramolecular assembles. In this context we have realized copolymers based on N-isopropylacrylamide (NIPAM), 2-dimethylaminoethyl methacrylate (DMAEMA) and itaconic acid (IA), monomers found in different ratio.

Itaconic acid may have two negatively charged carboxylic acid groups in each unit, which allow further an easier complexation of various compounds mimicking the 'egg-box' model structure in complexes with them. The inclusion of IA into macromolecular chains structure will induce as well partly biodegradable character for the prepared compounds.

(Meth)acrylate-based polycations, such as poly(2-dimethylaminoethyl methacrylate) (PDMAEMA), are known for their use in the biomedical field, but their high cytotoxicity and lack of biodegradability limit their potential in gene delivery [8-13]. PDMAEMA is as well under investigation as a non-viral transfectant for achieving tumor targeting of therapeutically relevant plasmids [14].

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Taking into account the special effects which may be generated by N-isopropylacrylamide, 2-dimethylaminoethyl methacrylate and itaconic acid comonomers – network formation, biodegradability and biocompatibility, gel formation capacity, binding properties, amphilicity, good oxidative and thermal stability, good films formers, acid pH and thermal sensitivity – the interest in the development of polymeric structures that include these monomers, with emphasis on theoretical aspects is thoroughly justified.

This study is devoted to the synthesis of a set of copolymers based on NIPAM, DMAEMA and IA comonomers in different ratio, synthesized through radical polymerization in water in the presence of ammonium persulfate (APS) as initiator. The purpose was to prepare polymeric structure with dual sensitivity to temperature and respectively pH, and able as well to ensure intramolecular strategies for coupling applications of inorganic or bioactive compounds. The polymers composition was confirmed by FTIR and ^{1}H-NMR spectra. The thermal stability of the polymeric compounds was evaluated; SEM investigations of the polymers morphology are presented. The polymers dispersions were also characterized from the viewpoint of their hydrodynamic radius, zeta potential and conductivity.

EXPERIMENTAL PART

Materials

NIPAM, purified by recrystallization in toluene/n-hexane mixture, IA used as supplied, DMAEMA, distilled from CaH_2, and APS, purified in methanol/water alcoholic solution of 75%, were purchased from Sigma–Aldrich. The water used in all experiments was purified using an Ultra Clear TWF UV System.

Polymerization Process

The reaction recipes are presented in Table **1**. The continuous radical polymerization processes were conducted under nitrogen atmosphere, at 70^{0}C for 8 h and then at 80^{0}C for other 8 h, in a constant temperature bath, with a stirring rate of 250rpm.

After synthesis the polymeric particles were precipitated three times with methanol from water solution and finally freeze-dried by lyophilization during 24 h.

The idealized structure of the synthesized copolymers is illustrated in the following scheme:

Characterization

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

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

Table 1: Recipes Used for the Copolymers Preparation

Polymer variant	Sample cod	Monomer	Content, M/l	Ratio, %	APS, M/L
Poly(NIPAM50-co DMAEMA40-co-IA10)	1	NIPAM	0.9	50	2.6 x 10^{-3}
		DMAEMA	0.508	40	
		IA	0.154	10	
Poly(NIPAM60-co DMAEMA30-co-IA10)	2	NIPAM	1.06	60	2.6 x 10^{-3}
		DMAEMA	0.382	30	
		IA	0.154	10	
Poly(NIPAM65-co DMAEMA25-co-IA10)	3	NIPAM	1.15	65	2.6 x 10^{-3}
		DMAEMA	0.318	25	
		IA	0.154	10	
Poly(NIPAM70-co DMAEMA20-co-IA10)	4	NIPAM	1.237	70	2.6 x 10^{-3}
		DMAEMA	0.254	20	
		IA	0.154	10	

