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The preparation and characterization of co-polymer microgels with transition temperature at or near physiological values

Xiaomei Ma (✉), Yacheng Xing

School of Chemical Engineering, Qingdao University, Qingdao 266071, P R China

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Summary

In this study, triethyleneglycol methacrylate (TREGMA) containing long functional hydrophilic side chains (*viz.*, -(-OCH_2CH_2-)$_3$-OH), was selected to copolymerize with N-isopropylacrylamide (NIPAM) for the first time to prepare temperature-sensitive microgels. The structure and morphology of the microgels obtained were investigated through ^{1}H NMR, transmission electron microscopy (TEM). Experimental results show that TREGMA can copolymerize well with NIPAM to prepare microgels with regular spherical morphology. Investigation on the volume phase transition of the microgels through turbidimetric method, dynamic light scattering (DLS) and differential scanning calorimetry (DSC) reveals that incorporation of hydrophilic side chains -(-OCH_2CH_2-)$_3$-OH has strong influence on the sizes, size distribution and the deswelling properties of the microgels. The microgels exhibit much larger deswelling ratios (α) than pure poly(N-isopropylacrylamide)(pNIPAM) microgels. Foremost, the volume-phase transition temperature (VPTT) of the microgels can be modulated to well close to the normal body temperature of human beings. The characteristic makes the microgels competitive candidates for biomaterials.

Introduction

Since Pelton and Chibante reported the synthesis of the first temperature-sensitive microgel from N-isopropylacrylamide (NIPAM) and N, N'-methylene bisacrylamide (BA) in 1986 [1], responsive microgels have attracted a great deal of attention due to their appealing prospects in an increasing number of technical applications (such as sensing [2], drug delivery [3,4], catalysis [5], pollution control [6] and optical devices [7,8]) and the considerable lack of theoretical understanding of these systems. Till now, the most intensely studied responsive microgels are temperature-responsive poly(N-isopropylacrylamide) (pNIPAM) microgels [9-11].

PNIPAM microgels are temperature-sensitive sponge-like particles that can shrink/swell in response to change in temperature, and undergo a large-magnitude volume change around certain temperature, which is called volume-phase transition temperature (VPTT). The VPTT of pNIPAM microgels is ~34 ^{o}C determined by dynamic light scattering (DLS) in water [12]. The phase-transition behavior of pNIPAM microgels is generally attributed to the reversible formation and breakage of

the hydrogen bonding between water molecules and hydrophilic groups and the hydrophilic/hydrophobic balance between hydrophilic and hydrophobic groups within pNIPAM polymer chains [13].

Compared to macroscopic pNIPAM hydrogels, pNIPAM microgels show attractive potentials in biomedical area (such as drug delivery [3], diagnostic agent [14], biomolecular separation [15].), due both to their rapid response to changes in temperature and the VPTT being close to the normal body temperature of human being. However, many biologic reactions related to human life can only carry through around 37 ^{o}C, which requires the VPTT of the thermo-sensitive materials used as temperature-controlled carrier must match the reaction condition (37 ^{o}C). In this way, it is necessary to carry out some modification to pNIPAM microgels to elevate the VPTT.

In this study, hydrophilic triethyleneglycol monomethacrylate (TREGMA) was selected as a comonomer to modify the physical properties of pNIPAM microgels. TREGMA is a commonly used monomer for biomacromolecules with good biocompatibility and biodegradation and low toxicity [16]. It is expected to modulate the VPTT of pNIPAM microgels due to its hydrophilicity. In addition, the functional hydroxyl groups it bears can direct recognition and selectivity through binding certain molecules *via* physical interaction (*e.g.*, H-bonding) and can be modified chemically [17]. Thus, it is hopeful to obtain good materials for biomedical uses when combining the thermosensitivity of pNIPAM with the functionality of TREGMA.

