BULLETIN OF NATIONAL ACADEMY OF SCIENCES
OF THE REPUBLIC OF KAZAKHSTAN
ISSN 1991-3494
Volume 5, Number 369 (2017), 30 – 36

A. Esimova[1], M. Muratalin[2], S. Aidarova[3], B. Mutaliyeva[1], G. Madybekova[4]

[1]M. Auezov South-Kazakhstan State university, Shymkent, Kazakhstan,
[2]Tengizchevroil LLP,
[3]K.Satpayev Kazakh National research Technical University, Almaty, Kazakhstan,
[4]South-Kazakhstan State Pedagogical institute, Shymkent, Kazakhstan.
E-mail: Mbota@list.ru

RESEARCH OF STIMULI-RESPONSIVE MICROGELS FOR USE IN MICROENCAPSULATION

Abstract. Surfactant free emulsion polymerization (SFEP) technique was employed in order to copolymerize PNIPAM with acrylic acid (AA). The resultant microgel particles exhibited multi-responsive behaviour being sensitive to changes in temperature, pH.These microgel particles were characterized using dynamic light scattering (DLS), scanning electron microscopy (SEM) and transmission electron microscopy (TEM). The behaviour of the particles under various conditions of temperature, pH are described and discussed in this paper and several observations, such as swelling/deswelling transitions of PNIPAM-based microgelswere reported for the first time.The microgel containing AA exhibit characteristic temperature-sensitive behaviour with volume phase transition temperature (VPTT) being in the range of 25-50 ^{0}C and showed pH-sensitive features as the particles collapsed at low and swelled at high pHs. Results of researches show the changing size and consequent swelling/desweling of the microgel particles. The results clearly show that in swollen state the microgels are largerdue to the presence of COO-groups in the microgel. The concentration of acrylic acid has impact on the particle size of the collapsed particle, i.e. the particle size at pH 1,0. It was established that the diameter of the collapsed particle is increasing with the increase of incorporated acrylic acid concentration. PNIPAM microgels containing added acrylic acid undergo considerable shrinking/swelling transition with the change of pH, i.e. microgels contract at lower pH levels and swell with increasing of pH.Swelling of the particles at the pH level of the blood in the human body, which is in range of 7.35 to 7.45, as well as having lower critical solution temperature in the range of temperature of human body gives an opportunity to develop further these microgel particles as potential drug-delivery agents.

Keywords: N-isopropylacrylamide-based microgels, drug-delivery systems, pH-sensitive, temperature-sensitive microgels.

1. Introduction. A gel is a solid, jelly-like material which is a three-dimensionally crosslinked network in a fluid, and, therefore, exhibits properties which are ranging from soft and weak to hard and tough. Mostly, gels consist of fluid which ensnares a solid three-dimensional crosslinked polymer network; hence such gels have a density close to that of the fluid which is composing them. The internal solid network of the gel can result from physical bonds or chemical bonds, as well as any crystallites or junctions that will remain intact within the extending fluid. Virtually any fluid can act as an extender including water (hydrogels), oil and air (aerogel) [1].

A hydrogel is a network of crosslinked polymer chains which themselves are water-soluble (hydrophilic). The crosslinks act to join the structure together. The chemical nature of the polymer network of the hydrogel dictates its behaviour. Hydrogels consisting of such materials as N-isopropylacrylamide (NIPAM) are temperature-sensitive, hence swell/shrink with the changes of temperature [2]; poly(2-vinylpyridine) and polyacrylic acid hydrogels are pH-sensitive as they respond for the changes of pH in the surrounding media [3]. Moreover, it is possible to produce hydrogels which are responsive to ionic strength, presence of certain materials and other external stimuli.

Microgels, which are essentially small particles of hydrogels, have the same polymer chemistry but their physical molecular arrangements are different. A microgel particle is usually a crosslinked latex particle which is swollen by a good solvent [4].