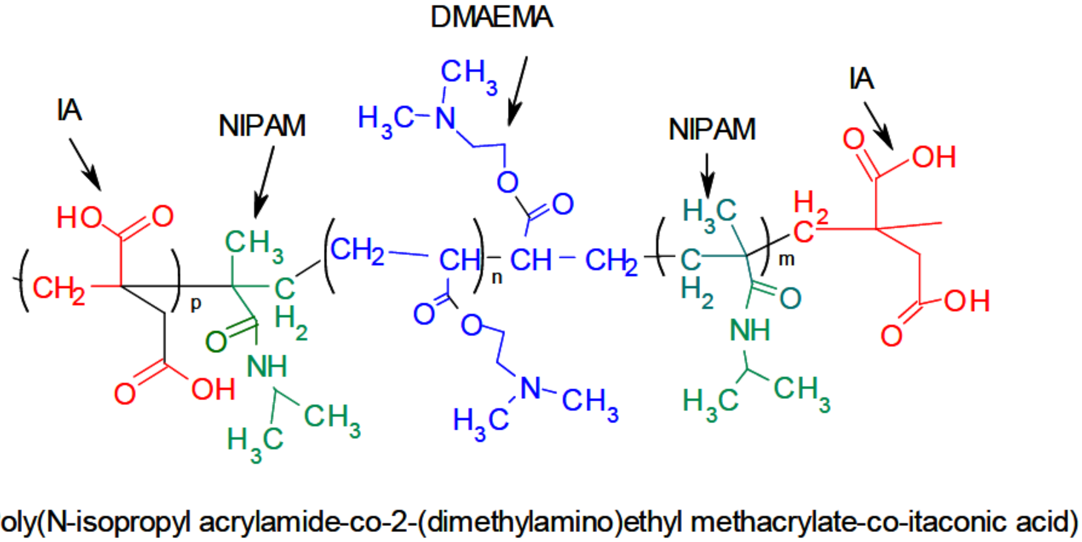


Figure 1: Idealized structure of poly(NIPAM-co-DMAEMA-co-IA).

Thermal analysis of polymers was performed using a STA 449F1 Jupiter model (Netzsch-Germany) system. The system is equipped with an apparatus of simultaneous thermogravimetric and differential scanning calorimetry analyses. Samples ranging between 7.4-7.6 mg were heated from 30^0C to 580^0C, at heating rate of 10^0C/min. As carrier gas was used the nitrogen (99.95 % purity) with the flow rate of 50 ml/min. The samples were heated in an open Al_2O_3 crucible with Al_2O_3 as reference material.

SEM studies were performed on samples 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 (ESEM) type Quanta 200 operating at 30 kV with secondary electrons in high vacuum mode.

Hydrodynamic radius, zeta potential (ζ), and conductivity of as-prepared polymer dispersions were estimated by using a dynamic light scattering technique (Zetasizer model Nano ZS, with red laser 633 nm He/Ne; Malvern Instruments, UK). The determinations were made on 2 ml dispersion sample and correspondingly dilution. All measurements were carried out at 25°C, except those performed with temperature variation made in order to confirm the sensitivity of copolymers at temperature. The zeta potential was calculated from the electrophoretic mobility (μ) using the Smoluchowski relationship:

$$\xi=\eta\mu/\varepsilon, \text{ with the condition } k\alpha >> 1$$

where η – viscosity, ε – dielectric constant of the medium, k, α – Debye–Hückel parameter and particle radius, respectively. The average of five measurements is presented as the mean value for the zeta potential. Also, the difference between the measurements and their average is less than 2.5%. During the same determination of acquiring the zeta potential values the conductivity was also determined.

SIGMAPLOT program was used for 3D graphic illustration.

RESULTS AND DISCUSSION

The registered **FT-IR** spectra of the synthesized copolymers (Figure **2**) confirm the achievement of the polymeric structure.

The spectra include the main characteristic bands of all monomers comprised into the copolymers composition. Thus, NIPAM characteristic bands appear in the spectra at wavelengths of 3292 cm^{-1} (owing to the secondary amide vibration), 2970 cm^{-1} (characteristic to the asymmetric vibration of $-CH_3$ group), 1650 cm^{-1} and 1550 cm^{-1} (specific to the C=O vibration with secondary amide). The characteristic bands of DMAEMA are found at 1675 cm^{-1} and respectively 1500 cm^{-1}. IA presence is evidenced by the elongated band of 2800-3400 cm^{-1} correspondingly to –OH group, a strong and narrow peak at 1710 cm^{-1} of the carbonyl group, another peak at 1400 cm^{-1} correspondingly to C-O-H, and at 1200 cm^{-1} for C-O group and a new peak at 920 cm^{-1} for O-H. Forming bonds between the comonomers is evidenced by the new bands at 1100 cm^{-1} and 1750 cm^{-1}, which are changing their intensity and shape depending on the amount of NIPAM and respectively DMAEMA.

