Rapid Communication

Yongqi Yang*#, Zekai Ren#, Xiawei Li#, Youjun Yan, Jun Liu, Meng Lian, Guangyao Liu*, and Xin Luo*

Preparation and characterization of magnetic microgels with linear thermosensitivity over a wide temperature range

https://doi.org/10.1515/epoly-2023-0161
received October 12, 2023; accepted November 16, 2023

Abstract: Hybrid nanogels that are both thermosensitive and superparamagnetic, and have good biocompatibility are expected to have applications in the biomedical field. In this article, a linearly thermosensitive magnetic microgel was prepared by a radical copolymerization reaction in aqueous dispersion. In this reaction, poly(ethylene glycol) diacrylate was used as a crosslinker, polyvinylpyrrolidone was used as a stabilizer, and 2-methoxyethyl acrylate, poly (ethylene glycol)methyl ether acrylate, and 2-(methacryloyloxy)ethyl acetoacetate were used as copolymer monomers. The thermosensitive magnetic microgel displays a linear volume phase transition in water upon heating over a wide range of temperatures. Transmission electron microscopy, scanning electron microscopy, and dynamic light scattering were used to characterize the morphology and dimensions of the thermosensitive magnetic microgel. This material is expected to be used in magnetically targeted drug delivery systems that require linear drug release.

Keywords: magnetic microgels, linear thermosensitivity, wide temperature range, radical copolymerization reaction, preparation and characterization

1 Introduction

Polymer-based platforms have the ability to encapsulate large amounts of chemotherapeutic drugs and deliver them to a specific site (tumor) and are therefore being widely investigated as drug delivery systems for the treatment of cancer (1). Of these, microgels have become the most studied polymeric platforms over the past few years. Microgels are soft and malleable materials with slightly cross-linked particles in the colloidal size region that, in addition to exhibiting various properties of hydrogels and microspheres, have high porosity and a clearly defined morphology (2). Smart colloidal microgels, a class of intelligent responsive polymers, can adjust their dimensions in response to external stimuli, including ionic strength, pressure, light, pH, and temperature (3,4). In addition to the typical properties of bulk hydrogels, such as biocompatibility, deformability, and softness, they exhibit the colloidal stability of microparticles and a high surface area to volume ratio (5). Microgels are capable of crystallizing at high concentrations, respond rapidly to environmental stimuli and have unique interface properties (6).

The potential applications of microgels depend on their chemical/physical properties, dimensions, and polydispersity. Thus, the selected synthesis method must be able to generate microgels with the desired properties. Precipitation polymerization (or dispersion polymerization) by free radicals is the most commonly used method for the preparation of monodisperse, thermostable microgels in an aqueous medium. A key factor determining microgel homogeneity is the reversible phase separation behavior of thermotropic polymers, and the temperature

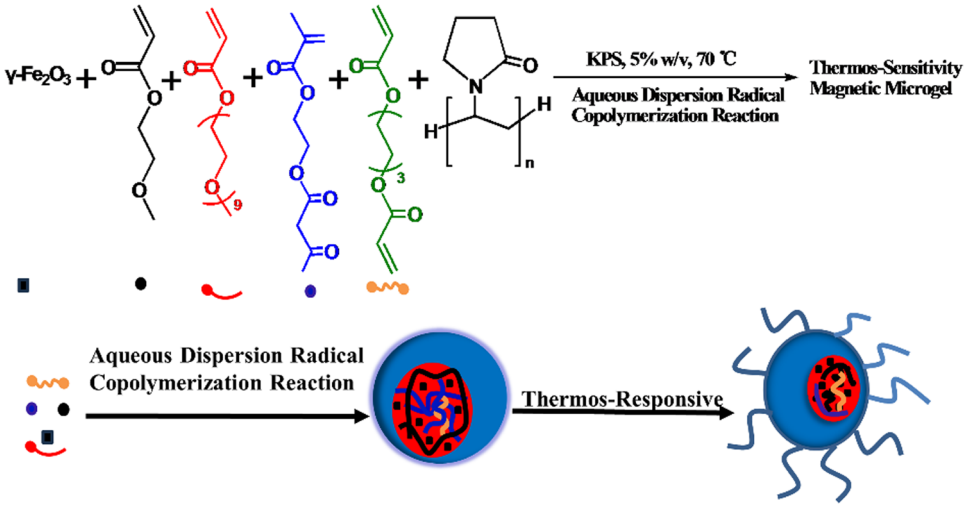
# These authors contributed equally to this work.

