ISSN : 2249 - 8877 Volume 6 Issue 3

Research & Reviews On Polymer

Full Paper

RRPL, 6(3), 2015 [083-093]

Synthesis, characterization and investigation of thermal response of novel hydrogel based on PEG and AN

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ABSTRACT

The blending hydrogel of hydrophilic- hydrophobic networks produce phaseseparated composite hydrogels. In this report, we have synthesized blend hydrogel based on PEG with molecular weight (2000 MW) and AN as monomer. Hydrogel were characterized by the swelling of the network, namely by the equilibrium- swelling ratio. Swelling of the hydrogel was studied in buffer solution of phosphate saline buffer (PBS) at 25°C. In order to characterization, hydrogel structure was investigate via FT-IR, Scanning electron microscopy (SEM) (LEO-1455VP) was usedto investigation the surface morphology of nanohydrogel,Transmission electron microscopy (TEM) and dynamic light scattering (DLS) techniques were use to measurement size of the nanoparticles. Thermal response ofa novel nano-P (AN-c-PEG) hydrogel has been studied too. The glass transition temperature (Tg)and LCST measured by using DSC. The LCST of the Samples are 28-32° Ctemperature range. Swelling of hydrogels has been investigated with gravimetric method. The swelling rate of the samples decreased with increasing AN content.

KEYWORDS

Hydrogel;
Swelling;
Thermal response;
pH sensitivity.

INTRODUCTION

Hydrogels are polymeric networks that absorb large amount of water while remaining insoluble in aqueous solutions due to chemical or physical cross linking of individual polymer chains[1-4]. We have synthesized thermo sensitive novel blendnanogel based on PEG with molecular weight (2000 MW) and AN as monomer by using a simple method in which used unique and inexpensive monomers. PEG and its "stealth " properties, that is once its attached to definite formulations, allow slow release of the formulation, thus enabling controlled release, as well as reduce uptake of injurious immunoglobins[6,7]. PEG is non toxic, thus, suitable for biological applications and can be injected into the body without harmful effects. It is also an FDA approved material to be utilized in biological applications. Acrylonitrile, containing cyano groups, has been recognized to certainly interact with sugar moieties located in antibodies[8]. Acrylonitrile was chosen as an utilizable andunique monomer, because it is hydrophobic and can further be manipulated to make new functional groups in the nanonetwork to prognosticate

future applications.

In synthesized hydrogel, hydrogen bonding has been observed between polymers chain and cross linker. We used glucose as cross linker that it is not toxic, thus it is ideal choice for biological application.

Transmission electron microscopy (TEM) and dynamic light scattering (DLS) techniques were usedto measurement the size of nanoparticles. We investigated the effect of the difference monomer ratio on the size of particles via dynamic light scattering (DLS). The blending hydrogel of hydrophilic-hydrophobic networks produce phaseseparated composite hydrogels[12]. It is clear that hydrophilic monomers provide a separable advantage in both production and application of hydrogels. If the polymer solution (mostly water) hassingle phase below a specific temperature, which depends on the monomer concentration, and are phaseseparated above this temperature, these hydrogels generally have a lower critical solution temperature (LCST) and the lowest temperature of the phase separation curve onconcentration–temperature diagram. Most applications are related to LCSTbased on polymer systems[13]. Hydrogels with hydrophilic monomers have higher and broader LCST[15-17]. The water solubility of AN was reported to be around 80 gL^{-1}[8], so it can be anticipated that almost all AN molecules should be exclusively be in the organic phase of the micelles formed by the self-assembled SDS molecules.

EXPERIMENTALSECTION

Materials

The monomers used in this study were polyethyleneglycol, (PEG 2000 MW), and acrylonitrile (AN). D-glucose, (GLU), was used as a cross linker and ammonium persulfate (APS) was used as the initiator. Furthermore, Sodium dodecyl sulfate (SDS) used in micelle formulations. All chemicals were purchased from the Aldrich Chemical Company, Inc.

Synthesis

Emulsion polymerization was used to prepare the composite polymer particles. In a typical one pot one-to-one (1:10) mole ratio of PEG to AN hydrogel synthesis, 0.4 ml AN (6.076 mmol) was dissolved in 15 ml of 0.1 M SDS solution in water and 0.158 g glucose was addedto the mixture. Then, 1.213 g PEG was added and the solution was mixed in order to obtain complete dissolution. The whole mixture was then placed in a temperature controlled water bath at 75°C under constant stirring for 15 min and simultaneous polymerization-cross linking was initiated by the addition of 1 ml of APS solution(0.5 M) in water. The polymerization was carried out for at least 2.5h. The monomer feed ratios were varied to obtain information on polymer particle size and thermal property of hydrogel. All nanoparticles were purified by dialysis (Spectra/por 7 dialysis membrane, MWCO 10,000) by changing water every day for 14 days. A series of samples were prepared in which PEG valuewas kept constant and AN level was systematically increased over on PEG: AN (1:10, 1:20, 1:30 and 1:40). The ratio of PEG, AN, crosslinker, initiator and surfactant are listed in TABLE (1).