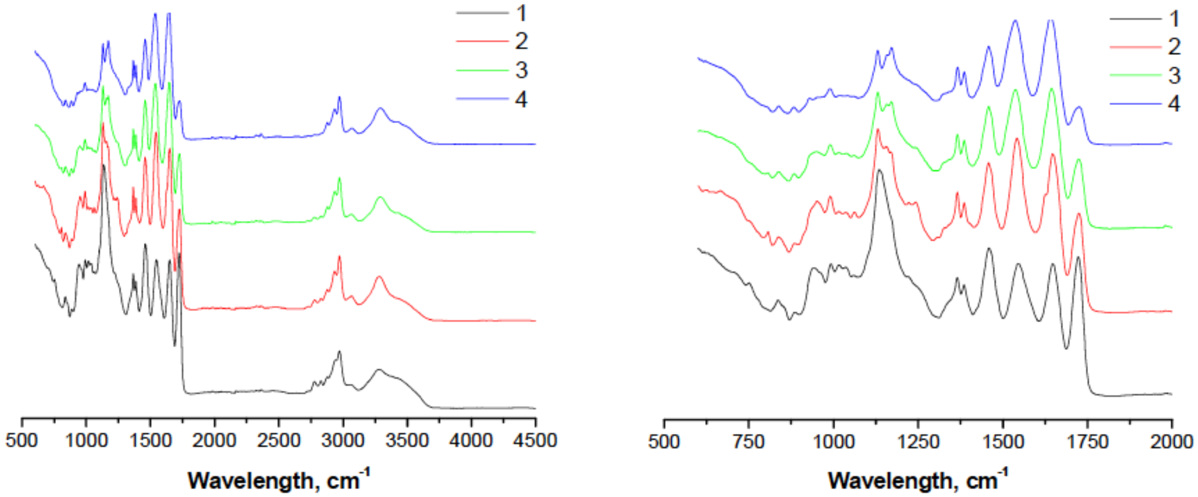


Figure 2: FTIR spectra of the of poly(NIPAM$_{50}$-co- DMAEMA$_{40}$-co-IA$_{10}$)(1), poly(NIPAM$_{60}$-co- DMAEMA$_{30}$-co-IA$_{10}$)(2), poly(NIPAM$_{65}$-co- DMAEMA$_{25}$-co-IA$_{10}$)(3) and poly(NIPAM$_{70}$-co- DMAEMA$_{20}$-co-IA$_{10}$) (4) copolymers.

^{1}H-NMR – spectra, illustrated in Figure **3**, give us as well information concerning the composition of the synthesized copolymers. The protons from –CH and –NH groups of NIPAM are located at 3.96 ppm (c) and respectively 6.3 ppm, having also the peak intensity in correlation with the content of the monomer into the copolymer composition. The peaks corresponding to protons of -CH$_2$ groups of IA are identified at 5.88 ppm (B) and 3.42 ppm (D), and have constant peak intensity as IA content is constant into the copolymers composition. The proton peaks corresponding to DMAEMA are found around 2 ppm (b 'and c'), 2.8 ppm (d '), 3.5 (e') and 4.2 ppm (g '). The intensity of these peaks decreases with increasing the amount of NIPAM (or decreasing the amount of DMAEMA), many of them are also overlapped by proton peaks from NIPAM especially in case of copolymer variant with 70% NIPAM content.

Poly(NIPAM$_{50}$-co-DMAEMA$_{40}$-co-IA$_{10}$), poly(NIPAM$_{60}$-co-DMAEMA$_{30}$-co-IA$_{10}$), poly(NIPAM$_{65}$-co-DMAEMA$_{25}$-co-IA$_{10}$) and poly(NIPAM$_{70}$-co-DMAEMA$_{20}$-co-IA$_{10}$)

