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РЕСПУБЛИКИ КАЗАХСТАН

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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 25^0-50^0C 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 25^0C to 55^0C.

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.

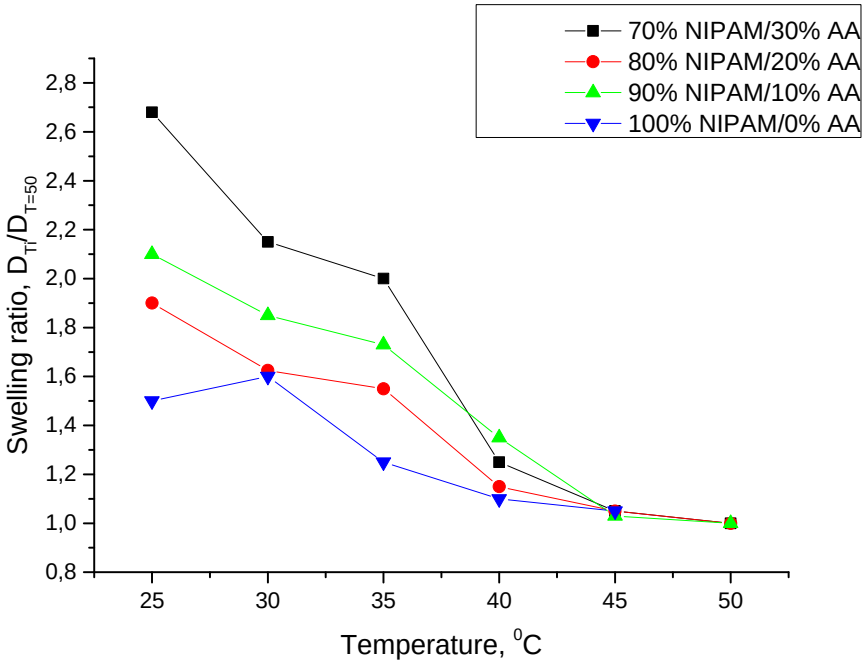

Figure 1. Swelling ratio of the microgel particles with different concentration of acrylic acid groups as a function of temperature at pH=6.0 (electrolyte concentration $2 \cdot 10^{-5}$mol/l)

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 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 $2 \cdot 10^{-5}$ mol/L), thus the charges are only weakly screened by the solvent and so the charges repel each other causing the microgel to swell. Not surprisingly the greatest swelling is seen in the microgel containing 30% of acrylic acid groups.

Careful inspection of Figure 1 shows that the greatest swelling of the microgel containing no acrylic acid occurs between 35^0-30^0C, whilst for those with acrylic acid occurs between 40^0-35^0C, suggesting that the LCST of the acrylic acid containing PNIPAM microgels is increased somewhat. This is hardly surprising as the charged incorporated acrylic acid does increase the hydrophilicity of the copolymer and so it is expected to shift the LCST to higher temperatures. It is of interest to note that the LCST has been shifted to close to body temperature, i.e. approximately 37^0C; a shift of the VPTT for analogous hydrogels has also been reported recently by other authors [18]. Both the presence of counterions, which increase osmotic pressure, and increase in the average interchain distance due to Coulombic repulsion are the reasons for this shift. Other researchers observed similar behaviour of microgels with partial deprotonation of acrylic acid groups as well [19], [20], [21]. For example, Jones et al. [19] observed such behaviour of microgel particles; however, the concentration of acrylic acid groups in the microgel particles synthesized by these researchers was lower (approximately 5%) in comparison with those samples of microgel dispersions employed in this research. Hence, similar behaviour of the microgel particles at different temperatures occurs due to increase of acrylic acid groups which have to be deprotonated.

The ZetaPALS instrument not only measures the particles size, but also provides data about polydispersity of the microgels. For all samples the polydispersity is lower than 0.1; hence, did not change significantly with temperature, suggesting that the microgels are dispersed and not flocculated.

Response of the Microgels to pH

The effect of pH on size of the microgel dispersions consisting of the copolymer of NIPAM and acrylic acid particles were investigated using a ZetaPALS instrument.