Characterization of nanoparticles

Dynamic light scattering (DLS) (Brookhaven Instruments Corporation)were utilized to obtain information about the size of the nanoparticles. DLS allows the determination of hydrodynamic radius of a particle based on the relevance between the time dependent fluctuations in the scattered light and the rate of diffusion of a particle in solvent. For each measurement 4 continuous runs were performedand the arithmetic average mean diameter was deter-

TABLE 1 : Composition of the prepared hydrogels

AN(ml)	PEG(gr)	APS(0.1 M)	GLU(gr)	Monomer ratio	Sample
0.4	1.213	1ml	0.158	1/10	1
0.8	1.213	1ml	0.158	1/20	2
1.2	1.213	1ml	0.158	1/30	3
1.6	1.213	1ml	0.158	1/40	4

TABLE 2 : Measured parameters

Maximum point(°c)	Onset point(°c)	Tg(°c)	Size of particle (determind by DLS)	Monomer ratio ($PEG/_{AN}$)	Sample
53.025	33.925	-7.76	146.9	$1/_{10}$	1
58.725	31.175	-7.59	138.9	$1/_{20}$	2
59.075	28.025	-7.14	115.5	$1/_{30}$	3
56.625	32.925	-6.46	179.7	$1/_{40}$	4

mined. Also, FT-IR(Thermo NicoletNexus®670, USA) spectroscopy was used for determination of hydrogel structure. In order to prepare the hydrogels, the samplewas placed in oven at 50°C, the obtained particles were placed in the KBr powder and the spectra were recorded against the background of KBr powder. Samples for TEM were prepared by placing a drop of purified hydrogel suspensionon a formvar coated copper grids and dried at ambient temperature prior to measurement. The TEM micrographs were obtain using a PHILIPS CM120Electron Microscope under vacuum operating at 120 kV. The surface morphology of the hydrogel was examined by scanning electron microscopy (SEM). To obtain SEMmicrographs after swelling,the hydrogel were first equilibrated in PBS at 25°C, then quickly frozen in liquid nitrogen and further freeze-dried for 3 days. The dried powder thus obtained were mounted on specimen stubs with double-sided taps, coated with gold in a sputter coater and examined at 12-16 kV with a tilt angle 45°.

Swelling measurement

Dry hydrogels were weighed and permitted to reach equilibrium swelling state at 25°C in distilledwater and PBS. Accordingly, the hydrogels were taken out from the solvent and the extra of solvent present on their surface was removed by blotting with filter paper. Equilibrium hydration or swelling percent (W (%)) ofsynthesized samples was determined as defined byfollowingeqn:

$$\text{Water content (W \%)} = \frac{W_t - W_d}{W_d} \cdot 100$$

Where W_d is the weight of the dried polymer sample and W_t is the weight after 24 hours of equilibrium[11].

Tg(glass transition temperature) determination

The thermal property of hydrogel was measured by DSC (823e METTLER TOLEDO). The fresh samples were cut into small pieces, and about 10 mg of such hydrogel samples were placed inside an aluminum sample pan. The thermal analysis was performed from -50 °C to 50 °C at the heating rate of 10 °C /min under dry nitrogen atmosphere with a flow rate of 25 mL/min. The inflection of the DSC curve was used to determine Tg by TA software.

LCSTdetermination

The LCST of the swollen hydrogels was determined by DSC. The fresh hydrogel samples were swollen in PBS at room temperature for 4 h before testing. About 10 mg swollen fresh hydrogels were placed inside a aluminum pan, and sealed tightly by a aluminum lid. The samples were heated from 20 °C to 100 °C at the rate of 2°C/min under dry nitrogen atmosphere with a flow rate of 25 mL/ min. The onset point of the endothermic peak of the DSC curve was referred to LCST. Full information about the measured parameters was tabulated in TABLE (2).

RESULTS AND DISCUSSION

Figure (1) shows the proposed reaction scheme for the simultaneous polymerization andcross linking of AN,andPEG monomers in an oil-water micro emulsion system. In the next stage,cross linker and, PEG, started to float on the surface of micelles. When temperature reached to 75° C, PEG and GLU permeated in micelles and by adding the initiator, thepolymerization process is started. Finally, by removing the initiator, surfactant and enreaction monomers, hydrogel networkremained. Structural analysis of samples has been carried out using FT-IR spectroscopy. FT-IR spectra of samples are displayed in Figure (2). Following peaks: (3100-3200)cm^{-1}, (3300-3500)cm^{-1}, (1720-1740)$cm^{-1}$and (1085-1150) cm^{-1}have been observed in all spectra due to OH,NH

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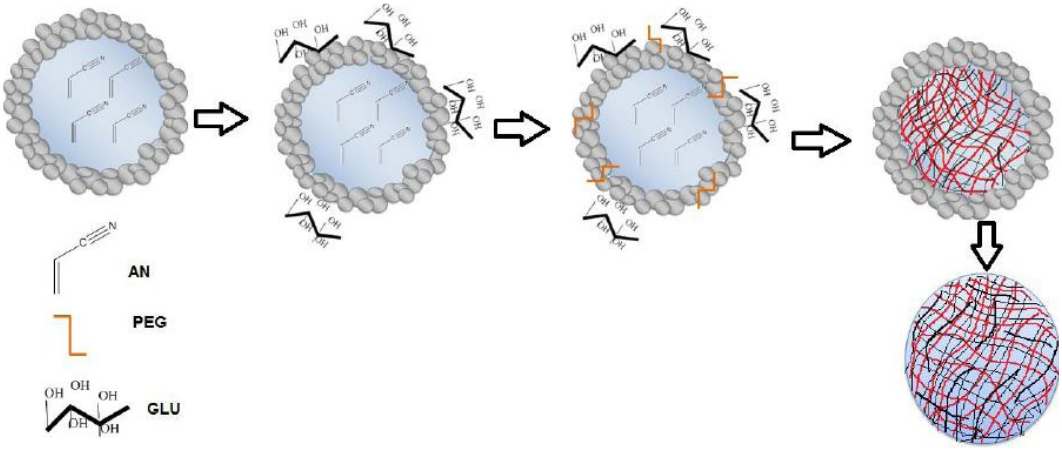


Figure 1 : A shematic representation of the polymerization and cross-linking reaction mechanism of AN with PEG in SDS micelles