*** Corresponding author: Yongqi Yang,** Shandong Engineering Laboratory for Clean Utilization of Chemical Resources, Weifang University of Science and Technology, Weifang, 262700, China, e-mail: yongqiyang@wfust.edu.cn
*** Corresponding author: Guangyao Liu,** Institute of Optical Functional Materials for Biomedical Imaging, School of Chemistry and Pharmaceutical Engineering, Shandong First Medical University & Shandong Academy of Medical Sciences, Tai'an, Shandong 271016, P. R. China, e-mail: guangyao515@163.com
*** Corresponding author: Xin Luo,** Shandong Key Laboratory of Biophysics, Institute of Biophysics, Dezhou University, Dezhou 253023, China, e-mail: luoxin474@live.com
Zekai Ren: College of Chemistry and Chemical Engineering, College of Materials Science and Engineering, Institute of Biomedical Materials and Engineering, Qingdao University, Qingdao 266071, China
Xiawei Li: Inner Mongolia Institute of Quality and Standardization, Inner Mongolia Administration for Market Regulation, Hohhot 010000, China
Youjun Yan, **Jun Liu**, **Meng Lian:** Shandong Engineering Laboratory for Clean Utilization of Chemical Resources, Weifang University of Science and Technology, Weifang, 262700, China

at which this occurs is often referred to as the lower critical solution temperature (LCST). The most widely studied thermostable polymer in this area is poly(*N*-isopropylacrylamide) (PNIPAM). PNIPAM has an LCST in aqueous solution of ~32°C and a sudden phase transition from coil to globule as it passes through the LCST (7,8). In this process, the phase transition manifests itself in terms of the volumetric phase transition temperature. Polymers with similar properties include poly(*N*-isopropyl methacrylamide) and poly(*N*,*N*-diethylacrylamide) (9,10). However, such polymers suffer from disadvantages such as low biocompatibility and toxicity of the monomers, which can limit the use of such microgels in the field of biological or pharmaceutical carriers (11). Recently, a polymer with short oligo(ethylene glycol) (OEG) side chains has emerged as a potential replacement for PNIPAM as an ideal biomedical polymer (12). OEG (meth)acrylate copolymers have been widely and intensively researched for their special properties, such as excellent biocompatibility, adjustable LCST, and antifoulant properties (13).

However, microgels prepared by the copolymerization of two or more monomers still have limitations in terms of single functionality and limited applications. To overcome these drawbacks, a proposed approach is the development of hybrid microgels. These hybrid microgels aim to combine the properties of electronic, magnetic, optical, or colloidal stability and responsiveness by incorporating inorganic nanoparticles (14). Recent reports from various research groups have indicated that by focusing on and locally heating polymeric magnetic nanoparticle (MNP) nanocarriers at the specific site of drug release, MNPs can effectively deliver their cargo without requiring macroscopic heating (15). The internal structure of dual-stimulus microgels composed of methacrylic acid, di(ethylene glycol) methyl ether methacrylate (MEO_2MA), and OEG methyl ether methacrylate (OEGMA) monomers was investigated by Billon's group (16). The study focused on analyzing the impact of different cross-linkers on the internal structure of the microgel and its transition from swelling to collapse. Recent work has investigated the optical and solvative response of functional hybrid gold nanoparticles and poly(2-(2-methoxyethoxy) ethylmethacrylate) P(MEO_2MA) nanoparticles of variable shell thickness (17). To our knowledge, there is little literature on organic–inorganic nanodevices based on OEGMA monomeric encapsulation of MNPs in nanoscale materials with good biocompatibility and thermotropic stretchability.

In this study, we synthesized magnetically responsive and linearly thermoresponsive microgels using 2-methoxyethyl acrylate (MEA), poly(ethylene glycol)methyl ether acrylate (PEGA), and 2-(methacryloyloxy)ethyl acetoacetate (AAEM) as copolymer monomers. These microgels were loaded with γ-Fe_2O_3 superparamagnetic nanoparticles at different mass ratios ranging from 0.1 to 5 wt%. To prevent the agglomeration of γ-Fe_2O_3 during the reaction process, we tested various surfactants as stabilizers for the polymerization system. We found that polyvinylpyrrolidone (PVP) was the most effective stabilizer compared to the macromolecular chain transfer agent poly(*N*,*N*′-dimethylacrylamide) and sodium dodecyl sulfate. A schematic representation of the process used to prepare the linear thermosensitive microgel and its temperature-dependent changes is illustrated in Scheme 1.