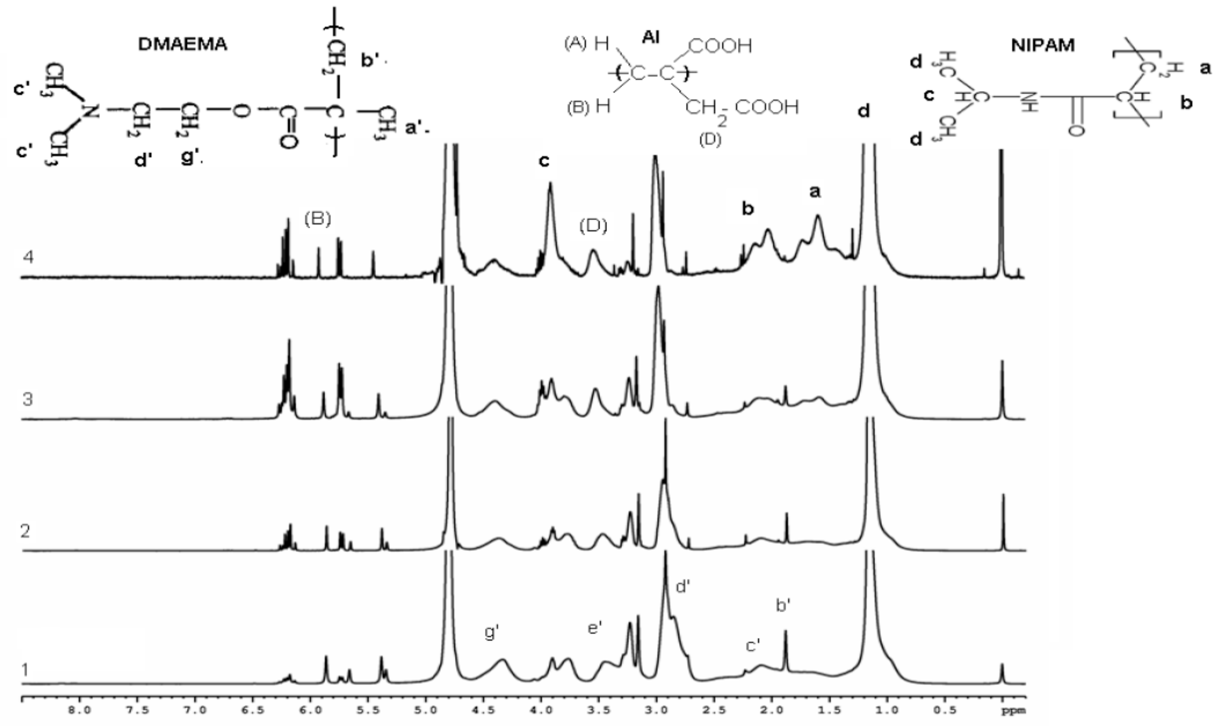
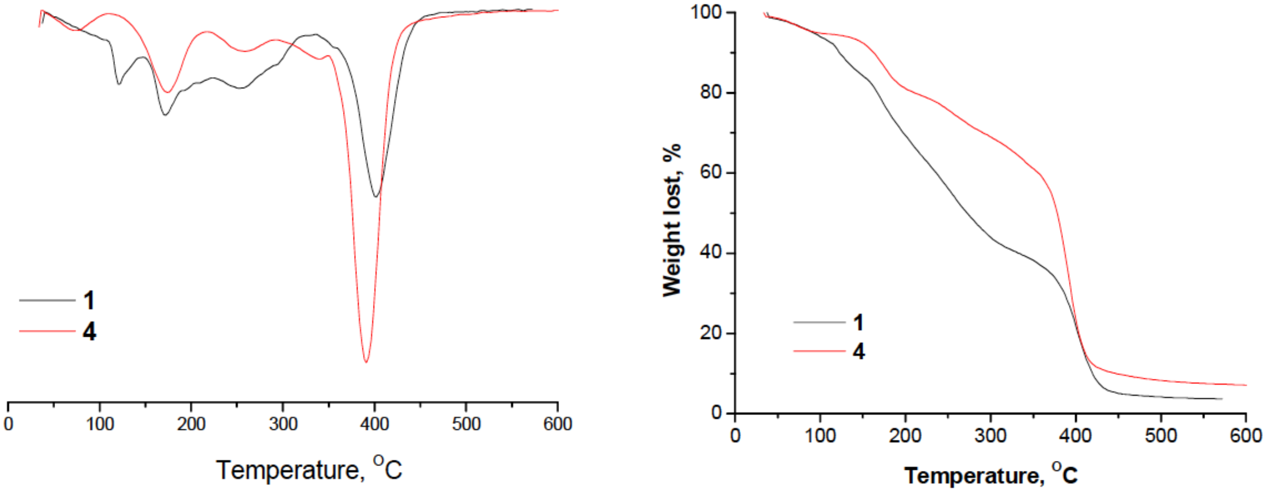


Figure 3: ^{1}H-NMR spectra of poly(NIPAM$_{50}$-co- DMAEMA$_{40}$-co-IA$_{10}$)(1), poly(NIPAM$_{60}$-co- DMAEMA$_{30}$-co-IA$_{10}$)(2), poly(NIPAM$_{65}$-co- DMAEMA$_{25}$-co-IA$_{10}$)(3) and poly(NIPAM$_{70}$-co- DMAEMA$_{20}$-co-IA$_{10}$) (4) copolymers.



(**a**) (**b**)

Figure 4: TG (**a**) and DTG (**b**) curves of poly(NIPAM$_{50}$-co- DMAEMA$_{40}$-co-IA$_{10}$) (1) and poly(NIPAM$_{70}$-co- DMAEMA$_{20}$-co-IA$_{10}$) (4) copolymers.

copolymers were analyzed from the viewpoint of their thermogravimetric behavior. The field of temperature was between 30°C to 600°C and Figure **4a** and **b** illustrates TG and DTG curves of the copolymers with the smallest and the highest content of NIPAM, respectively poly(NIPAM$_{50}$-co-DMAEMA$_{40}$-co-IA$_{10}$) and poly(NIPAM$_{70}$-co- DMAEMA$_{20}$-co-IA$_{10}$).

The thermal properties of the copolymers are presented in Table **2**. The presence of IA and DMAEMA comonomers has brought other two steps of decomposition between 100°C – 250°C during thermal analysis of the copolymers. These steps are attributed to the elimination of water and formation of itaconic anhydride, processes which are followed by the decarboxylation into the range of 270°C - 500°C. DMAEMA determines as well two stages of decomposition: the first one between 260-330 °C attributed to degradation of dimethyl-aminoethyl groups, and the second one in the range of 350 to 450°C attributed to CO_2 and CO removal and carbonization processes.

This stage overlaps with the main stage of NIPAM decomposition. From the values of the main thermal parameters of each decomposition stage as well of the residual mass (Table **2**) it observes the increase of the thermal stability of polymers synthesized with increased content of NIPAM.

