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EXPLORATORY RESEARCH PROJECT

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POLYMER MATERIALS WITH SMART PROPERTIES

- 2012 -

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BRIEF REPORT

concerning the results obtained by the project team between December 16th, 2011 – December 15th, 2012

Goals:

Objective 1. Evaluation of the interactions established in multicomponent polymer systems in solution

Associated activities:

- 1.1. Studies concerning the compatibility of PVA/Pluronic mixtures in solution by considering the viscometric/rheological data
- 1.2. Correlation of the rheological data with turbidimetric and light scattering curves

Objective 2. Chemical gels based on natural and/or synthetic polymers

Associated activities:

- 2.1. In-situ monitoring of the sol-gel transition for chemical gels in presence of natural or synthetic crosslinkers
- 2.2. Establishment of the optimal conditions of gelation for obtaining elastic hydrogels
- 2.3. Investigation of the properties of synthetic and natural hydrogels

Objective 3. Physical gels based on multicomponent polymer systems

Associated activities:

- 3.1. Investigation of the conditions of gel formation (gelation point, kinetic aspects)
- 3.2. Elaboration of physical gels which present the sol-gel transition around 37°C
- 3.3. Influence of the environmental conditions on the gel properties

Introduction

Thermoreversible hydrogels are used most often in the controlled release of drugs, proteins, but they are also of great interest for tissue engineering and regenerative medicine. Injectable hydrogels are particularly advantageous for biomedical applications because it can fill any form or defect can be easily combined with cells and a complicated surgical procedure is not required. In the case of biodegradable materials, there is no need to be removed. Hydrogels formed in situ are suitable for such applications, especially if they possess elastic properties similar to tissues. Investigations carried out in 2012 showed "intelligent properties" (formation of thermoreversible macromolecular networks) that occurs at a temperature close to body temperature, where the biomacromolecules (polyamino acids, polynucleotides, polysaccharides) can work.

Experimental Part

Materials: Poly(vinyl alcohol) (PVA, Aldrich and Loba); Chitosan (CS, Aldrich); Xanthan (Aldrich); Poly(aspartic acid) (PAS, synthesized by Dr. A. Chiriac); Poly(ethylene oxide) (PEO, Fluka); Pluronic F127 (PL, BASF, 1.27×10^4 g/mol); Polyurethanes obtained by bulk polymerization using Pluronics and poly (isopropyl lactate) diol as flexible segments and different aliphatic diisocyanates as rigid segments (synthesis made by M.L. Gradinaru)

Methods: Capillary viscometer Lauda; stress control rheometer Bohlin CVO (Malvern); Zetasizer Nano-ZS (Malvern Instruments); HACH 2100AN turbidimeter.

Objective 1. Evaluation of the interactions established in multicomponent polymer systems in solution

1.1. Studies concerning the compatibility of PVA/Pluronic mixtures in solution by considering the viscometric/rheological data

The solutions of PVA/Pluronic F127 mixtures were investigated in detail through rheology and viscometry in order to establish the interactions established at different temperatures and to design physical gels with predictable response. Here we present some results obtained for dilute and concentrated solutions. Figure 1 shows the dependence of the intrinsic viscosity on temperature for aqueous solutions of PVA ($M=6.5 \times 10^4$ g/mol), Pluronic F127 (PL, $M=1.27 \times 10^4$ g/mol) and their mixture 25% Pluronic F127 and 75% PVA, in the temperature range 25°C - 40°C.