(stretching) C=O (stretching) and C-O-C (stretching-vibration) bandsrespectively. In addition,the newly appeared FTIR peak in Figure (2, sample 4) at theregion of (2230-2250)$cm^{-1}$is assigned to symmetrical C≡N stretching vibrations while in other the samples (1, 2 and 3) this peak is not observed. This phenomena shows that the number of nitryl groups increase by increasing of AN valueand a number of them without hydrogen banding were increased change of region absorption banding due to constitute of hydrogen banding among of monomer functional groups with cross linkers that shown in Figure (3). To gain further insight into the features, morphologies and size of the samples analysis of them was performed using SEM, DLS and TEM techniques. Figure (4) shows the SEM micrograph of thenano-P (AN-c-PEG) hydrogelbefor (a) and after (b) swelling. Hydrogel sizes were also analyzed through DLS measurements. In DLS technique, all themeasurements were made with a tilt angle 45°. In these experiments, intensity fluctuations are analyzed using photon correlation spectroscopy (PCS) due to Brownian motion of nanoparticles, to give either a simple mean size and polydispersity or more complete distribution of the data[13]. Particle size distribution and diagram of particle size vs. samples illustrated in Figures (5) and (6),respectively. These figures show that the size of the hydrogels in samples (1-3) decreases and then increase in sample 4. Transmission electron images in Figure (7)displays the sample obtained under optimum conditions. We also investigated the effect of variant monomer ratio on the size and swelling of nanoparticles. The size of swelling behavior was observed in prepared hydrogel nanoparticle in PBS and was investigated in a controlled temperature. Figure (8) shows the diagram of swelling. From Figure (8), the swelling ofsamples in PBS buffers after 30 and 510 min is plottedthatillustrates swelling data similar to DLS information. Weobserved a minimum point in sample 3. There are various parameters that affect the size of nanoparticle, such as, nature and level of monomer, cross linker, and surfactant, temperature, and time of reaction[14, 15]. Figure (6) shows that the change of particle size depends on the increase of AN value. DSC can measure the degree of crystalline and glass temperature (Tg) changes. Tg is an important parameter since in polymers, systems above the Tg are characterized by a rubbery state and high mobility of polymer chains, leading to a free volume for diffusion of drug to occur. If the system is below the Tg, then the polymer is in glassy state and diffusion is difficult[18]. Tg for poly (AN) is in the range of 85-100 °C with increasing (AN) wt%, the Tg increase. The Tg of PEG depend on its molecular weight and, temperature glass is increase with molecular weight increasing. In the blend hydrogels when the monomer ratio change, Tg nearly to effective monomer in hydrogel structure. Figure (9) shown that with increasing AN concentration the Tg is increased. In thishydrogel,Tg has a negative value that causes diffusion in body temperature that is more effective.