The morphology of the synthesised copolymers reflects as well the composition of thus prepared macromolecular compounds (Figure **5a-e**). Thus, the NIPAM content influences the morphological appearance. Growth of the DMAEMA amount determines the increase of the intramolecular bonds between methyl groups of DMAEMA and carboxyl groups of IA. This aspect is concretized into a more homogeneous structure of these copolymers (Figure **5a**). Instead the increased content of NIPAM provides intermolecular bonds concretized into a mesh structure (Figure **5b-d**).

Hydrodynamic radius, zeta potential (ζ), and conductivity characteristics were also, evaluated for the

Table 2: The Main Thermal Characteristics of the Synthesised Copolymers

Sample	I stage of decomposition				II stage of decomposition				Main stage of decomposition				Rezidue %
	T_i (°C)	T_{max} (°C)	T_f (°C)	ΔW%	T_i (°C)	T_{max} (°C)	T_f (°C)	ΔW%	T_i (°C)	T_{max} (°C)	T_f (°C)	ΔW%	
Poly(NIPAM$_{50}$-co-DMAEMA$_{40}$-co-IA$_{10}$)	104	146	219	33	219	257	319	23	319	401	462	36.6	4.4
Poly(NIPAM$_{70}$-co-DMAEMA$_{20}$-co-IA$_{10}$)	104	172	216	15	216	255	305	10	305	390	450	61.2	7.8

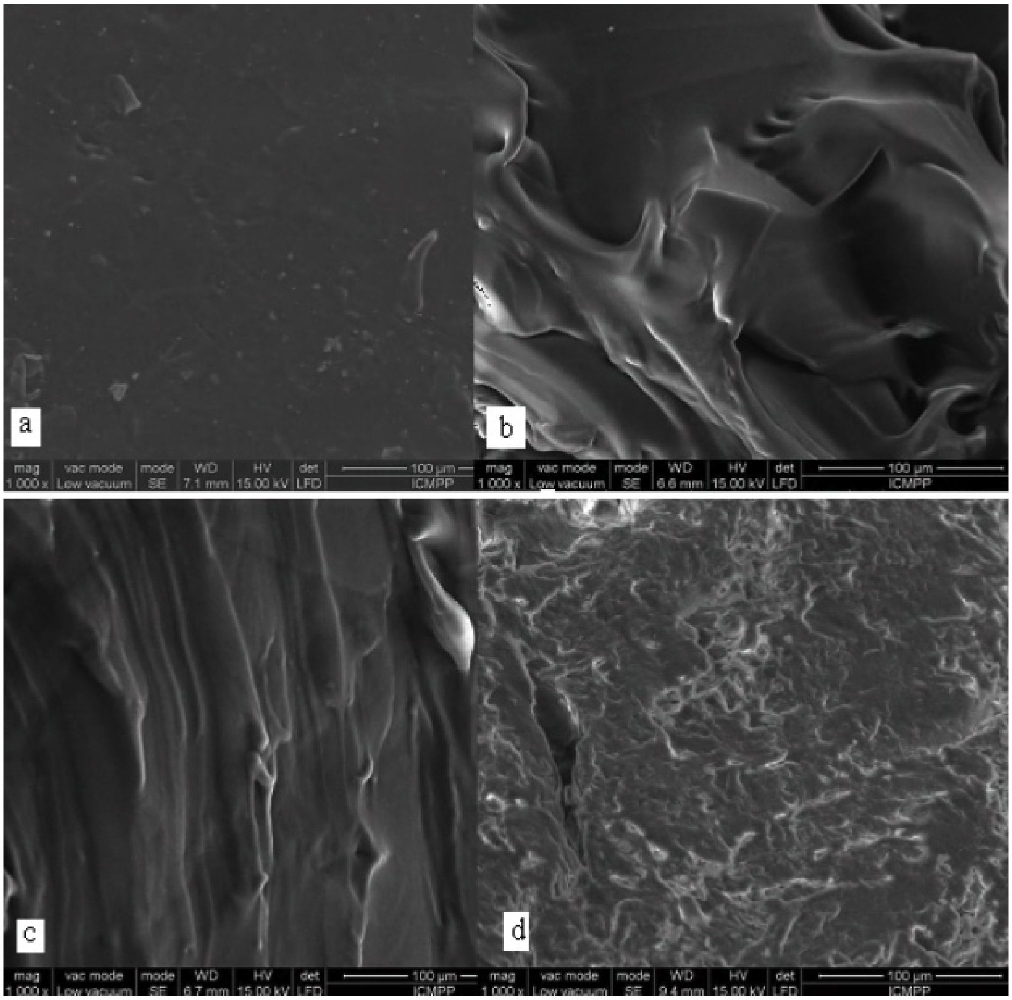
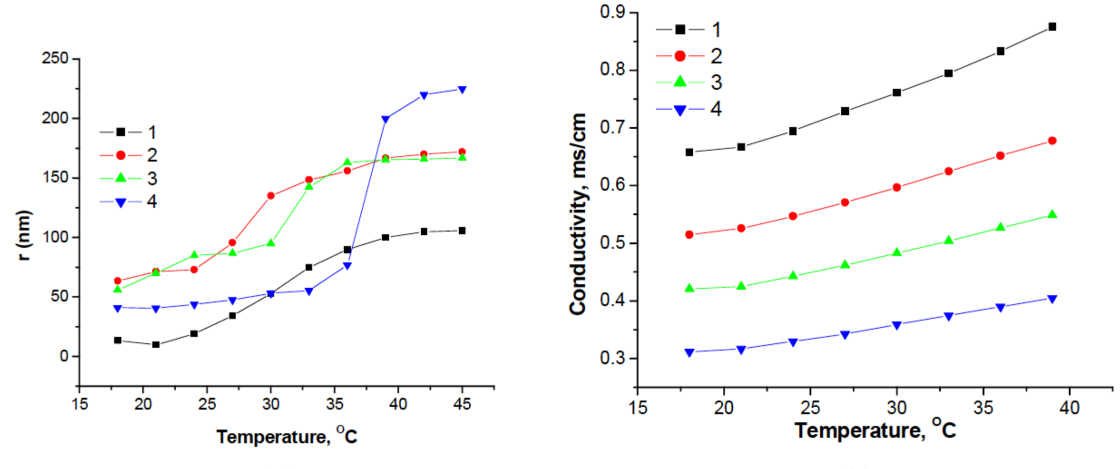