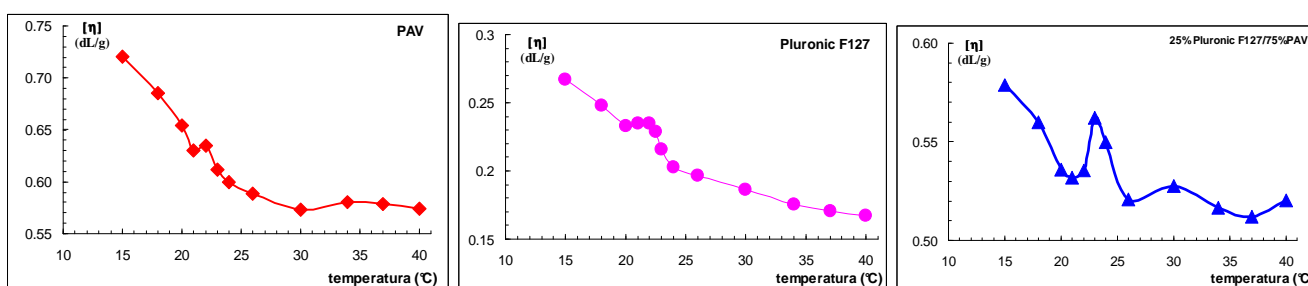


Figure 1. $[\eta]=f(\text{temperature})$ for dilute aqueous solutions of PVA, Pluronic F127 and their mixture (25% PL/75%PVA).

From 15°C to 25°C it is observed a significant decrease in viscosity of PVA aqueous solutions, followed by a very small variation above 25°C. For the solutions of Pluronic F127, we observed the appearance of a peak at 22°C associated with a conformational transition and above 23°C there is a change in the slope of the intrinsic viscosity dependence on the temperature. Different mixtures PVA/Pluronic F127 were investigated and they present more pronounced maxima at 23°C.

The presence of PVA chains in the vicinity of block copolymer ones diminishes the self-assembling tendency of PL and favors the manifestation of conformational transition at the same temperature, 23°C, followed by a change in viscosity dependence on temperature.

1.2. Correlation of the rheological data with turbidimetric and light scattering curves

The flow curves for PVA/PL and their mixtures were determined at different temperatures and the Newtonian viscosity was followed as a function of polymer composition. We present here 2 different behaviour observed for these systems. Figure 2 shows the dependence of viscosity on the weight fraction of PL (w_2) in the mixture PAV/PL in concentrated solutions at 10°C and at a temperature close to body temperature. In can be observed that at low temperature negative deviations from additive behavior appear for $w_2 > 0.25$, the maximum deviation being registered for $w_2 = 0.5$.

As the temperature increase, due to the interactions between PAV chains and hydrophilic copolymer segments, we see positive deviations from additive rule, more pronounced for excess of PVA in the mixture.

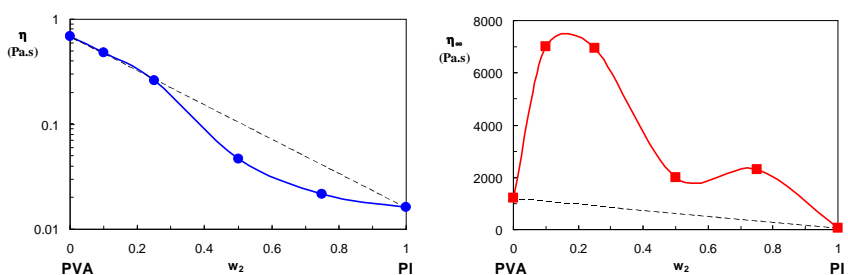


Figure 2. Viscosity as a function of polymer composition for concentrated PVA/PL solutions at 10°C and gels at 37°C.

Some discontinuities were observed in the optical properties dependences on temperature (Figure 3) and the particles size increase around 15°C when the aggregate formation starts.

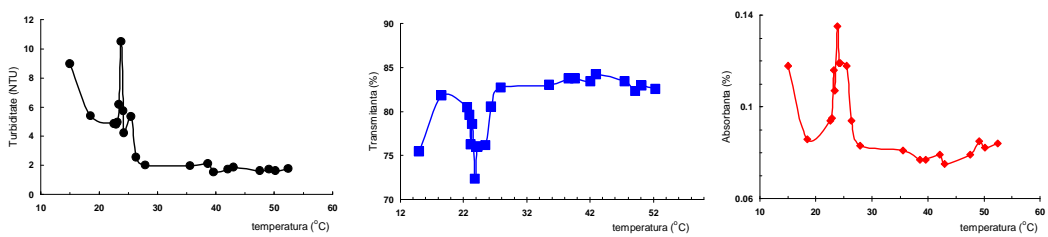


Figure 3. Optical properties as a function of for PVA/PL mixtures in aqueous solutions.