Microgels that have good swelling/deswelling properties and also temperature and pH sensitivity can be considered as good candidates for environmental applications. This paper is devoted to principally poly(N-isopropylacrylamide) [PNIPAM] microgel particles and its derivatives and is based on the monomer N-isopropylacrylamide (NIPAM). PNIPAM microgel particles are temperature-responsive because of the presence of the hydrophobic isopropyl group and the hydrophilic amide group in its side chains. PNIPAM microgels should therefore be temperature and pH sensitive respectively and exhibit good swelling ratios in making them suitable to be developed as functional agents for environmental and pharmaceutical applications in further work. For example, such "smart" materials could be used as water-shutoff agents to reduce the volume of water that is extracted from an oil well in addition to the oil [5].

Moreover, modified poly(N-isopropylacrylamide) [PNIPAM] microgel particles could be synthesized with other functionalities making the resultant microgels sensitive not only to temperature but to other stimuli [6, 7]. Such microgels could have the potential to be used in both environmental and pharmaceutical applications. Conceptually, microgels could also be developed to be sensitive for certain molecules whereby they swell, or contract, in their presence. In this work microgels sensitive to copper or glucose have been prepared. Thus, the microgels have the potential to be used as sensors, extractants or as drug-delivery systems. For example, if a microgel is sensitive to glucose at physiological pH and temperature can be developed it could be used to control the release of insulin and hence be used in the treatment of diabetes, which according to the World Health Organization diabetes causes 5% of total death in the world [8]. At the present time insulin is mainly delivered by injection. So, controlled insulin release could solve such problems as repeated glucose level checking and injections several times a day, which is either painful, or not performed frequently enough, to ensure a stable glucose level in the blood.

Such microgels have been investigated by many researchers in the past [9-14],pH- and temperature-responsive microgels were employed as introductory materials in this work. As the literature relating to microgel dispersions of different structure and physico-chemical properties was studied, it was decided to produce NIPAM based microgel particles firstly in order to understand the polymerization procedure and generally practice the synthesis process. After that acrylic acid was incorporated into the microgel structure by copolymerizing the corresponding monomer with NIPAM; this led to producing pH- and temperature-responsive microgels. These microgel particles have a higher lower critical solution temperature (LCST) in comparison with PNIPAM microgels. The surfactant-free emulsion polymerization technique was employed to produce the microgel dispersions mentioned above.

Thus, the microgels have the potential to be used as sensors, extractants or as drug-delivery systems.

2. Materials and methods.

2.1. Materials and procedure. The classical surfactant-free emulsion polymerization method was used to prepare the microgel dispersion of PNIPAM and P(NIPAM-co-Acrylic acid) [P(NIPAM-co-AA)] [15]. The main monomer which was employed to synthesize the microgels was N-isopropylacrylamide (NIPAM). Acrylic acid was put in an inhibitor remover column in order to remove the inhibitor, hydrochinonemethylether. The crosslinker N,N'-methylenebisacrylamide (BIS) was used to prepare all microgel particles.The initiator, potassium persulfate (KPS), was Analar grade material.

Dialysis membrane with molecular weight cut-off (MWCO) of 12-14000 Daltons was used for removing unreacted monomer.

All chemicals were purchased from Sigma Aldrich, except N-isopropylacrylamide, which was purchased from Acros Organics and BDH Chemicals, respectively. Analytical grade deionized water (Imperial College London: Triple Red, resistivity > 18 MΩ cm) was used in all experimental procedures. Dialysis was employed for purification of all the colloidal dispersion of microgels.

2.2. Dynamic Light Scattering. A Brookhaven ZetaPALS, zeta potential and particle size analyzer, was used to determine the size of the microgels for all samples.The sizes of the PNIPAM-based microgels were measured at different temperatures ranging from 25 to 55^{0}C.

2.3. Freeze-drying. Due to the fact that samples have to be completely dry for SEM imaging and drying in the oven resulted in the formation of a film. 10 mL of each sample were poured into glass tubes, and tubes immersed in liquid nitrogen. Frozen samples were placed in standing 50 mL centrifuging tubes (Sterilin), which were put into freeze-dryer Heto Power Dry LL1500 (Thermo Scientfic) for one week.

2.4 Scanning Electron Microscopy. Dry samples were pasted to the carbon pads (Agar), which were stuck on the aluminium stubs (Agar) of the SEM. Samples were sputter coated (Emitech K575X) with a 10 nm film of gold (Emitech) and images obtained with a JEOL JSM 5610LV electron microscope.