Figure 5: SEM micrographs of the synthesised copolymers: poly(NIPAM$_{50}$-co- DMAEMA$_{40}$-co-IA$_{10}$) (**a**), poly(NIPAM$_{60}$-co-DMAEMA$_{30}$-co-IA$_{10}$) (**b**), poly(NIPAM$_{65}$-co- DMAEMA$_{25}$-co-IA$_{10}$) (**c**) and poly(NIPAM$_{70}$-co- DMAEMA$_{20}$-co-IA$_{10}$) (**d**). Magnitude:1000X.

copolymers. These specific aspects are as well related on the synthesized copolymers composition (Figure **6**). Generally the incorporation of higher amount of ionic comonomer (DMAEMA), into the detrimental of NIPAM, determines the decrease or even disappearance of copolymers LCST as it is evidenced from the trend of hydrodynamic radius with the temperature (Figure **6a**). The copolymer with the higher content of NIPAM presents a narrow domain of temperature for the phase transition (Figure **6a**). Instead, the copolymers with higher content DMAEMA shows increased conductivity, which is expected, taken into account the ionic character of this comonomer.

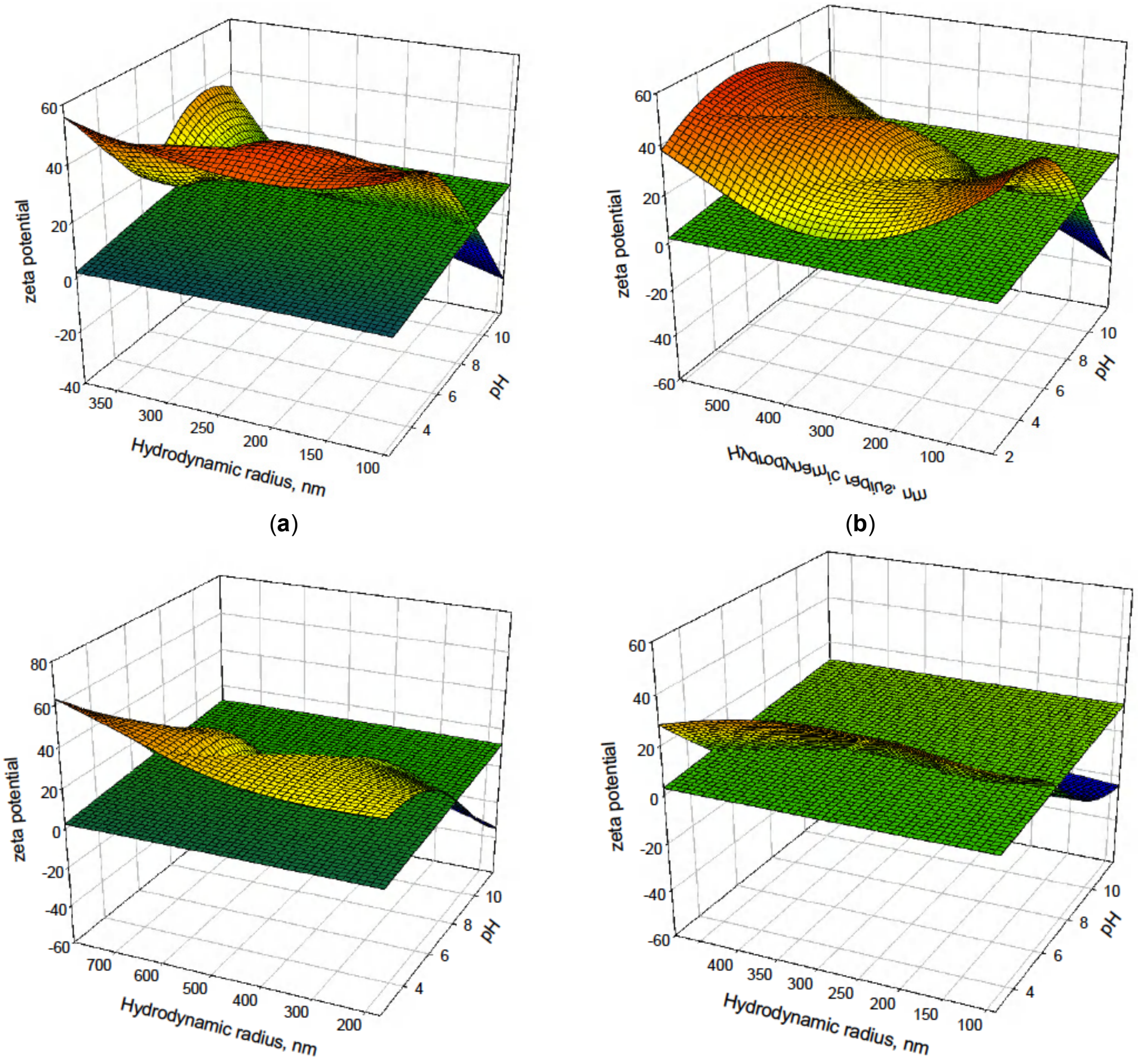
As was mentioned before the synthesised copolymers has dual sensitivity to pH and respectively temperature. In this context the behavior of the copolymers from the viewpoint of their hydrodynamic radius, zeta potential, and conductivity, it was evaluated (Figures **7** and **8**). Again it is underlined the dependence of these characteristics on copolymers composition. Thus, hydrodynamic diameter is influenced by pH, the variants with 65% and 70% NIPAM show the most pronounced conformational changes with basic pH (maximum being for both samples at pH 10) (Figure **7**). In case of sample with the highest content of ionic comonomer (sample with 50% NIPAM) which includes supplementary ionizable amino and carboxyl groups correspondingly to DMAEMA, present two maximum peaks at acidic pH (pH=4) and one neutral to slightly alkaline pH (pH = 7-8).

Regarding the variation of zeta potential with pH (Figure **8**), at acidic pH the differences between copolymers samples are small (excepting the copolymer with maximum content of NIPAM - 70%). The shift to the basic pH range causes linear dependence of zeta potential on the copolymers composition.



(**a**) (**b**)

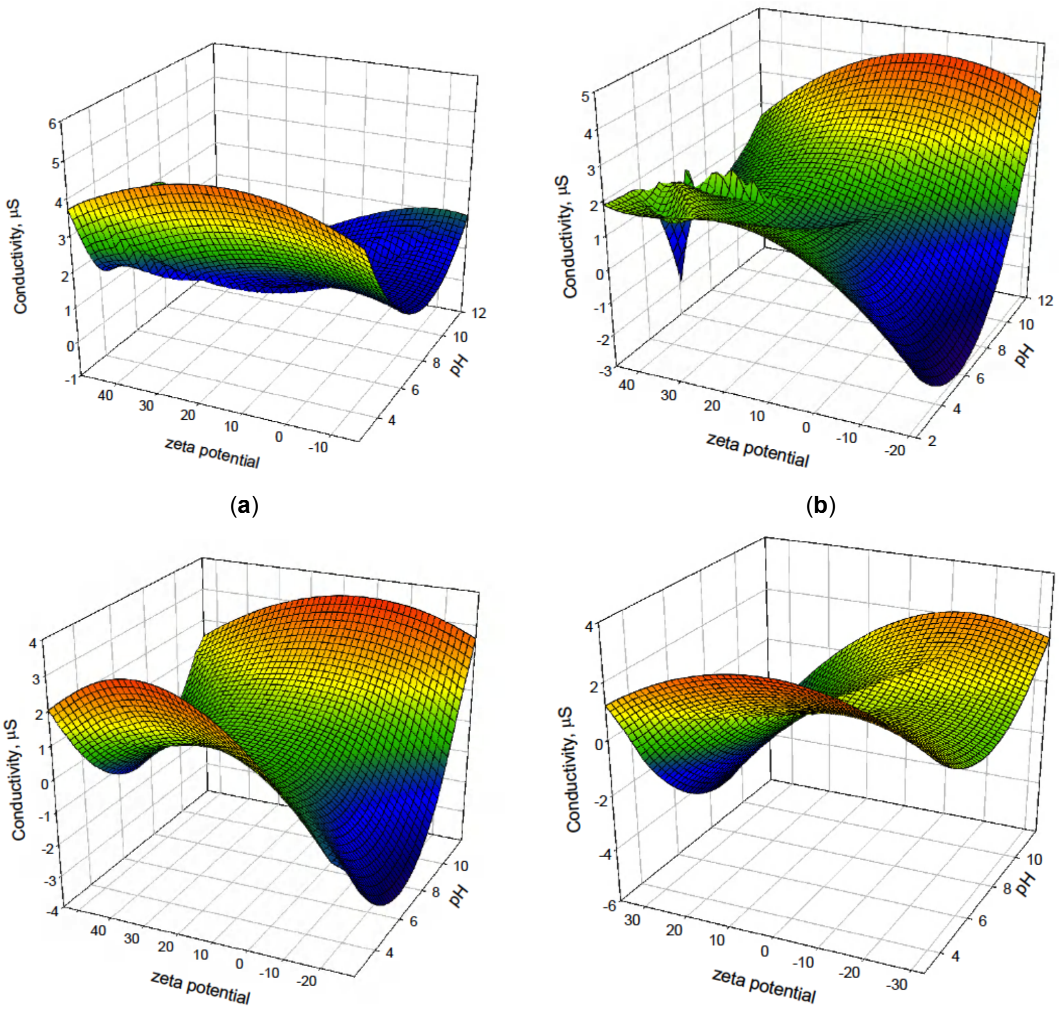
Figure 6: Trend with temperature of the hydrodynamic radius (**a**) and of the conductivity (**b**) for the synthesized copolymers: poly(NIPAM$_{50}$-co- DMAEMA$_{40}$-co-IA$_{10}$) (1), poly(NIPAM$_{60}$-co- DMAEMA$_{30}$-co-IA$_{10}$) (2), poly(NIPAM$_{65}$-co- DMAEMA$_{25}$-co-IA$_{10}$) (3) and poly(NIPAM$_{70}$-co- DMAEMA$_{20}$-co-IA$_{10}$) (4).