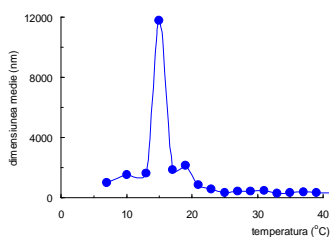


Figure 4. Average particles size as a function of temperature for PVA/PL mixture in aqueous solution.

Objective 2. Chemical gels based on natural and/or synthetic polymers

2.1. In-situ monitoring of the sol-gel transition for chemical gels in presence of natural or synthetic crosslinkers

Hydrogels are chemically or physically crosslinked macromolecular networks with the ability to swell in water or biological fluids. The main disadvantage of the physical gels consists in their inferior mechanical properties compared to the gels obtained by means of a chemical crosslinking. Chemical gels based poly(vinyl alcohol) and chitosan (Figure 5) has special interest for applications in medicine because they are non-toxic, biocompatible and able to absorb efficiently the water.

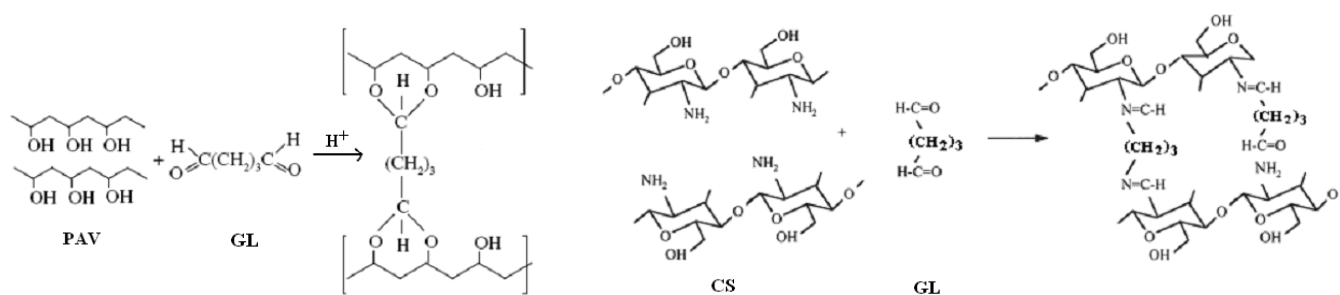


Figure 5. Crosslinking reaction of poly(vinyl alcohol) and chitosan in the presence of glutaraldehyde.

Monitoring the sol-gel transition during chemical gelation was performed by following the viscoelastic parameters (storage modulus, G' , and loss modulus, G'') during the crosslinking of poly(vinyl alcohol) (PAV) and chitosan (CS) in the presence of glutaraldehyde (GL). We established the optimal conditions for obtaining a hydrogel with superior viscoelastic properties as compared with the individual polymers.

Figure 6a shows the evolution of the viscoelastic parameters G' and G'' during the crosslinking reaction at 37°C, the gelation time for which $G' = G''$ was identified about 240 s. It was observed that the gelling time is independent of frequency oscillation at which the crosslinking reaction was followed (Figure 6b). In addition, the final viscoelastic parameters of the obtained hydrogel reached the same values regardless of the oscillation frequency at which the crosslinking reaction was performed. The gelation time, t_g , corresponds to the time at which $\tan \delta$ is independent of the oscillation frequency. It was noted that $\tan \delta (= G''/G')$ decreases in time and gelation time determined by this method has the same value as those determined by studying the viscoelastic parameters in time, i.e., approx. 240 s for PVA and 2400 s for CS.