Scheme 1: Schematic representation of the synthesis and thermoresponsiveness of the linear thermosensitive magnetic microgel.

2 Materials and methods

2.1 Materials

MNPs (5 mg·mL^{-1} in H_2O) of γ-Fe_2O_3 with an average particle size of 10 nm and PVP (M_n = 24,000) were purchased from Aladdin Chemical Reagent Co. Ltd. PEGA (Adamas-beta, average M_n ~480), Al_2O_3 (Adamas-beta, 99%, γ phase, 20 nm), MEA (Adamas-beta, ≥98%), 2-(methacryloyloxy) ethyl acetoacetate (AAEM, Adamas-beta, 94%), *N*,*N*′-dimethylformamide (DMF, Adamas-beta, ≥99.8%), ethanol (EtOH, Adamas-life, ≥99.5%), and potassium persulfate (KPS, Adamas-beta, ≥99.5) were purchased from Shanghai Titan Co., Ltd. Poly (ethylene glycol)diacrylate (PEGDA, M_n = 258) was purchased from Sigma-Aldrich. All other chemicals were of analytical grade. All monomers were passed through a neutral aluminum(III) oxide column to remove the inhibitor before use. KPS was recrystallized twice in deionized water prior to use.

2.2 Synthesis of P(MEA-*co*-PEGA-*co*-AAEM) magnetic microgels

Radical copolymerization of γ-Fe_2O_3, MEA, PEGA, and AAEM in different molar ratios was carried out in aqueous dispersion (water) at 70°C for P(MEA-*co*-PEGA-*co*-AAEM) magnetic microgel synthesis. Herein, KPS was used as an initiator, PEGDA as a crosslinker, and PVP as a stabilizer. Typical steps in the preparation process are described below. In a 20 mL reactor, MEA (139.3 mg, 1.07 mmol), PEGA (96.3 mg, 0.20 mmol), AAEM (14.3 mg, 0.07 mmol), PEGDA (7.5 mg, 0.03 mmol), and PVP (50 mg, 2.08 μmol) were dissolved in 5 mL of distilled water. Then, 89.3 μL of aqueous γ-Fe_2O_3 (1.4 mg·mL^{-1}) was added, and the mixture was stirred for 30 min using a Rotamax 120 shaker. The solution was degassed with nitrogen at room temperature for 30 min prior to immersion in a preheated oil bath at 70°C. Next 100 μL of an aerated aqueous solution containing 1.875 mg of KPS was injected into the reaction mixture using a microsyringe. The aqueous dispersion was allowed to undergo radical copolymerization for 6 h under nitrogen protection with stirring at high speed. Subsequently, it was cooled to room temperature. Then, 0.05% w/v solutions were used for dynamic light scattering (DLS), and the crude products were dialyzed in water for three days using a Millipore dialysis system (cellulose membrane, MWCO 100000) for transmission electron microscopy (TEM) and scanning electron microscopy (SEM).

2.3 Polymerization kinetics of aqueous dispersion polymerization of P(MEA-*co*-PEGA-*co*-AAEM) magnetic microgels

Periodic aliquots of P(MEA-*co*-PEGA-*co*-AAEM) magnetic microgels were studied by aqueous dispersion copolymerization at 10% w/v solids at full conversion. In a 20 mL reactor, MEA (278.6 mg, 2.14 mmol), PEGA (192.6 mg, 0.40 mmol), AAEM (28.6 mg, 0.14 mmol), PEGDA (15.0 mg, 0.06 mmol), PVP (100 mg, 4.16 μmol), and 0.05 mL DMF were dissolved in 5 mL of distilled water. Then, 178.6 μL γ-Fe_2O_3 (1.4 mg·mL^{-1}) aqueous was added and the mixture was stirred for 30 min using a Rotamax 120 shaker. Then, 100 μL of the mixture was removed from the system and labelled as the 0 h sample. Before immersion in a preheated oil bath at 70°C, the solution was degassed with nitrogen at room temperature for 30 min. Next 0.1 mL of a vented aqueous solution containing 3.75 mg of KPS was injected to the reaction mixture through a microsyringe. At 5, 10, 15, 30, 45, 60, 90, 120, 150, and 180 min, 100 μL of the reaction solution was withdrawn under nitrogen using a 100 μL microsyringe and placed in a 1 mL centrifuge tube together with the 0 h sample, and 500 μL of D_2O was added to each sample to measure the ^{1}H NMR spectrum.