DSC samples are shown in Figure (10), maxi-

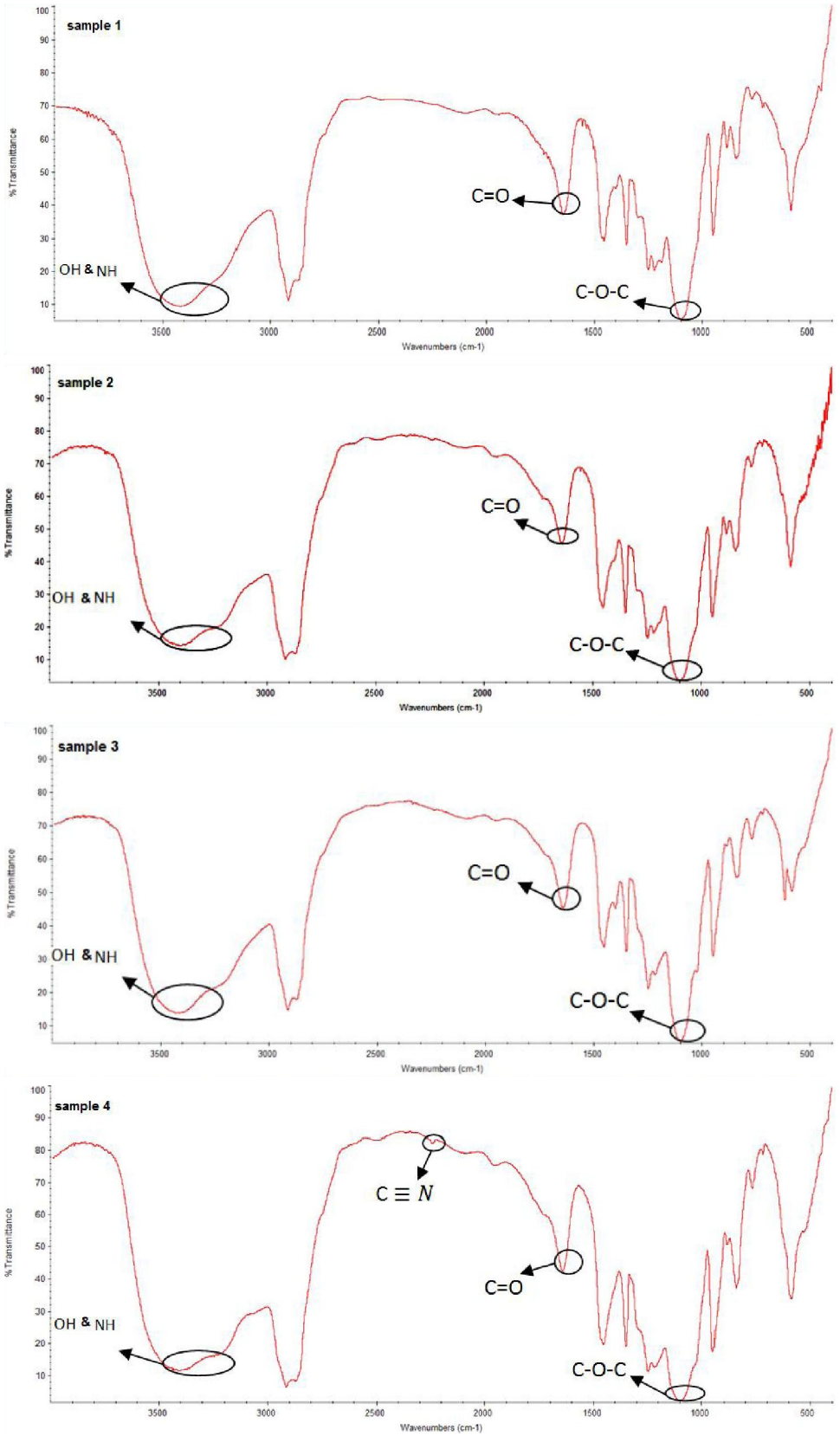


Figure 2 : FT-IR spectra of samples

mum and onset point on the graph to increase the percentage of AN are presented in Figures (11)and

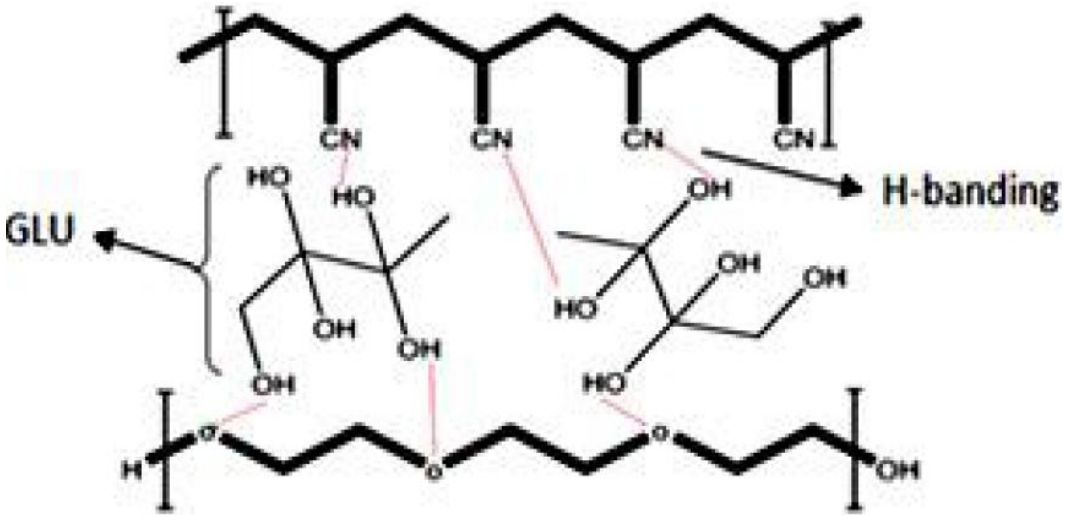
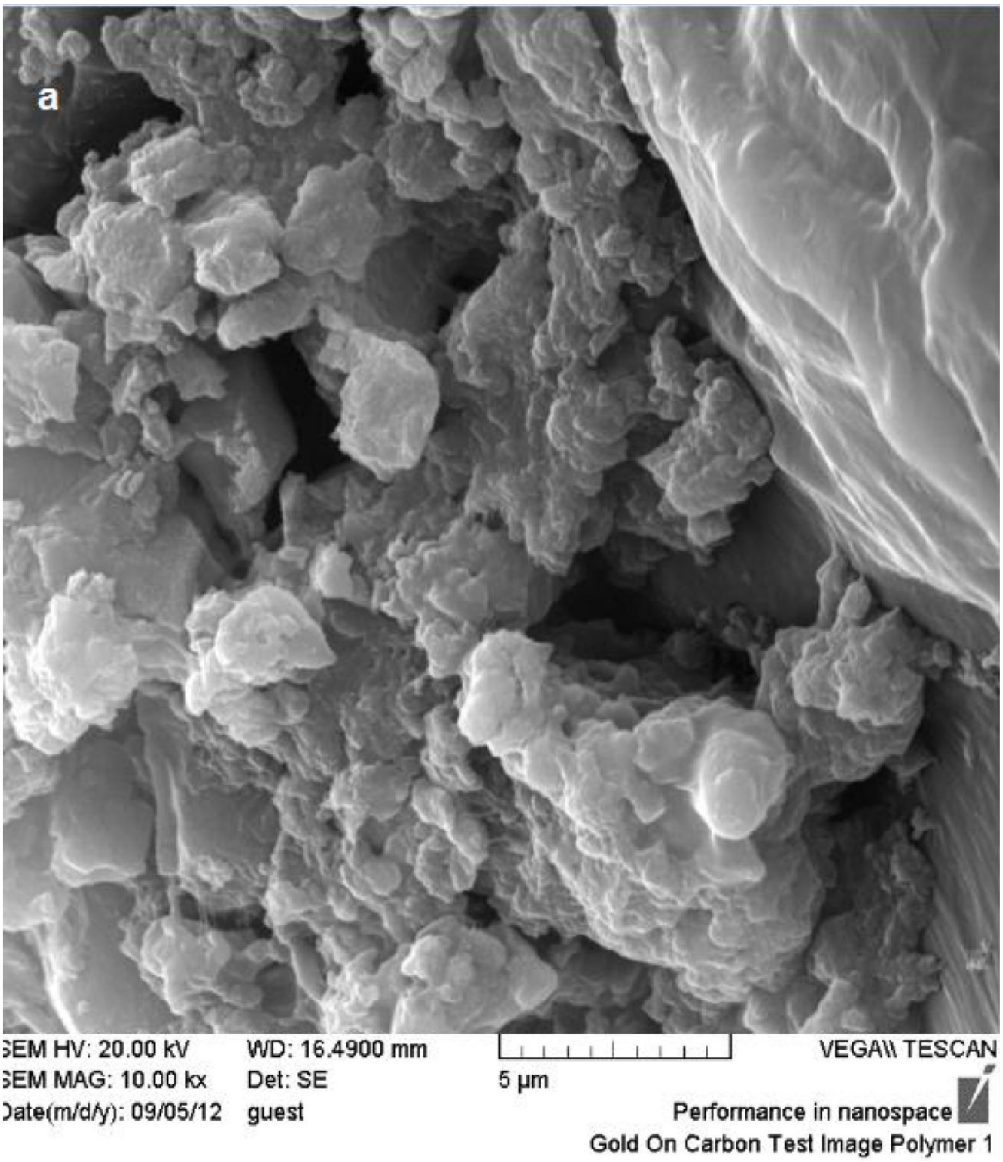