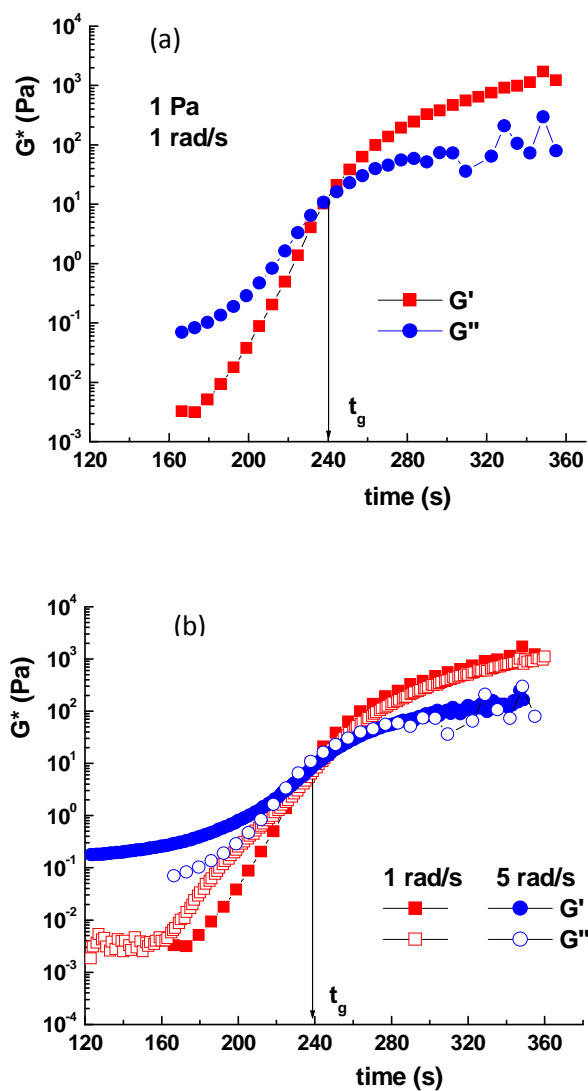


Figure 6. (a) Evolution of the viscoelastic parameters during the crosslinking reaction of PVA in the presence of GL for a molar ratio GL /monomer units of 1/33. (b) Evolution of viscoelastic parameters during the crosslinking reaction of PVA in the presence of GL for different oscillation frequencies (37°C).

Table 1. Parameters obtained from crosslinking PAV and CS in the presence of GL.

Polymer	G'_{∞} (Pa)	G''_{∞} (Pa)	θ' (min)	$\tan \delta$	reaction time (min)
PAV	4660	568	7	0.121	13
CS	850	67	80	0.080	150

2.2. Establishment of the optimal conditions of gelation for obtaining elastic hydrogels

Structure and properties of the chemical hydrogels depends on molecular weight and concentration of the polymer and the concentration of crosslinking agent. To investigate the effect of chemical crosslinker concentration on the final properties of the hydrogel, the crosslinking reaction of PVA with various concentrations of glutaraldehyde were monitored by rheology. The decrease of the amount of glutaraldehyde causes an increase of gelling time for PVA. By increasing the molar ratio GL/structural units of PVA from 1/33 to 1/100, the gelling time increases from 240 s to 690 s and the time to achieve the complete crosslinking reaction increases from 13 min to 54 min.