3 Results and discussion

3.1 Synthesis of the microgels

In this communication, temperature-sensitive microgels were prepared at 70°C by radical dispersion copolymerization using MEA, PEGA, and AAEM as terpolymer monomers, PVP as a stabilizer, KPS as an initiator, and PEGDA as a crosslinker. Stable milky-white dispersions were obtained in all cases. The higher water solubility of MEA may explain the relatively high solid content (5% w/v) obtained compared to those of other precipitation polymerization microgel systems. To monitor the time required to achieve high monomer conversion in the free-radical dispersion polymerization reaction for the preparation of microgels, aliquots were taken from the reaction mixture at regular intervals for nuclear magnetic resonance hydrogen spectroscopy (^{1}H NMR), and full conversion was achieved at 5% w/v. From the ^{1}H NMR spectra, it can be seen that the signals from the double bonds between the chemical shifts 5.5 and 6.5 decrease as the conversion rate increases. After 15 min, the polymer rapidly became transparent, and after 3 h, the monomer conversion was 99% (Figure 1).

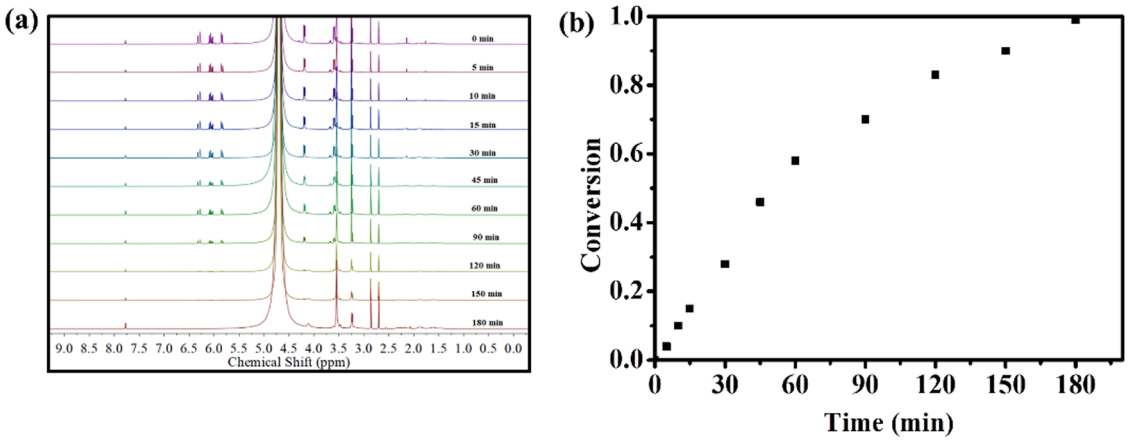


Figure 1: Dispersion polymerization kinetics results of microgels at 5% w/v and 70°C: double bond peak signals vs polymerization time in ^{1}H NMR spectra (a) and monomer conversion vs polymerization time (b).

To study the size distribution of the synthesized microgels, DLS measurements were performed. As shown in Figure 2, a narrow polydispersity index (PDI) with a unimodal peak was observed for the hydrodynamic diameter (D_h) of the microgels, indicating a uniform size.

It was therefore possible to monitor the effect of cross-link density on the final gel size. The higher the cross-linking density was, the larger the particles of the microgels.