Experimental

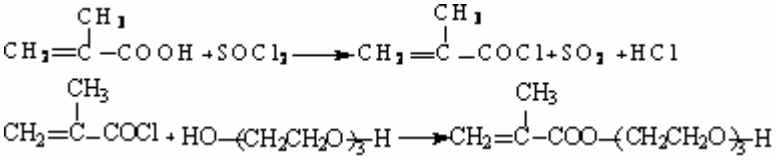
Materials

Methacrylic acid (MAA, C.P, Yonghua Special Chemicals Factory, Shanghai), was dried by 4A molecular sieves before use; thionyl chloride (A.R, Shanghai chemical reagent corporation, Shanghai), was used without further treatment; triethylene glycol (TEG, A.R, Tianjin No.1 chemical reagent factory), dried for two weeks by 4A molecular sieves before use; triethyl amine (TEA, A.R, Shanghai chemical reagent corporation, Shanghai), refluxed for 1h over CaH_2 and distilled (bp 88.8 ^{o}C); diethyl ether (A.R, Shanghai chemical reagent corporation, Shanghai), refluxed over $CaCl_2$ for 1h and distilled (bp 34.6 ^{o}C); NIPAM (Acros, purity>99%), BA (Aldrich, 99+%, electrophoresis grade), potassium persulfate (KPS, A.R, Shanghai chemical reagent corporation, Shanghai) were used without further purification. Water (super-clear water) used for synthesis and dialysis of the microgels was distilled, purified to a resistance of 18.2 MΩ • cm and filtered through a 0.2μm filter to remove particulate matter.

Synthesis of TREGMA

TREGMA was synthesized in two steps referred to literature [18,19] (*See Scheme 1.*). The crude TREGMA was purified to remove triethyleneglycol dimethacrylate (TREGDMA, as a by-product) and unreacted TEG through silica gel column (petroleum ether: ethyl acetate=1:1; the Rfs of TREGDMA, TREGMA and TEG were 0.75, 0.25 and 0.07 respectively.). The purity is ≥98.5% by gas chromatography (HP6890 Series, HEWLETT PACKARD; column: DB-5 (30m×0.25mm×0.25μm)).

^{1}H NMR (MERCURY Plus 400 NMR spectrometer, 400MHz, ppm in $CDCl_3$): 6.13 (1H) and 5.57 (1H) (CH_2=C), 4.30 (2H, $COOCH_2$), 3.58~3.76 (10H, CH_2CH_2O), 1.93~1.94 (3H, CH_3).
IR (/cm^{-1}) (Perkin Elmer Paragon 1000 FT-IR spectrometer, liquid film): 3444(OH), 1717.5 (COO), 1636.5 (C=C).
Elemental analysis (Vario EL III, CHNOS Elemental Analyzer): Calcd.(%) for TREGMA ($C_{10}H_{18}O_5$): C, 52.63; H, 7.89; O, 39.47. Found: C, 52.15; H, 7.70; O, 40.15.



Scheme 1. Schematic synthetic routines of TREGMA

Preparation of microgels

Table 1. Feed composition of p(NIPAM-*co*-TREGMA) microgels

Code	Feed(g)				True mol % of comonomer in the microgels[1]
	NIPAM	TREGMA	BA	KPS	
M-TEGMA0	0.7200	0.0000	0.0491	0.0172	0.00
M-TEGMA4	0.6664	0.0536	0.0473	0.0166	4.14
M-TEGMA8	0.6166	0.1034	0.0456	0.0160	8.08
M-TEGMA12	0.5700	0.1500	0.0441	0.0155	12.01

[1]The true mol % of the comonomer in the microgels was calculated according to the results of ^{1}H NMR.

For microgel preparation, NIPAM, TREGMA and BA were copolymerized under the initiation of KPS in the absence of surfactants. Simply, the desired amount of NIPAM, TREGMA and BA were dissolved in 0.05L super-clear, degassed water and was transferred into a 0.25L, four-necked round-bottomed flask equipped with a condenser, a thermometer, a N_2 inlet and a mechanical stirring paddle. The synthesis was performed under a nitrogen atmosphere to exclude oxygen. After heating the solution to 75 ^{o}C, KPS (dissolved in 0.01L water) was added to start the polymerization. The mixture became turbid and the reaction proceeded for 6 h at the constant temperature. Then the microgel suspension was cooled for 12h under continuous stirring. The crude microgels were dialyzed with well-boiled visking dialysis tubing (MWCO 14000) for 20 days against super-clear water in order to remove unreacted monomers and other low-molecular-weight impurities (the conductivity of the dialysate was consistently below 1μS cm^{-1}).
Microgels with different feed ratio of TREGMA were coded as M-TEGMAx, where x is the molar percentage of TREGMA in the feed. The composition of the feed is listed in table 1.