2.5 Transmission Electron Microscopy

A small amount of diluted solution of each sample was dropped on a copper grid Formvar/Carbon 300 Mesh Cu covered with carbon (Agar). Samples left for 24 hours to dry out at room temperature.

Two samples were heated up to 600C in the oven and a small amount of the sample was dropped on to similar grids as mentioned above. Samples were dried in the oven at 600C for 2 h. This was made in order to obtain the images of collapsed microgel particles. Images were obtained with a TEM JEOL 2010 200 kV and the microscope.

2.6 UV-VIS spectroscopy

According to the Beer-Lambert law, which states that the absorbance of the solution is directly proportional to the concentration of the absorbing species in the solution and the path length, UV-VIS can be used to determine the concentration of the absorber in the solution.

3. Results and discussion. The particle sizes of P(NIPAM-co-AA) microgels were determined as a function of temperature at pH 6.0. These investigations were run on a ZetaPALS instrument which has an internal heating facility. The samples were investigated in the range of temperature between $25^0$and 50^0C. Figure 1 shows the consequent swelling/desweling of the microgel particles. The swelling of the particles occurs because as the temperature decreases, the PNIPAM dissolves further into the water as the lower critical solution temperature (LCST) is reported to be 32^0C [16]. Although swelling occurs above the LCST, it must be remembered that the LCST is the phase transition temperature for an infinite molecular weight polymer and that the solvency will be improving before the LCST is reached. Also the N,N'-methylenebisacrylamide (BIS) is more hydrophilic than NIPAM (it has no isopropyl groups), and so it may be expected to have a volume phase transition temperature (VPTT) slightly higher than 32^0C.

The effect of adding acrylic acid to the microgels is to increase their particle size. This can be seen both in the collapsed state at 50^0C, but more particularly in the swollen state at 25^0C. In order to investigate this behaviour more simply in Figure 2 the swelling ratio, i.e. the particle size at any given temperature divided by the collapsed particle size (i.e. 50^0C), is plotted.

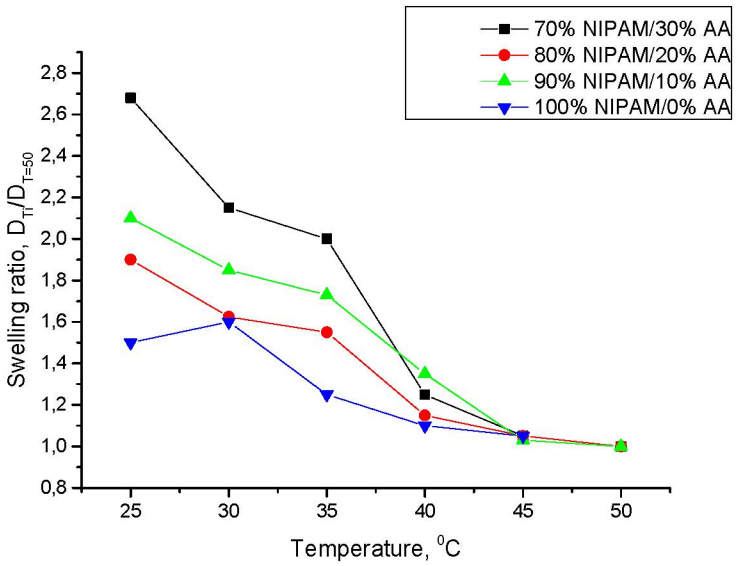

Figure 1 – Swelling ratio of the microgel particles with different concentration of acrylic acid groups as a function of temperature at pH=6.0 (electrolyte concentration $2\cdot10^{-5}$mol/l)

Figure 1 clearly shows that in swollen state the acrylic acid containing microgels are larger. This is due to the presence of COO- groups in the microgel. The pH of the microgels was 5.5-6.0, well above the pKaof acrylic acid which is 4.4 [17]. Likewise the electrolyte concentration is very low (approximately $2\cdot10^{-5}$ mol/L), thus the charges are only weakly screened by the solvent and so the charges repel each other