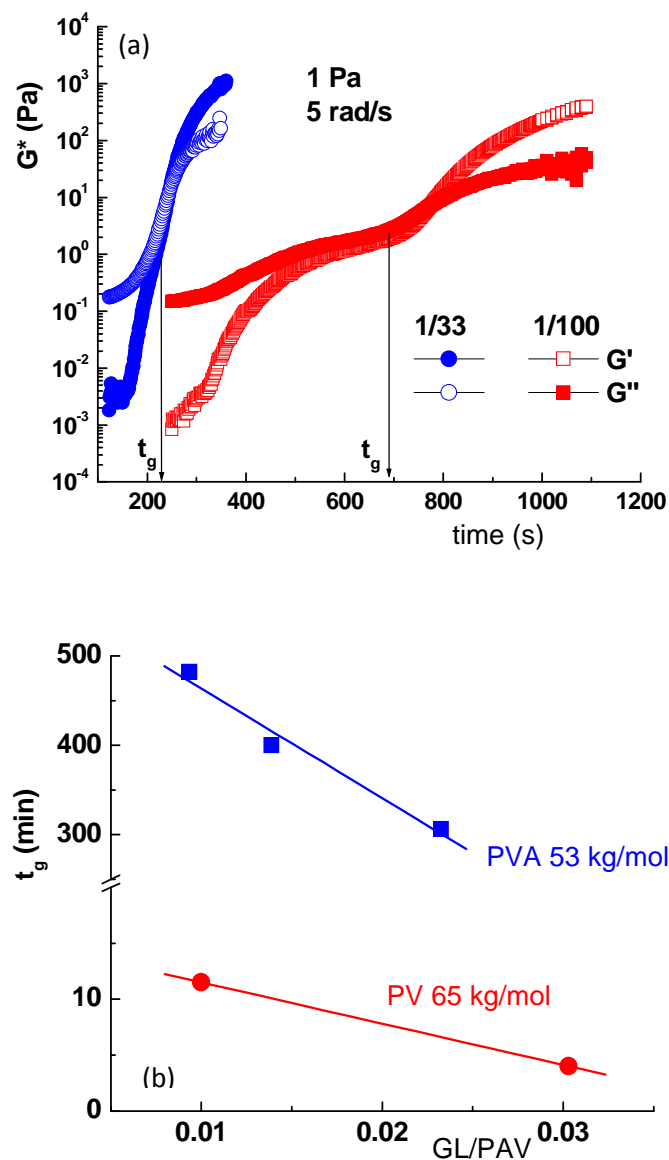


Figure 7. (a) Evolution of viscoelastic parameters during the crosslinking reaction for PVA in the presence of GL for different GL/PVA molar ratios at 37°C. (b) Influence of chemical crosslinker content on the gelation time (●) – our data; (■) - literature data [Kjøniksen and Nystrom, *Macromolecules*, 29, 5215, 1996]

The experimental results concerning the gelation times were in agreement with the literature data [Kjøniksen, *Macromolecules*, 29, 5215 1996]. For the same concentration of polymer in the initial solution, the decrease of the ratio of glutaraldehyde moles to the number of PAV monomer units causes the increase of gelling time. For the same ratio, the gelation time increases with decreasing polymer concentration in the initial solution. Lower temperatures cause an increase of gelation time.

Table 2. Parameters resulted by the monitoring PAV crosslinking reactions with various quantities of GL

GL/PAV structural units	G'_{∞} (Pa)	G''_{∞} (Pa)	θ' (min)	$\tan \delta$	t_{reaction} (min)
1/33 (0.030)	4660	568	7	0.121	13
1/100 (0.01)	4510	520	28	0.115	54

2.3. Investigation of the properties of synthetic and natural hydrogels

PAV gels are characterized by high capacity of water absorption, depending on the degree of crosslinking influenced by the amount of crosslinker (glutaraldehyde) added to the reaction system. The swelling behavior of the PVA gels is shown in Figure 8. A small amount of GL (1/100 ratio) leads to the formation of hydrogel with a low crosslinking degree and a high swelling capacity due to small number of GL bridges formed between PVA chains allowing the penetration of a higher quantity of water. The maximum degree of swelling increases approximately 4.5 times by decreasing the ratio GL/PVA from 1/33 to 1/100. For PAV gel with large amount of chemical crosslinker (1/33), the maximum degree of swelling was achieved in 20 minutes unlike hydrogels with ratio GL/PVA of 1/100 (low content of crosslinker) who achieve the maximum degree of swelling after approx. 80 minutes.