Figure 3 : Shematic of formation of hydrogen bandin between monomers and Crosslinker; (Red lines demonstrator hydrogen banding)



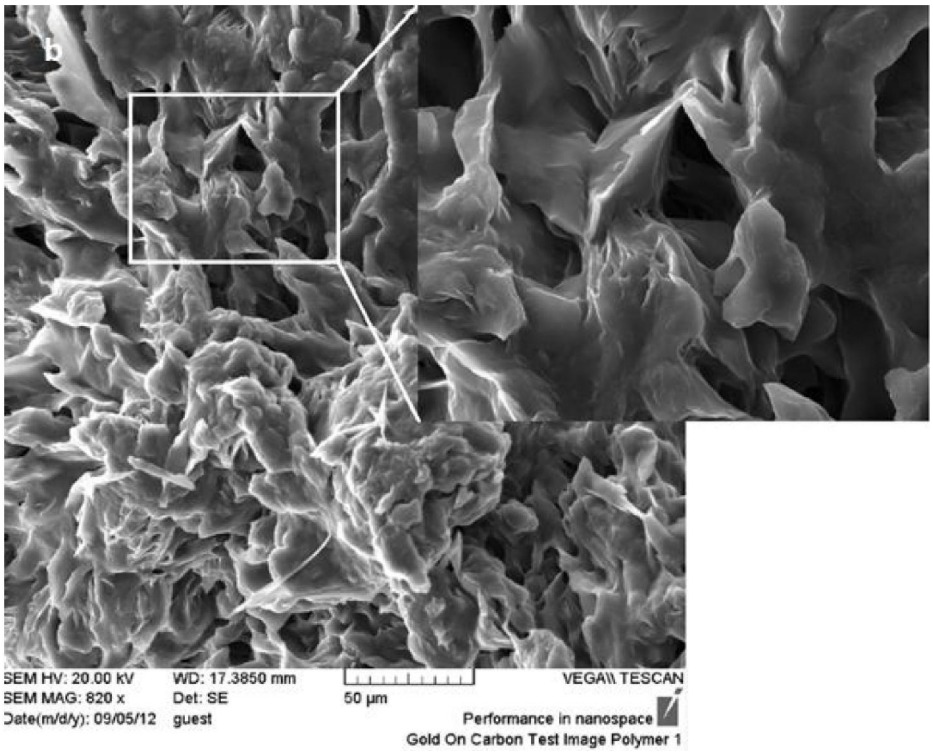


Figure 4 : SEM of the hydrogel, show surface morphology of hydrogel. (sample 1: monomer ratio of PEG To AN 1/ 10.before swelling(a), after swelling (b).show surface morphology of hydrogel