(**a**) (**b**)

(**c**) (**d**)

Figure 7: The variation with pH of the hydrodynamic radius and zeta potential, for the synthesized copolymers poly(NIPAM$_{50}$-co- DMAEMA$_{40}$-co-IA$_{10}$) (**a**), poly(NIPAM$_{60}$-co- DMAEMA$_{30}$-co-IA$_{10}$) (**b**), poly(NIPAM$_{65}$-co- DMAEMA$_{25}$-co-IA$_{10}$) (**c**) and poly(NIPAM$_{70}$-co- DMAEMA$_{20}$-co-IA$_{10}$) (**d**).



(**a**) (**b**)

(**c**) (**d**)

Figure 8: The variation with pH of the conductivity and zeta potential, for the synthesized copolymers poly(NIPAM$_{50}$-co-DMAEMA$_{40}$-co-IA$_{10}$) (**a**), poly(NIPAM$_{60}$-co- DMAEMA$_{30}$-co-IA$_{10}$) (**b**), poly(NIPAM$_{65}$-co- DMAEMA$_{25}$-co-IA$_{10}$) (**c**) and poly(NIPAM$_{70}$-co- DMAEMA$_{20}$-co-IA$_{10}$) (**d**).

Also, in this range of pH, shift occurs from positive values to negative values of zeta potential and the occurrence of the isoelectric pH was registered dependent also on copolymers composition, as follows:

$$pH_{iz-NIPAM\,50\%} = 10.2 \rangle \; pH_{iz-NIPAM\,60\%} = 9.1 \rangle$$

$$pH_{iz-NIPAM\,65\%} = 8.6\% \rangle \; pH_{iz-NIPAM\,70\%} = 7.3$$

The conductivity is also dependent on both pH and copolymers composition (Figure **8**). Conductivity is even greater as the NIPAM content is smaller, which implicitly corresponds to a higher content of ionic comonomer DMAEMA.

CONCLUSIONS

The study evidences the possibilities for the syntheses of a set of copolymers based on N-isopropylacrylamide, 2-dimethylaminoethyl methacrylate and itaconic acid, which are able for ensuring intramolecular strategies for further coupling applications owing to the specific functional groups presence. The composition of the macromolecular chains was confirmed by FT-IR and H-NMR spectra which attest the presence of the comonomers into the chemical structure of the synthesised copolymers. The dual sensitivity of the copolymers was also put into evidence by determining zeta potential, hydrodynamic radius and conductivity of the copolymers dispersion in interdependence with the variation of temperature and/or pH. Thus, a growth content of ionisable comonomer - 2-dimethylaminoethyl methacrylate – induces an increase of the zeta potential, hydrodynamic radius and conductivity. At the same time, a higher content of NIPAM determines a network like structure for the polymer and higher stability. In order to evaluate the possibilities of coupling various small-molecular compounds onto the synthesised copolymers further investigations are in course.

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