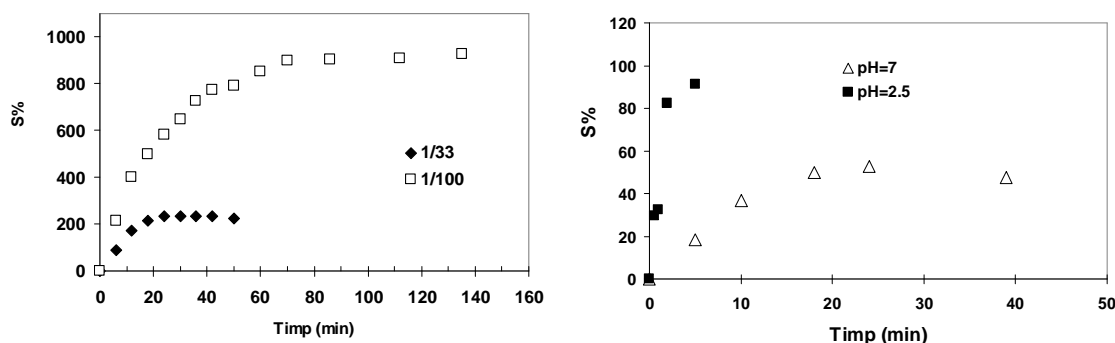


Figure 8. Swelling behavior of PVA (different GL/PVA ratios) and chitosan hydrogels (different pH values) obtained in the presence of glutaraldehyde as crosslinker.

The value of pH influence the swelling of CS hydrogels and at low pH value the solvent diffusion obeys a Fickian mechanism.

Objective 3. Physical gels based on multicomponent polymer systems

We investigated mainly PVA based physical hydrogels: mixtures of PVA with Pluronic F127 were investigated in order to design elastic thermoresponsive hydrogels and PVA with chitosan mixtures were investigated for obtaining robust pH-sensitive hydrogels. The gel formation was monitored through rheological and dynamic light scattering measurements and the conditions of gel formation were optimized for each system. Figure 9 shows for example the evolution of viscoelastic parameters on the temperature at constant composition of the polymer, $w_{PVA} = 0.25$. At low temperatures, the mixture PL/PVA in water presents a liquid-like behaviour. Sol-gel transition occurs between 18 and 28°C and above 28°C the viscoelastic parameters indicate solid-like behavior, a physical network structure is formed.

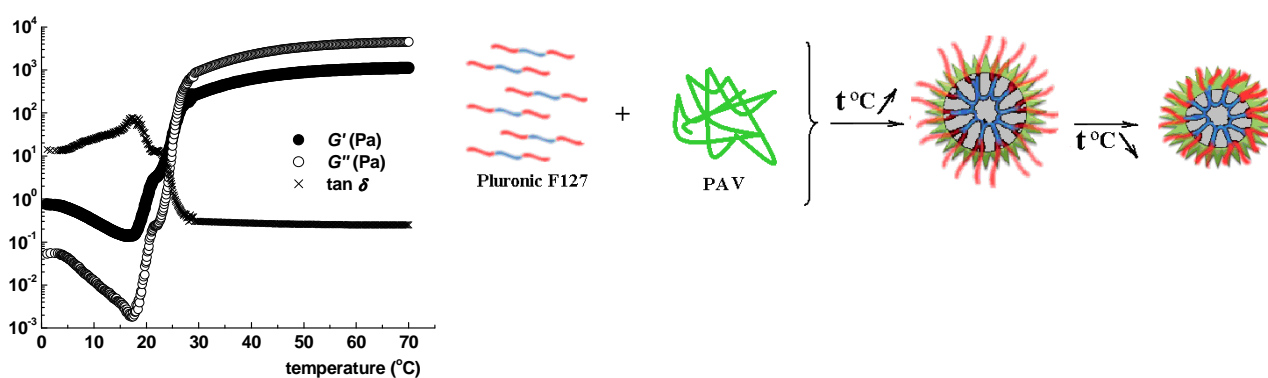


Figure 9. Variation of viscoelastic parameters (G' , G'' and $\tan \delta$) with temperature for Pluronic F127/PVA mixture with $w_{PVA} = 0.25$; Schematic representation of the formation of hydrogels at increasing the temperature. The process is partially reversible, at low temperature the system is colloidal and stable, the polymers are not separated from the aqueous medium.