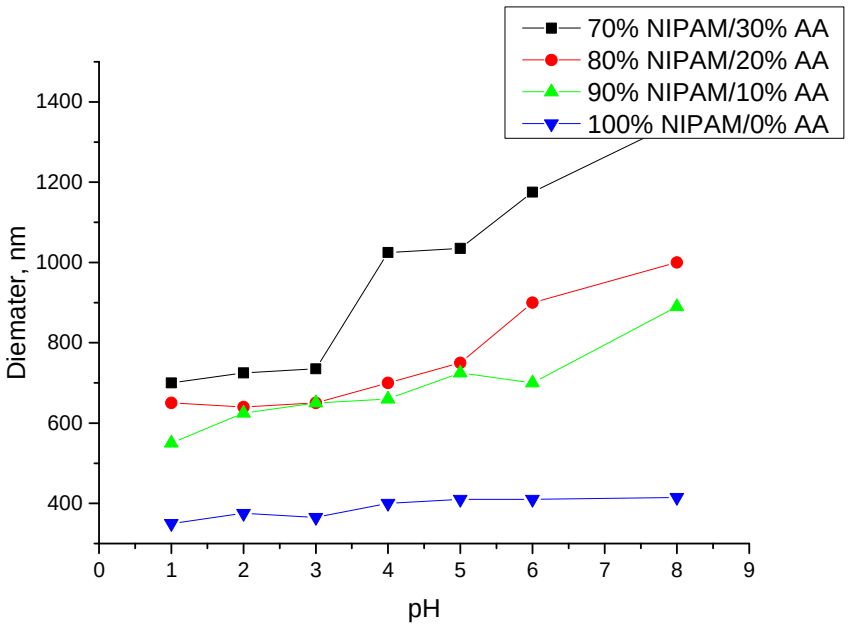

Figure 2. The diameter of the microgels with different concentrations of acrylic acid groups as a function of pH at 25^0C

Figure 2 shows the results of these investigations. As can be seen from Figure 2, considering firstly the microgel without acrylic acid in its structure, the particle size remains almost constant over all the range of applied pH changes. In fact there is a slight contraction of the particles below pH 4.0. This may simply be due to the error in the measurement, but may be due to some hydrolysis of the amide group of NIPAM, either following impurities in the synthesis or the monomer which was quoted as being 97% NIPAM. Thus, pure PNIPAM microgel may contain a low concentration of COO- groups. However, those 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. Figure 2 implies that concentration of the acrylic acid has an impact on the particle size of the collapsed particle, i.e. the particle size at pH 1.0. The diameter of the collapsed particle is increasing with the increase of incorporated acrylic acid concentration. For example, the diameter of the microgels containing 30% acrylic acid is approximately 700±50 nm whereas for 10% and 0% acrylic acid it is 540±50 nm and 360±30 nm respectively. pH 1.0 is well lower the pKa of acrylic acid, therefore it is the electrolyte concentration, which is approximately 0.1 mol/l at pH 1.0, that is causing this effect by reducing the solvent quality for N-isopropylacrylamide, e.g. hydrophobic hydration around polymer side chains is weakened by the solvation of salt ions, while at the same time electrostatic repulsion is diminished.

Thus we conclude that at pH 1.0 the particles are not fully collapsed. Such a difference in the diameter of the collapsed particles that were deswelled via different stimuli is probably due to the chemical nature of the microgel, i.e. temperature-induced shrinking is governed by the hydrophobic isopropyl groups in the NIPAM moieties which are present in the microgel backbone with considerably higher concentrations rather than acrylic acid groups which are inducing the shrinkage at low pH. Another reason for the difference in the diameter of collapsed particles might be high electrolyte concentration at pH 1.0, which weakens the hydrophobic hydration around polymer side chains as the salt ions undergo solvation.

The analysis of the response of the microgels at different pHs implies that being both pH- and temperature-responsive with the certain concentration of acrylic acid groups in the backbone, the resultant microgel particles are dual-responsive. However, the microgels aggregated at pH 1.0 at higher temperatures. Although at pH 3.0 the microgels containing 10% acrylic acid groups aggregated, those containing 20% and 30% acrylic acid groups in the microgel backbone did not. This led to an attempt to synthesize microgel particles with increased concentration of acrylic acid but these attempts were unsuccessful as microgels could not be produced with acrylic acid concentration higher than 30%. Since the increase of acrylic acid concentration caused linear polymerization rather than the synthesis of microgels.

Conclusion

The work presented in this paper demonstrates successful preparation of microgel dispersions consisting of PNIPAM and various functional groups such as AA via an emulsion polymerization technique.The resultant microgels swelled or shrunk in response to various external stimuli, such as change in temperature, pH of the surrounding media. Overall, swelling properties of the resultant microgels and volume phase transition temperature which is near temperature of human body give an opportunity to modify these materials for environmental and pharmaceutical applications, the LCST shifted towards the temperature of human body makes these materials potentially useful as a sensors or controlled release agents for drug-delivery systems.