It is well known that the encapsulation of superparamagnetic γ-Fe_2O_3 requires a large microgel particle size, so it is necessary to investigate the effect of γ-Fe_2O_3 content on the D_h and PDI of microgels (18). The effect of the γ-Fe_2O_3 content on the D_h and PDI of the microgel solution was studied in detail by fixing the molar ratio of the three monomers at MEA:PEGA:AAEM = 160:30:1 and keeping the total mass ratio of other components constant relative to the monomers, as shown in Table 1 and Figure S1. As seen from Table 1 and Figure S1, the microgel system was stable when the mass of γ-Fe_2O_3 was 0.5 wt% of the total monomer mass, the number-average diameter of the prepared microgel was large, and the PDI was narrow. Therefore, 0.5 wt% is the optimum concentration for this system. Subsequently, we studied in detail the effects of the molar ratios of the monomers MEA, PEGA, and AAEM, the amount of the cross-linking agent PEGDA, the amount of the stabilizer PVP, and the amount of the initiator KPS on the stability of the magnetic microgel system and on the D_h and PDI of the microgels (see Tables S1–S4 for details). The optimal experimental conditions were investigated as follows: the mass ratios of γ-Fe_2O_3, PEGDA, PVP, and KPS to monomer were 0.5%, 3%, 20%, and 0.75%, respectively, and the MEA:PEGA:AAEM molar ratio was 160:30:10, with a monomer concentration of 5% w/v, reaction temperature of 70°C, and reaction time of 4 h.

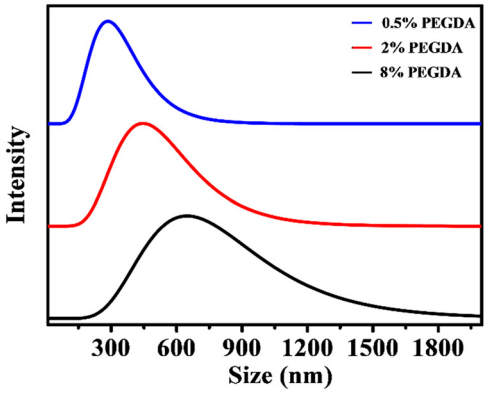


Figure 2: Size distribution of P(MEA-*co*-PEGA-*co*-AAEM) microgels (25°C) synthesized with different nominal amounts of cross-linking agent. Concentration: 0.01% w/v in water.

Table 1: Effect of the amount of γ-Fe_2O_3 on the D_h and PDI of magnetic P(MEA-*co*-PEGA-*co*-AAEM) microgels obtained by dispersion polymerization[a]

Entry	γ-Fe_2O_3 (%)	PEGDA (%)	PVP (%)	KPS (%)	D_n/nm	PDI
1	0.1	3	20	0.75	395.1	0.033
2	0.5	3	20	0.75	401.7	0.043
3	1	3	20	0.75	360.1	0.057
4	2	3	20	0.75	381.6	0.144
5	5	3	20	0.75	396.1	0.146

[a]Synthetic condition: temperature is 70°C, monomer concentration is 5% w/v, the volume of final mixture is 5 mL. D_n, number-average diameters, PDI, polydispersity index. All the molar ratios of MEA:PEGA:AAEM = 160:30:10, all the percentages are relative to the mass of the monomer.

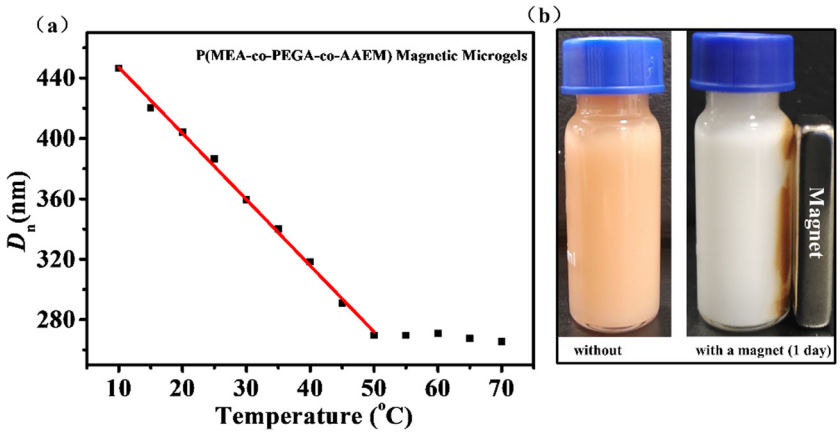


Figure 3: DLS curves of magnetic P(MEA-*co*-PEGA-*co*-AAEM) microgels with different upon heating (0.05% w/v in water) (a), magnetic behavior of nanogels in the presence of a permanent magnet (b).