Characterization of the microgels prepared

^{1}HNMR

A Varian Mercury plus 400 NMR spectrometer (400MHz for proton, Varian, Inc., USA) was employed to determine the structure of the microgels. The microgels were freeze-dried at -60 ^oC first and were then redispersed in D_2O. The spectra were recorded at 25 ^oC.

Transmission electron microscopy (TEM)

The shape and dispersity of the microgels were investigated by JEM-100X(II) transmission electron microscopy. In order to obtain clear TEM micrographs of the microgels, the samples were stained with solution of phosphotungstic acid. A few droplets of the samples were spread onto the surface of a 200-mesh copper grid and were allowed to dry for 24h at 25 ^oC. The dried specimen was clamped onto a TEM specimen rod, inserted into the sample chamber, and observed at 100 kV.

Dynamic light scattering (DLS)

The hydrodynamic radii (*R*hs) of the dialyzed microgels (dilute dispersions) were measured using DLS technique (Wyatt QELS: scattering angle 110.7°; collection instrument: DAWN EOS, laser wavelength 690.0 nm) at different temperature. Before data collection, the dispersions were allowed to equilibrate at each temperature for at least 15 min in order to arrive at swelling/deswelling equilibrium. The data were obtained using ASTRA 4.70 software. The *R*h value under each temperature was the mean *R*h of three measurements (the data collection time was >30s for each measurement.).

Turbidimetric Analysis

The temperature dependence of the conformational transition of the microgel dispersions was determined turbidimetrically (at 547nm) against super-clear water using a GBC Cintra 10e UV-Visible spectrophotometer (with a GBC thermocell, stability ±0.1 ^oC). The heating rate was 1 $^oC \bullet min^{-1}$ heating from 25 to 80 ^oC. The temperature in the sample cell was monitored using a platform thermocouple temperature probe.

Differential scanning calorimetry (DSC)

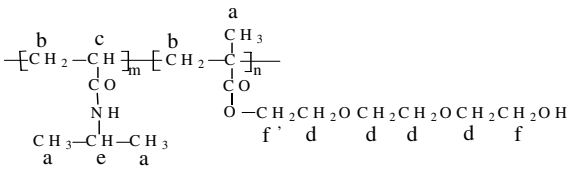
The volume-phase transition behavior of the microgels was investigated by DSC technique. The DSC analysis was carried out using a routine Perkin-Elmer Pyris-1 calorimeter at a scan rate of 2 $^oC \bullet min^{-1}$, scanning from 10~60 ^oC under nitrogen atmosphere to suppress bubble formation. The concentrated microgel dispersion was placed in an aluminium pot and weighed. Baseline was obtained over the range of 10~60 ^oC using super-clear water and was subtracted from microgel phase transition profiles. In each scan, an empty aluminium pot was used as a reference.

Results and discussion

Preparation and structural characterization of the microgels

The molecular structure of the microgels prepared is illustrated in scheme 2. It was observed after the reaction that stable microgel dispersions could be obtained when

the feed ratio of TREGMA was no more than 12 mol %, but could not be obtained when exceeded 12 mol %.The instability of the microgel dispersions should be caused by the interactions between the microgels and could have relations with the mechanism of the reaction process. In this study, preparation of the microgels takes advantage of the physical properties of linear pNIPAM possessing a lower critical solution temperature (LCST) around 31 ^{o}C. During the reaction, microgel particles formed in an aqueous solution upon temperature-induced free radical initiation with KPS at 75 ^{o}C. At this temperature, water-soluble monomers copolymerized first to form oligomers that were insoluble upon reaching a certain critical chain length.