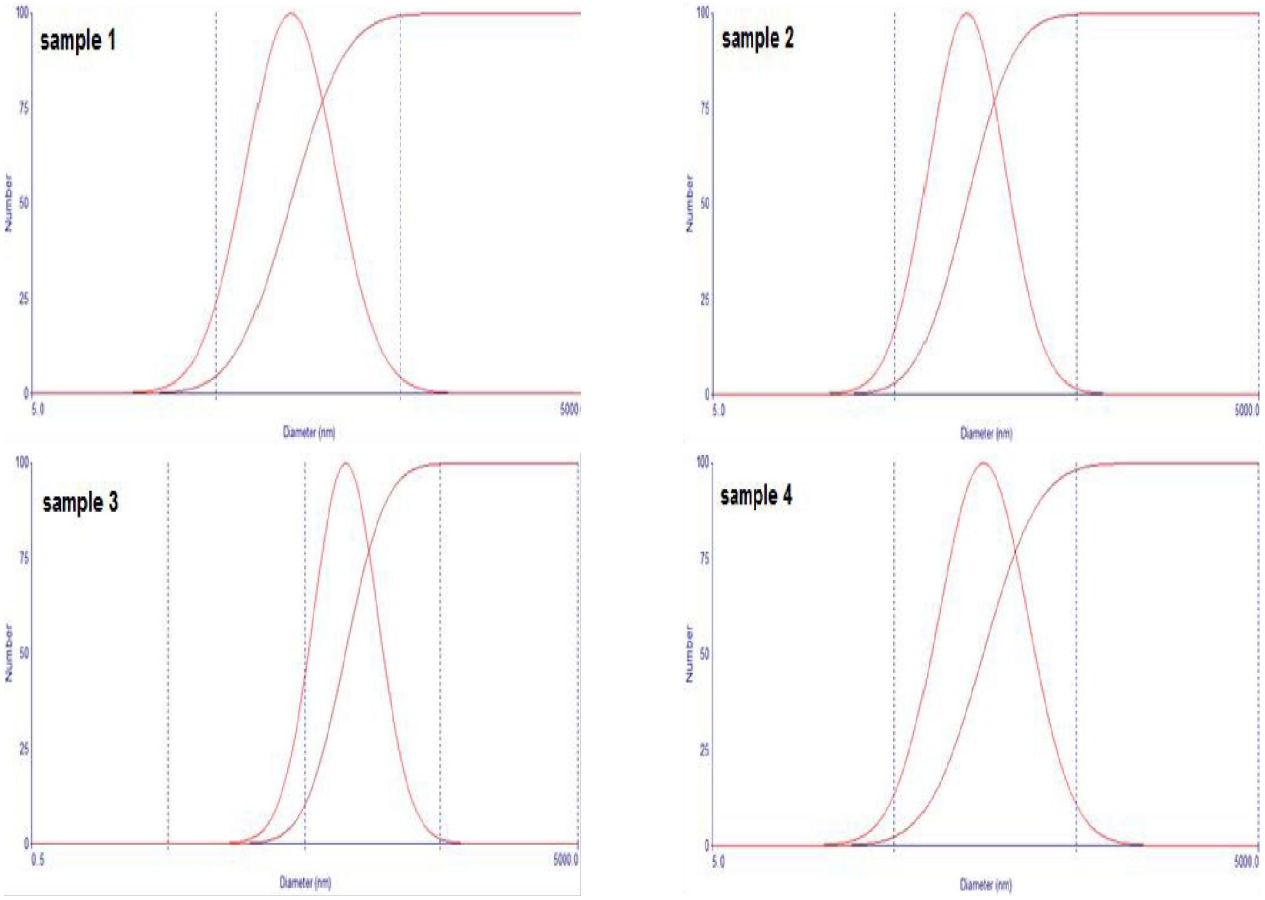


Figure 5 : Particle size distribution of samples determinedby DLS

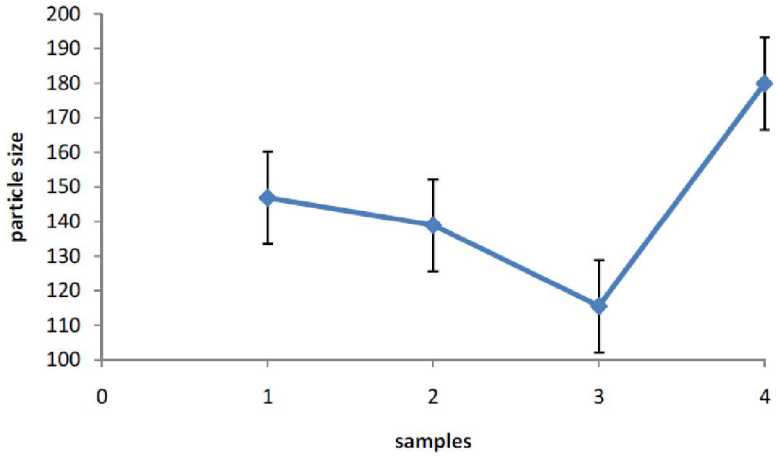


Figure 6 : Diagram of particle size v.s samples

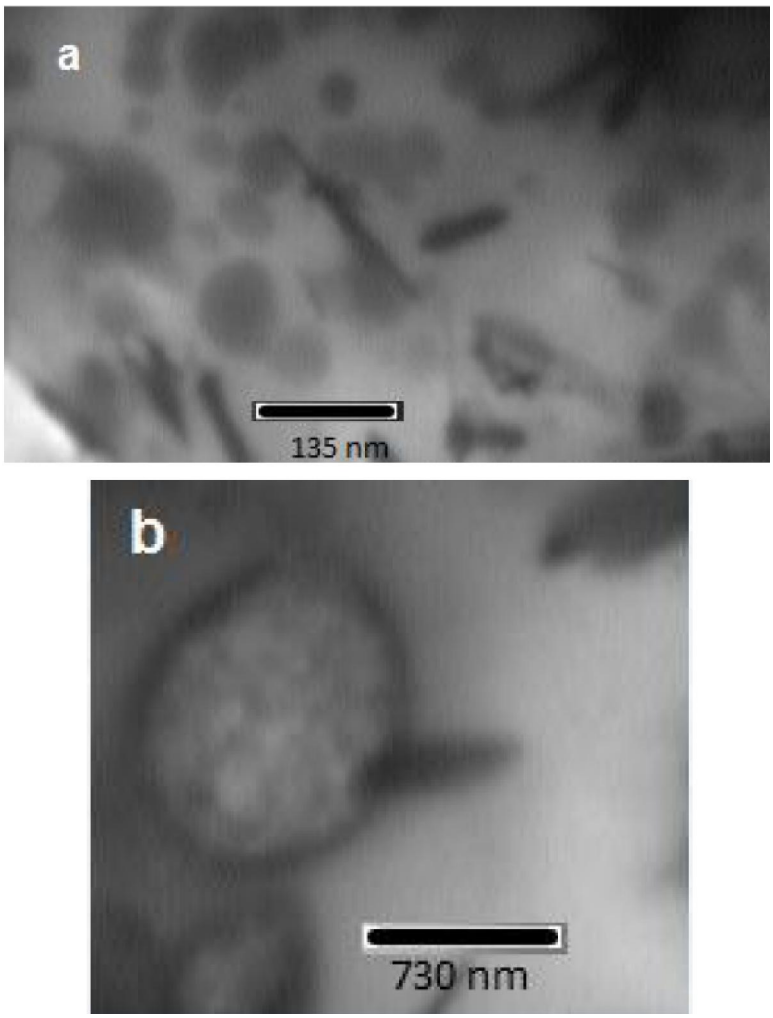


Figure 7 : TEM images of nanohydrogel based on PEG and AC crosslinked with GLU for sample 1(monomer ratio1/10), These images demonstrated formation of micelles

(12),particle size decrease with increasingof AN content, in the sample (1-3) but it increases in the sample 4 (particle size are obtained by DLS).