3.2 Thermosensitivity of the P(MEA-*co*-PEGA-*co*-AAEM) microgels

The thermosensitive volumetric phase transitions of P(MEA-*co*-PEGA-*co*-AAEM) microgels prepared under the optimal synthesis ratio conditions for DLS testing are shown in Figure 3a. Interestingly, the obtained microgels show a linear decrease in particle size with heating until a plateau is reached. This linear thermal sensitivity can be observed across a wide temperature range of 10–50°C. As the temperature continues to increase, the particle size of the microgels tends to remain more or less constant. Our method for synthesizing linearly thermosensitive microgels is more convenient and suitable for large-scale production than previous methods. In contrast to approaches in the literature, the linear P(MEA-*co*-PEGA-*co*-AAEM) terpolymer undergoes a rapid LCST transition in aqueous solution (19). Without the use of a permanent magnetic field, the magnetic P(MEA-*co*-PEGA-*co*-AAEM) microgels are well dispersed in water. As shown in Figure 3b, the microgels can be collected using permanent magnets. In the presence of a permanent magnetic field, the magnetic

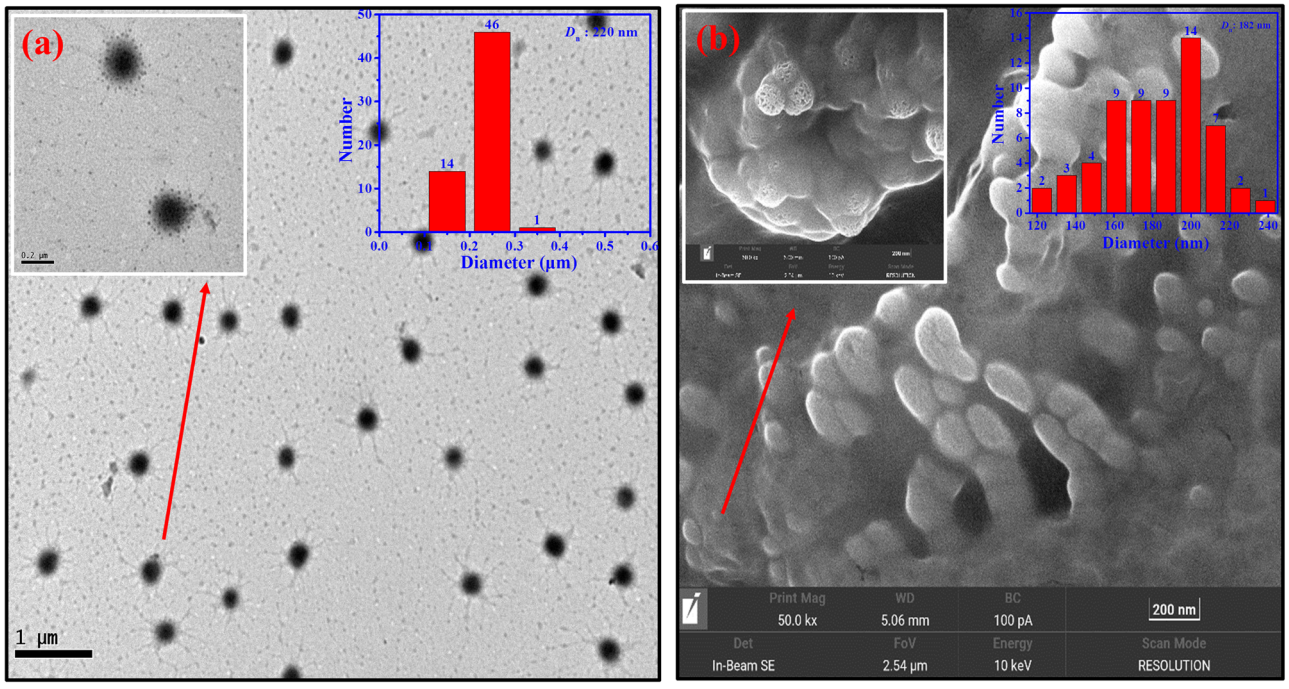


Figure 4: Representative TEM (a) and SEM (b) images of the magnetic P(MEA-*co*-PEGA-*co*-AAEM) microgels.