Scheme 2. Molecular structure of p(NIPAM- *co*-TREGMA) microgels prepared

These oligomers underwent entropically driven coil-to-globule phase transitions and aggregated and grew with other globules to form precursor particles, which then aggregated and grew to form colloidally stable microgels. The microgels were stabilized mainly by static repulsive interactions between charges incorporated on the growing particles from the initiator fragments. As TREGMA containing polar side groups was incorporated into the microgels, attractive interactions between polar -(-OCH_2CH_2-)$_3$-OH groups and amide groups would weaken the repulsive interactions between charges on the growing particles. The more -(-OCH_2CH_2-)$_3$-OH groups there are, the more heavily of the repulsive interactions were weakened. When the feed ratio of TREGMA is high enough (>12 mol %), attractive interactions between polar -(-OCH_2CH_2-)$_3$-OH groups and amide groups begin to exceed the repulsive interactions, leading to the instability of the microgels.

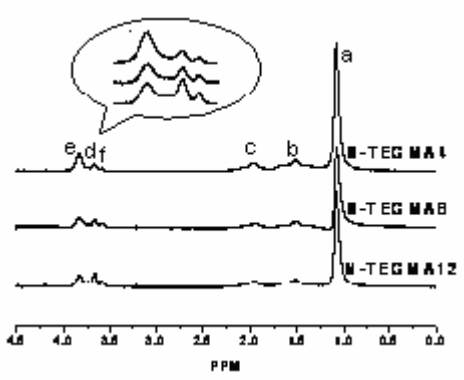


Figure 1. ^{1}H NMR spectra of p(NIPAM-*co*-TREGMA) microgels at 25 ^{o}C

The molecular structure of the TREGMA modified pNIPAM microgels was characterized by ^{1}H NMR (*See figure1*). In figure1, the peak at 1.08 ppm (peak a) can be attributed to the methyl proton of N-isopropyl (*See Scheme 2*). The broad peak

b and c are mainly due to backbone of the polymer. Peak d and f are caused by H of -(-OCH_2CH_2-)$_3$- groups of the comonomers and peak e is due to H of the methylene of the isopropyl groups. Figure 1 reveals that the relative intensity of peak d (or f) to peak e (or peak a) increases with the increase of the feed ratio of TREGMA, suggesting that TREGMA was well incorporated into the temperature-sensitive microgels. The real ratios of TREGMA in the microgels were calculated from the peak area ratios of peak d (or f) to peak e (or peak a). The results are listed in table 1. It can be seen from table 1 that the real ratios of TREGMA in the microgls are very close to the feed ratios indicating that TREGMA has good reactivity. While for pure pNIPAM microgels, there are no peak d and f because of the absence of TREGMA (omitted).

Morphology of the microgels

To observe the morphology and dispersity of the microgels prepared, TEM was employed. Shown in figure 2 is the representative TEM micrographs of p(NIPAM-*co*-TREGMA) microgels. It is evident that p(NIPAM-*co*-TREGMA) microgels with regular spherical morphology and narrow distribution were prepared. The low dispersity of the prepared microgels could be investigated by DLS (*see below*).

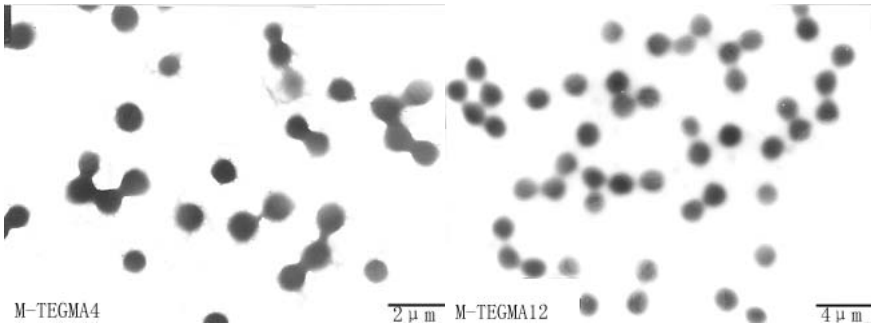


Figure 2. Typical TEM micrographs of p(NIPAM-*co*-TREGMA) microgels at 25^{o}C

Phase transition of the microgels

DLS analysis

Shown in figure 3 is the typical size distribution of the microgels at 22 ^{o}C. It is seen that microgels with narrow distribution were prepared by copolymerizing NIPAM with TREGMA. Incorporation of TREGMA makes the size distributions of the microgels broad first, then the size distribution becomes narrow when the feed ratio of TREGMA is high enough. The changing trend of the size distribution can be explained from the mechanism of microgel formation mentioned above. In the reaction process, the critical chain length upon precipitating is largely dependent on the hydrophobicity of the polymer chains in the system. Introduction of the hydrophilic comonomers (TREGMA) would be expected to diminish the hydrophobicity of the growing polymer chains at the reaction temperature. The growing oligomers thus must attain a higher degree of polymerization before