According to Figure (11), LCST in the samples (1-3) by increasing the AN has dropped. Whenhydrophobic monomer (AN) increased, the hydrogen bonding between water molecules and the hydrophilic hydroxyl groups of the hydrogel would

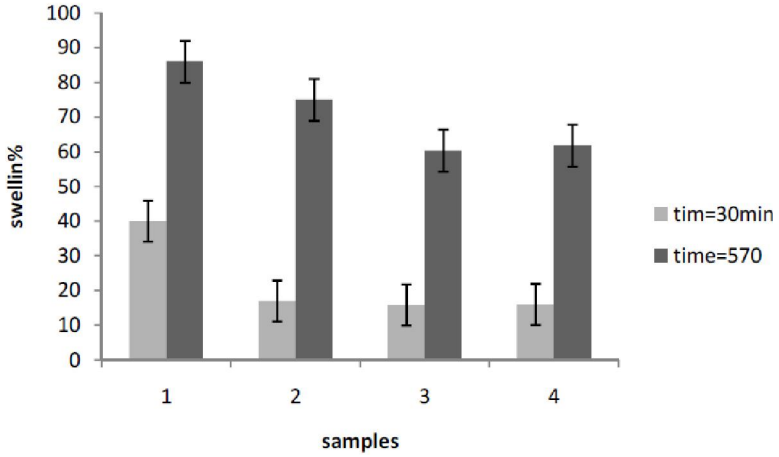


Figure 8 : Swelling dependency of AN after 30 and 510 min in PBS

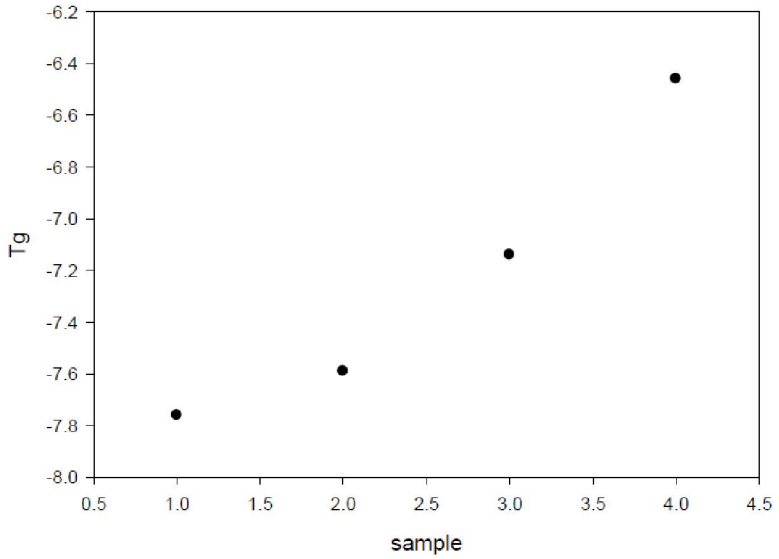


Figure 9 : Graph of sample Tg changes

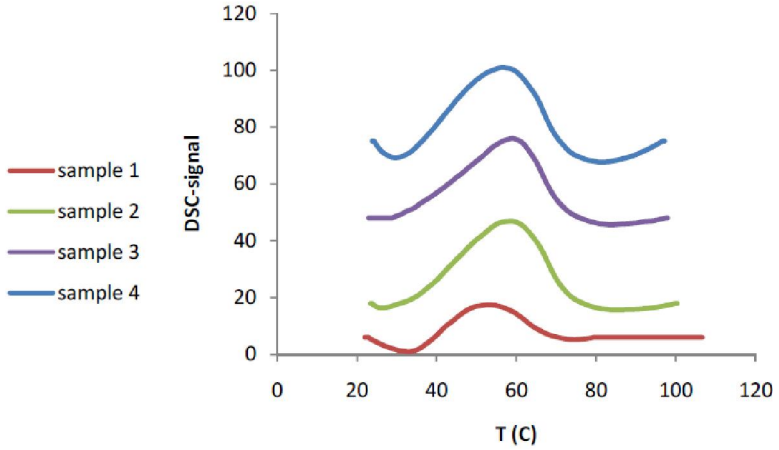


Figure 10 : DTA the rmograms of the P (AN-c-PEG) nanogel in PBS

be decreased. Thus, the number of hydrogen bonds need to be broken, would be decreased. As a result, the LCST of hydrogelshift to the lower temperature that is in significant accord with data given in the DLS in Figure 5. Generally, hydrophobicmonomer scan bereduced the LCST, ithasthe effect ofparticle