P(MEA-*co*-PEGA-*co*-AAEM) moves and forms particles on the wall of the container near the magnet. The magnetic microgels can also be purified using this technique.

3.3 TEM and SEM studies of the magnetic P (MEA-*co*-PEGA-*co*-AAEM) microgels

The TEM image of the γ-Fe_2O_3/P(MEA-*co*-PEGA-*co*-AAEM) hybrid microgels is shown in Figure 4a. This image confirms the good distribution of γ-Fe_2O_3 in the microgels, which also agrees with the DLS polydispersity results, that is, the uniform particle size distribution. In the TEM image, the contrast of the microgels is quite low (average diameter: 220 nm), which is an indication of their soft nature. To further observe the internal structure of the magnetic microgels, we subjected them to SEM analysis (average diameter: 182 nm, Figure 4b), which showed that the obtained microgels were homogeneously distributed microbeads with a uniform size distribution, which again confirmed the accuracy of the DLS results.

4 Conclusion

In this work, P(MEA-*co*-PEGA-*co*-AAEM) microgels were prepared using radical precipitation polymerization. The diameter of the resulting microgels decreased in a linear fashion upon heating. Through a thorough study, we obtained the optimal synthetic conditions for preparing such microgels: the mass ratios of γ-Fe_2O_3, PEGDA, PVP, and KPS to the monomer were 0.5%, 3%, 20%, and 0.75%, and the MEA:PEGA:AAEM molar ratio was 160:30:10, with a monomer concentration of 5% w/v, a reaction temperature of 70°C, and a reaction time of 4 h. Using the P(MEA-*co*-PEGA-*co*-AAEM) microgel as a template, γ-Fe_2O_3 could be uniformly encapsulated by *in situ* polymerization, and the microgel could be separated and purified by a permanent magnet. Our expectation is that this microgel based on magnetic MEA-*co*-PEGA-*co*-AAEM and exhibiting a linear volume phase transition can be easily prepared on a large scale, overcome the discontinuous thermal transition defects of most microgel systems studied thus far, and be applied in the preparation of functional materials and targeted drug delivery.

Acknowledgements: The financial support of Shandong Provincial Natural Science Foundation (ZR2020QB084), and Weifang University of Science and Technology (KJRC2019009) is greatly appreciated. We thank professor Zesheng An of Jilin University for his guidance and advice on experimental design. All individuals included in this section have consented to the acknowledgement.

Funding information: This research was funded by the financial support of Shandong Provincial Natural Science Foundation, grant number ZR2020QB084 and Weifang University of Science and Technology grant number KJRC2019009.

Author contributions: Yongqi Yang, Zekai Ren, and Xiawei Li: Designed this research; Youjun Yan, Jun Liu, and Meng Lian: conducted this research; Yongqi Yang, Guangyao Liu, and Xin Luo: analyzed the draft data; Yongqi Yang and Xin Luo: wrote – original draft; Guangyao Liu: modified the article; Yongqi Yang, Xiawei Li, and Xin Luo: edited the entire manuscript.

Conflict of interest: Authors state no conflict of interest.

Data availability statement: Data are contained within the article.

References

(1) Li Z, Xu K, Qin L, Zhao D, Yang N, Wang D, et al. Hollow nanomaterials in advanced drug delivery systems: From single to multiple shells. Adv Mater. 2023;35(12):2203890. doi: 10.1002/adma.202203890.

(2) Zhou B, Gasser U, Fernandez-Nieves A. Measuring the counterion cloud of soft microgels using SANS with contrast variation. Nat Commun. 2023;14(1):3827. doi: 10.1038/s41467-023-39378-5.

(3) Jelken J, Jung SH, Lomadze N, Gordievskaya YD, Kramarenko EY, Pich A, et al. Tuning the volume phase transition temperature of microgels by light. Adv Funct Mater. 2022;32(2):2107946. doi: 10.1002/adfm.202107946.

(4) Hu C, van Bonn P, Demco DE, Bolm C, Pich A. Mechanochemical synthesis of stimuli responsive microgels. Angew Chem Int Ed. 2023;62:e202305783.

(5) Schulte MF, Izak-Nau E, Braun S, Pich A, Richtering W, Göstl R. Microgels react to force: mechanical properties, syntheses, and force-activated functions. Chem Soc Rev. 2022;51:2939–56. doi: 10.1002/ange.202305783.