precipitation occurs, thereby leading to slow particle nucleation and perhaps a low charge density at the particle surface. It is most likely that these two factors lead to increased particle size distribution. While the content of the hydrophilic comonomer is high enough, the network structure of the microgels becomes tight as a result of the strong H-bonding interactions between -(-OCH_2CH_2-)$_3$-OH and amide groups, leading to the narrow distribution of the microgels.

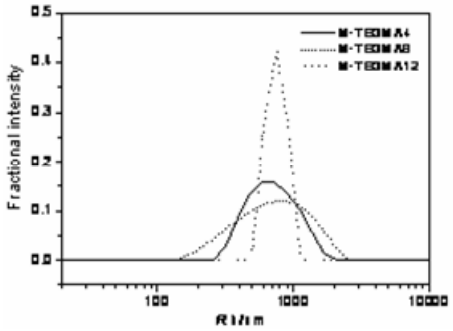


Figure 3. Size distribution of the microgels prepared in water at 22°C

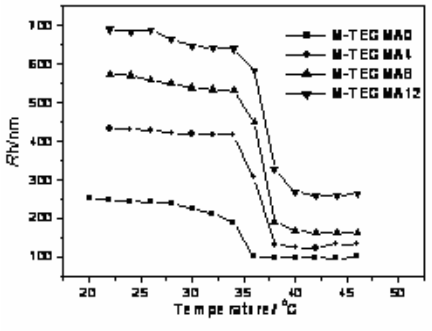


Figure 4. Temperature dependence of the *R* h of the microgels prepared

The sizes of the microgels were measured against temperature by DLS. The temperature dependence of the average hydrodynamic radius (*R*h) of p(NIPAM-*co*-TREGMA) microgels is shown in figure 4. Figure 4 reveals that the *R*hs of the microgels decrease sharply as temperature increased to certain values, suggesting that the microgels are temperature-sensitive. It is seen from Fig.4 that the VPTTs of M-TEGMA0, M-TEGMA4, M-TEGMA8 and M-TEGMA12 are 35 ± 1, 36 ± 1, 37 ± 1 and 38 ± 1 °C respectively, *i.e.*, incorporation of TREGMA makes the VPTTs of pNIPAM microgels shift to higher temperature, the VPTT being shifted more with more incorporation of TREGMA. This is plausible because TREGMA has hydrophilic side groups -(-OCH_2CH_2-)$_3$-OH, which can interact with water molecules and amide groups through hydrogen-bonding. The hydrogen-bonding effect enhances the thermodynamic stability of the microgels in water and can hinder the hydrophobic association of isopropyl groups, contributing to the shift of the VPTTs to higher temperature. The VPTTs of TREGMA modified pNIPAM microgels are well close to the normal body temperature of human being, which is beneficial for biomedical uses.
Another important factor to evaluate the thermosensitivity of the microgels was the deswelling ratio (α) which could be calculated using the hydrodynamic radii in the swollen and the shrunken state[20]. According to Equation (1), the α of p(NIPAM-*co*-TREGMA) microgels with different feed ratio of TREGMA were calculated from the radii in the swollen and shrunken state. The results are listed in table 2.

$$\alpha = \frac{Vswollen}{Vshrunken} = \left(\frac{R_h^{swollen}}{R_h^{shrunken}} \right)^3 \qquad (1)$$