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ИССЛЕДОВАНИЕ СТИМУЛ-ЧУВСТВИТЕЛЬНЫХ МИКРОГЕЛЕЙ ДЛЯ ИСПОЛЬЗОВАНИЯ В МИКРОКАПСУЛИРОВАНИИ

Аннотация. Для сополимеризации ПНИПАМ с акриловой кислотой (АА) применяли метод поверхностно-активной эмульсионной полимеризации (ПАЭП). Полученные частицы микрогеля проявляли мультичувствительное поведение к изменениям температуры, pH. Эти частицы микрогеля были охарактеризованы с помощью динамического светорассеяния (DLS), сканирующей электронной микроскопии (SEM) и просвечивающей электронной микроскопии (TEM). Поведение частиц в различных условиях температуры, pH описывается и обсуждается в этой статье, и впервые было сообщено о нескольких наблюдениях, таких как переходы набухания / сжатия микрогелей на основе ПНИПАМ. Микрогель, содержащий АА, проявляет характерное температурно-чувствительное поведение при температуре объемного фазового перехода (ТОФП), находящейся в диапазоне 25^0-50^0 С, и проявляет pH-чувствительные свойства, когда частицы разрушаются при низких и набухают при высоких значениях pH. Результаты исследований показывают изменение размера и последующее разбухание / сжатие частиц микрогеля. Результаты ясно показывают, что в набухшем состоянии микрогели больше из-за присутствия COO-групп в микрогеле. Концентрация акриловой кислоты оказывает влияние на размер частиц частицы, то есть размер частиц при pH 1,0. Установлено, что диаметр сплюснутой частицы увеличивается с увеличением концентрации акриловой кислоты. Микрогели ПНИПАМ, содержащие добавленную акриловую кислоту, подвергаются значительному сокра-

щению / набуханию с изменением pH, то есть микрогели сокращаются при более низких уровнях pH и набухают с повышением pH. Набухание частиц при уровне pH крови в организме человека, находящемся в диапазоне от 7,35 до 7,45, а также при более низкой температуре критического раствора в диапазоне температуры тела человека, дает возможность дополнительно развить эти частицы микрогелякак потенциальных агентов доставки лекарств.

Ключевые слова:микрогели на основе N-изопропилакриламида, системы доставки лекарств, pH-чувствительныемикрогели, чувствительные к температуре микрогели.

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МИКРОКАПСУЛЯЦИЯ ҚОЛДАНУҒА СТИМУЛ-СЕЗІМТАЛ МИКРОГЕЛЬДЕРДІ ЗЕРТТЕУ

Аннотация. ПНИПАМ-ды акрилды кышқылмен (АА) сополимеризациялау үшін жоғарғы активті эмуль-сионды полимеризация (ПАЭп) әдісін қолданды. Алынған микрогеляның бөлігі мультисезімталдыққа, температура мен pH-тың өзгеруіне әсер етті.

Бұл микрогеля бөліктері жарық динамикасының көмегімен (DLS), электронды микраскоп (SEM) және жарық беретін электронды микраскоппен (TEM) сканерлеп сипаттайды.

Әр түрлі жағдайдалардағы температура, pH-тың бөліктері осы кезеңде өңделіп, ең бірінші рет бірнеше зерттеулер кезінде байқалып, ПНИПАМ негізінде микрогелді сығудан кейін ісіну процесіне көшу. АА құрамында бар микрогель 25-50 ^{0}C температурада болатын фазаға өту кезінде температураға – өзгерісі байқалып және pH-қа өзгергіштігік қасиеті байқалып ісіну кезінде олардың pH көрсеткіші төмендеп кетеді.

Зерттеу нәтижелердің қорытындысы бойынша бөрту кезеңдерінде өлшемдерінің өзгеруі байқалып, микрогеляның бөліктері сығылды.Нәтижелердің анық болуына байланысты, бөрту кезінде СОО – топтарындағы микрогеляның қатысуларынан жүреді. Акрилді қышқылдың концентрациясы бөліктердің өлшеміне әсер етіп, pH- тың 1,0 өлшемі бөліктеріне әсер етеді.

Бекітілген, акрилды қышқылдың концентрациясы жалпы өлшем бөліктері үлкейеді.

ПНИПАМ микрогелясы, құрамында акрилды қышқылы бар, жақсы қысқартуға апаратын, ісіну кезінде pH – тың өзгеруі, содан кейін микрогелялар pH-тың төмен деңгейінде қысқарып және ісіну кезінде pH-тың деңгейі жоғарылайды.

Адам организміндегі бөрту кезінде қанның құрамындағы pH-тың деңгейі, 7,35 тен 7,45 аралығында болып, сонымен қатар төмен температурада адам денесіндегі сұйықтықтар критикалық жағдайда болып, микрогеля бөліктеріне қосымша дәрілердің таралуына мүмкіндік береді.

Тірек сөздер: N-изопропилакриламид негізіндегі микрогельдер, дәрілерді жеткізу жүйесі, pH- сезімтал микрогельдер, температура сезімтал микрогельдер.

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