(6) Bochenek S, Camerin F, Zaccarelli E, Maestro A, Schmidt MM, Richtering W, et al. In-situ study of the impact of temperature and architecture on the interfacial structure of microgels. Nat Commun. 2022;13(1):3744. doi: 10.1038/s41467-022-31209-3.

(7) Liang X, Shiomi K, Nakajima K. Study of the dynamic viscoelasticity of single poly(N-isopropylacrylamide) chains using atomic force microscopy. Macromolecules. 2022;55(24):10891–9. doi: 10.1021/acs.macromol.2c01466.

(8) Vijayakumar B, Takatsuka M, Kita R, Shinyashiki N, Yagihara S, Rathinasabapathy S. Dynamics of the poly(*N*-Isopropylacrylamide)

microgel aqueous suspension investigated by dielectric relaxation spectroscopy. Macromolecules. 2022;55:1218–29. doi: 10.1021/acs.macromol.1c02083.

(9) Nevolianis T, Scotti A, Petrunin AV, Richtering W, Leonhard K. Understanding the monomer deuteration effect on the transition temperature of poly(N-isopropylacrylamide) microgels in H_2O. Polym Chem. 2023;14(13):1447–55. doi: 10.1039/D2PY01511K.

(10) Choi YH, Hwang JS, Han SH, Lee CS, Jeon SJ, Kim SH. Thermo-responsive microcapsules with tunable molecular permeability for controlled encapsulation and release. Adv Funct Mater. 2021;31(24):2100782. doi: 10.1002/adfm.202100782.

(11) Agrawal G, Agrawal R. Functional microgels: recent advances in their biomedical applications. Small. 2018;14(39):1801724. doi: 10.1002/smll.201801724.

(12) Liu Y, Lei Y, Chen Y. Thermoresponsive properties of poly[oligo (ethylene glycol) sorbate]s prepared by organocatalyzed group transfer polymerization. Macromolecules. 2022;55(12):5149–63. doi: 10.1021/acs.macromol.2c00678.

(13) Constantinou AP, Wang L, Wang S, Georgiou TK. Thermoresponsive block copolymers of increasing architecture complexity: a review on structure–property relationships. Polym Chem. 2023;14:223–47. doi: 10.1039/D2PY01097F.

(14) Tzounis L, Doña M, Lopez-Romero JM, Fery A, Contreras-Caceres R. Temperature-controlled catalysis by core–shell–satellite AuAg@pNIPAM@Ag hybrid microgels: A highly efficient catalytic thermoresponsive nanoreactor. ACS Appl Mater Interfaces. 2019;11(32):29360–72. doi: 10.1021/acsami.9b10773.

(15) Sung B, Kim MH, Abelmann L. Magnetic microgels and nanogels: Physical mechanisms and biomedical applications. Bioeng Transl Med. 2021;6(1):e10190. doi: 10.1002/btm2.10190.

(16) Boularas M, Deniau-Lejeune E, Alard V, Tranchant J-F, Billon L, Save M. Dual stimuli-responsive oligo(ethylene glycol)-based microgels: insight into the role of internal structure in volume phase transitions and loading of magnetic nanoparticles to design stable thermoresponsive hybrid microgels. Polym Chem. 2016;7(2):350–63. doi: 10.1039/C5PY01078K.

(17) Guarrotxena N, Quijada-Garrido I. Optical and swelling stimuli-response of functional hybrid nanogels: Feasible route to achieve tunable smart core@shell plasmonic@polymer nanomaterials. Chem Mater. 2016;28(5):1402–12. doi: 10.1021/acs.chemmater.5b04517.

(18) Boularas M, Gombart E, Tranchant J-F, Billon L, Save M. Design of smart oligo(ethylene glycol)-based biocompatible hybrid microgels loaded with magnetic nanoparticles. Macromol Rapid Commun. 2015;36(1):79–83. doi: 10.1002/marc.201400578.

(19) Liu G, Qiu Q, An Z. Development of thermosensitive copolymers of poly(2-methoxyethyl acrylate-*co*-poly(ethylene glycol) methyl ether acrylate) and their nanogels synthesized by RAFT dispersion polymerization in water. Polym Chem. 2012;3(2):504–13. doi: 10.1039/C2PY00533F.