Data in Table 2 show that p(NIPAM-*co*-TREGMA) microgels have larger α than pure pNIPAM microgels (M-TEGMA0) (especially M-TEGMA4 and M-TEGMA8). Since incorporation of moderate amount of hydrophilic TREGMA could enhance the absorbed amount of water in the microgels, but the existence of small amount of TREGMA has little influence on the hydrophobic association of isopropyl groups. Hence, more water is expelled as temperature increased from below to above the VPTT. As the incorporation of TREGMA increased to certain extent, the absorbed amount of water in the microgel particles increase little because the interaction between $-(-OCH_2CH_2-)_3-OH$ groups themselves and the interaction of $-(-OCH_2CH_2-)_3-OH$ groups with amide groups increased instead of their interaction with water. On the other hand, too more hydrophilic side chains will hinder the hydrophobic association of isopropyl groups. The thermoresponsivity of pNIPAM microgels is usually weakened after hydrophilic modification in that the deswelling ratio of the copolymer microgels decreases and the phase transition becomes continuous with the introduction of hydrophilic monomers [21]. In marked contrast to previous report, p(NIPAM-*co*-TREGMA) microgels preserve good thermoresponsivity, indicating that TREGMA is an appropriate comonomer to prepare thermosensitive microgels with good responsivity.

Table 2. The calculated deswelling ratio (α) of p(NIPAM-*co*-TREGMA) microgels

code	M-TEGMA0	M-TEGMA4	M-TEGMA8	M-TEGMA12
Rh (nm), 22 °C	248.0	433.0	575.0	690.0
Rh (nm), 42 °C	97.2	112.3	163.2	268.5
α	16.6	57.3	43.7	16.9

Moreover, it can be seen from figure 4 and table 2 that the *R*hs of p(NIPAM-*co*-TREGMA) microgels in the swollen state are far larger than that of pure pNIPAM microgels, and increased more with more incorporation of TREGMA. This can be attributed to the increase in the hydrophilicity of the microgels due to the incorporation of hydrophilic TREGMA. The hydrophilic side groups $-(-OCH_2CH_2-)_3-OH$ in TREGMA can interact with water molecules through hydrogen-bonding, leading the microgels to a more extended state.

Figure and table 2 also indicate that the *R*hs of p(NIPAM-*co*-TREGMA) microgels in the shrunken state are larger than that of pure pNIPAM microgels and increase with the increase of hydrophilic TREGMA. This can be attributed to the increase in the hydrophilicity of the shrunken microgels. After the deswelling of the microgels, the hydrophilicity of the $-(-OCH_2CH_2)_3-OH$ units does not significantly change. They are in extended states *via* binding with water. The more are there hydrophilic $-(-OCH_2CH_2-)_3-OH$ units, the more extended are the microgels and the larger are the *R*hs of the microgels, or in other words the more incompletely do the microgels deswell.

Turbidimetric analysis

Figure 5 is the plot of turbidity (absorbance) of p(NIPAM-*co*-TREGMA) microgels as a function of temperature. It can be seen from figure 5 that the turbidity of the microgels increase suddenly in certain temperature range as the temperature increases, indicating that the microgels are thermosensitive.

The turbidity of microgels is dominated by the amount of water contained within the interstitial region as this indicates the difference in refractive index between the microgel and the bulk water. Below the VPTT, the microgel is in the swollen state, the difference of the refractive index between water and the microgels is small, so the turbidity of the microgels is small too; the more hydrophilic are the microgels, the smaller is the turbidity. With increasing the temperature, water is expelled out of the microgel network as a result of disruption of H-bondings and association of isopropyl groups, the difference of the refractive index between water and the microgels increase, so does the turbidity of the microgels[22].

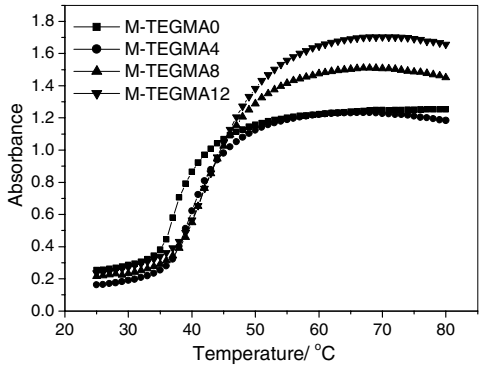


Figure 5. Turbidity dependence of the microgels prepared on temperature

The VPTT of the microgels can be obtained from the plot (omitted) of the first derivative of turbidity as a function of temperature. The results also show that the VPTTs shift to higher temperature with increasing incorporation of TREGMA, which is consistent with DLS result.