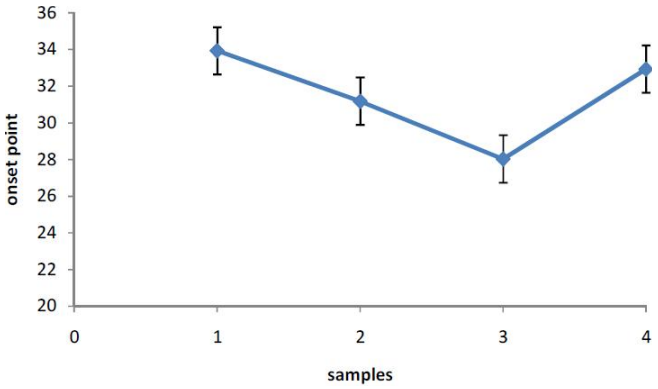


Figure 11 : Onset point vs. samples

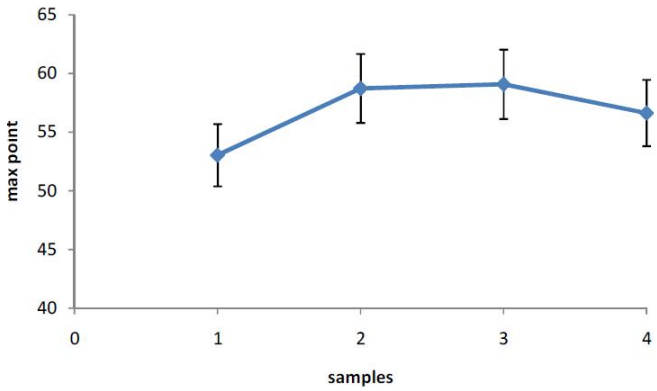


Figure 12 : Maximum point vs. samples

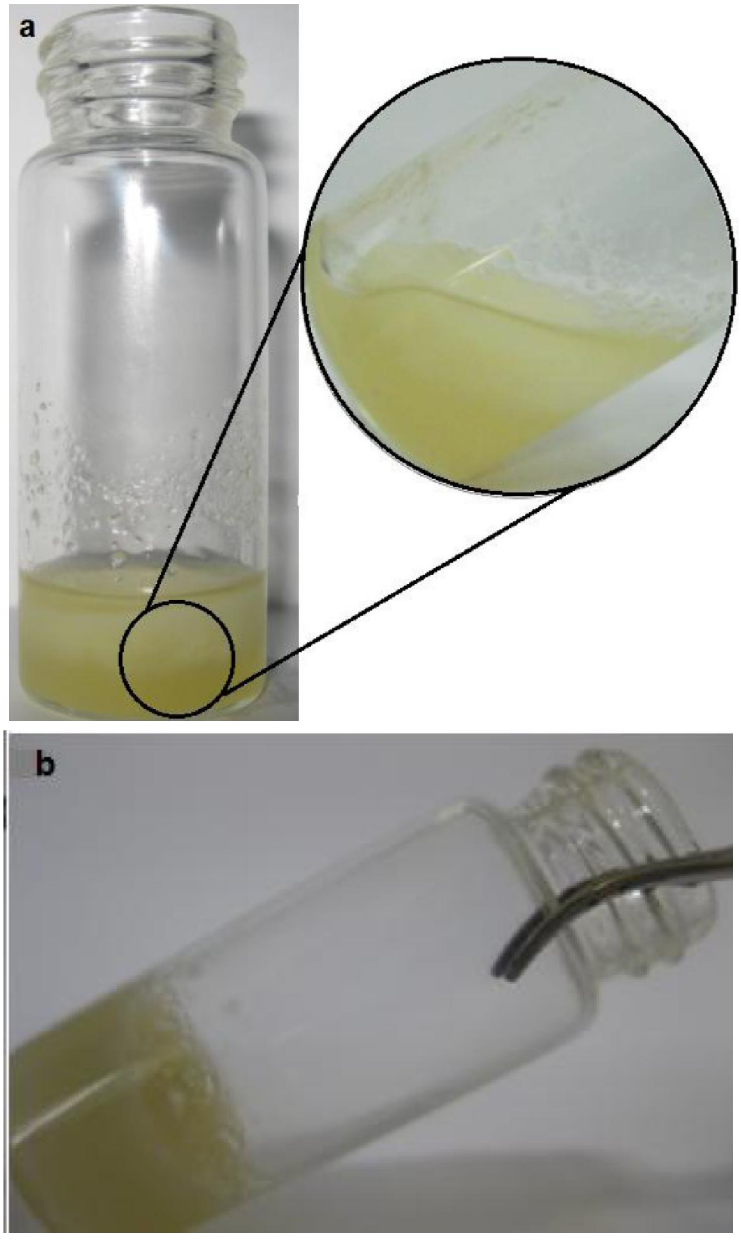


Figure 13 : P (AN-c-PEG) hydrogel at different temperatures: (a) above LCST (b) at room temperature

sizeon the peak. This property gives one the ability to control the release of active agents. Adjustment

of LCST near body temperature (37°C) is important especially for the drug delivery application. In other words, it is possible to liberate the active agents for longer periods of time from nanogel network with an appropriate hydrophobic group that provides broader LCSTs P (AN-c-PEG) hydrogel. Figure (13) shows that the hydrogel becomes insoluble when the temperature increases above the LCST,but it turned to gel at room temperature.

Although the LCSTof poly (PEG-c-AN) hydrogels could be modulated by adjusting the content of ANin the hydrogel network, the swelling ratio and of hydrogels decreased as ANcontent in polymers increased. The hydrogels network bearing cyano groups prepared in this study are potentially suitable as materials in the fields of the drug delivery.

CONCLUSION

In summary, a new hydrogel with simple monomers was synthesizedby glucose as a non toxic cross linker. Effects of increase AN on swelling and particle size were evaluated. We found that by increasing the AN value,the size of hydrogels first decreased and then increased. The glass transition temperature has an important role in controlling the diffusion rate. If temperature is less than the Tg the diffusion comes down. But reverse diffusion attemperatures above Tg rises sharply. This hydrogel hasa Tg lower than bodytemperature which is an advantage. Response to environmental stimuli, such as temperature makes this hydrogel as an idealchoice for nanocarrier in drug delivery systems.

ABBREVIATIONS USED

DSC, differential scanning calorimetry; LCST, lower critical solution temperature; HCST, higher critical solution temperature; UCST, upper critical solution temperature; Tg, glass temperature.

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