The transition temperature can be adjusted by mixing two polymers with different transition temperatures by changing the ionic strength of the solution, or by selection of thermal conditions. Thus, the transition state can be reached around 37°C (Figure 10). Hydrogels based on chitosan/PVA mixtures are promising biomaterials to replace skin, allowing rapid healing of wounds. For the same purpose, the polyurethane hydrogels can be also used, they develop physical networks with high elasticity near the human body temperature.

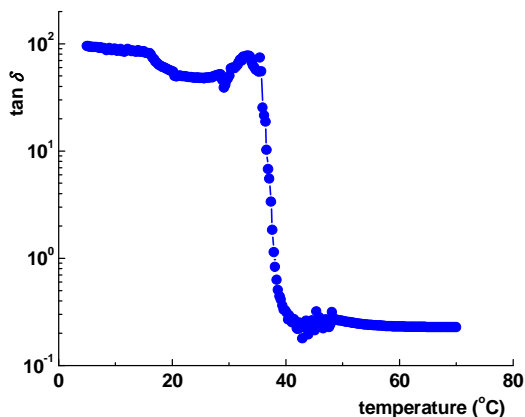
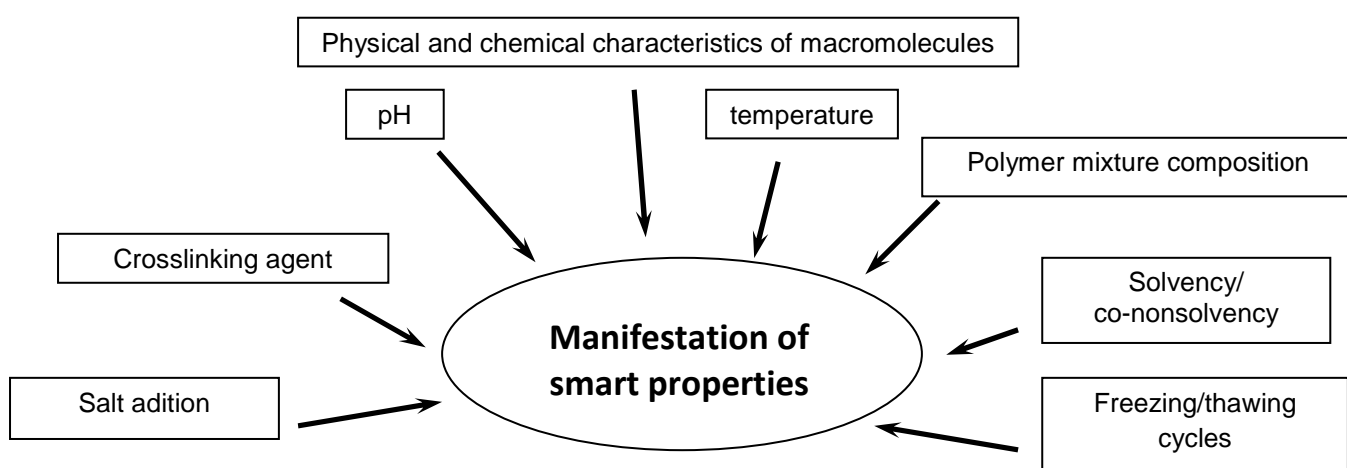


Figure 10. Dependence of loss tangent on temperature during physical gelation of 33% PL and 67% PVA mixture in water.

The main aspects investigated this year are outlined below. Physical mixture of polymers can be an effective strategy for the development of polymeric materials with desired properties, as required in different applications. A major objective was to identify the optimal formulations and working conditions necessary to design stimuli-responsive gels for biomedical and pharmaceutical applications.



All objectives were fully realized and most results were used in manuscripts submitted to publication.

The main results obtained by the project team were included in manuscript submitted to publication in different journals.

- 4 papers published in journals indexed by web of science;
- 8 papers published in volumes of international conferences;
- 7 book chapters were written;
- The team members participated at scientific events with 2 oral presentations and 8 posters.