DSC analysis

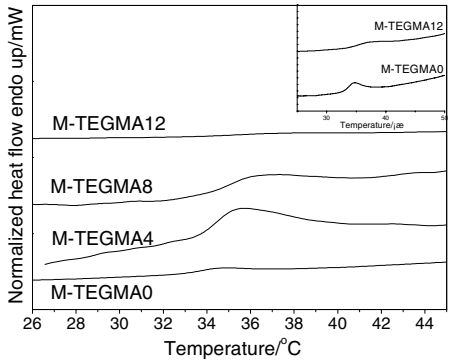


Figure 6. DSC scan plot of microgel dispersions (Inset was the enlarged plot of M-TEGMA0 and M-TEGMA12)

The dialysized microgels were concentrated to ~2.0 % (wt) and were subjected to calorimetric analysis. Figure 6 presents the DSC thermograms of p(NIPAM-*co*-TREGMA) microgels. It is found that the peak temperatures of these microgel dispersions are 34.6, 35.6, 36.3, 37.2 °C respectively, indicating that the VPTTs of the microgels shift to higher temperature as the ratios of TREGMA increased. The

transition exhibited by the p(NIPAM-*co*-TREGMA) microgels are a bit broader than pNIPAM microgels indicating the probable involvement of a kinetically limited conformational change.

Figure 6 also reveals that the feed ratios of the hydrophilic comonomers have strong influence on the enthalpy during the volume-phase transition (deswelling process) of the microgels. The enthalpy of the deswelling process is related to the deswelling ratio of the microgels, which is dependent largely on the complicated interactions (including H-bonging and hydrophobic associations) between the microgels and water (*See the above section*). During the deswelling of the microgels, water is expelled from the microgels due to both the breakage of H-bondings and the hydrophobic association of isopropyl groups. The more release is water, the larger is the enthalpy change. Thus microgels with larger α has higher enthalpy during the deswelling process.

Effect of the comonomer feed ratio on the VPTT of pNIPAM microgels

Table 3 lists the VPTTs of p(NIPAM-*co*-TREGMA) microgels determined from DLS, DSC and turbidimetric method respectively. It reveals that the VPTTs of the microgel dispersions shift to higher temperatures as the feed ratio of TREGMA increases. The result is attributed to the comprehensive result of the strengthened H-bonding and the weakened hydrophobic association due to the incorporation of hydrophilic TREGMA into the microgels (*See above*). There is some difference between different methods because of the inherent difference caused by the methods, but the changing trend of VPTT is doubtless. The VPTTs of the hydrophilic modified microgels are modulated to well close to or above the normal body temperature, which is very useful for biomedical application.

Table 3. VPTTs of p(NIPAM-*co*-TREGMA) microgels measured by different techniques

Microgel code	VPTTs determined by different techniques (^{o}C)		
	DLS	UV	DSC
M-TEGMA0	35.0±1	37.0	34.6
M-TEGMA4	36.0±1	39.0	35.6
M-TEGMA8	37.0±1	41.1	36.3
M-TEGMA12	38.0±1	42.2	37.2

Conclusions

Hydrophilic comonomer (TREGMA) containing functional -(-OCH_2CH_2-)$_3$-OH side chains that is often applied in the manufacturing of biomaterials was selected to prepare temperature-sensitive microgels for the first time. Studies on the microgels indicate that TREGMA can be well incorporated into the microgels. The microgels have regular spherical morphology with narrow distribution. Incorporation of hydrophilic side chains containing hydroxyl groups causes the volume-phase transition temperature (VPTT) of pNIPAM microgels shift high to well close to or above normal body temperature. P(NIPAM-*co*-TREGMA) microgels have much larger deswelling ratios (α) than pure pNIPAM microgels and undergo abrupt volume-change around certain temperature. As a whole, p(NIPAM-*co*-TREGMA) microgels

exihibit good thermosensitivity. They could be very competitive in biomedical areas. The present study then extends the range of applications of temperature-sensitive microgels by preparing thermosensitive microgels having higher VPTTs and containing functional hydroxyl groups.

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