Preparation of polymeric vesicles via redox-initiated RAFT dispersion polymerization

Fen Zhang*, Qian Yao, Yanling Niu, Yantao Li, Haijun Zhou, Xiaoqi Chen and Lu Bai

Institute of Energy Resources, Hebei Academy of Sciences, 050081, Shijiazhuang, Hebei Province, China

Abstract. 2-(diisopropylamino) ethyl methacrylate (DIPEMA) and glycidyl methacrylate (GlyMA) were used for the investigation of the redox-initiated reversible addition-fragmentation chain transfer (RAFT) dispersion polymerization, by using poly (ethylene oxide)-4-(4-Cyanopentanoic acid) dithiobenzoate (mPEG-CPADB) as the macro-chain-transfer agent (macro-CTA). The particle growth process study indicated that the particles changed from spheres to worms, and then to vesicles during the polymerization process. The degree of polymerization (DP) of the hydrophobic block P(DIPEMA-co-GlyMA) affected the particle morphology, particle diameter and molecular weight significantly. Pure polymeric vesicles could be obtained when DP was equal to or higher than 60, and with increasing of the DP of the hydrophobic block, the diameter and the molecular weight of the particles both increased.

Keywords: Polymeric vesicles; redox-initiated; reversible addition-fragmentation chain transfer (RAFT); dispersion polymerization

1. Introduction

Polymeric vesicles, which have the similar structure as that of the liposomes, have been got more and more attention for the adjustable chemical structures via changing the polymerization monomers.1 Reversible addition-fragmentation chain transfer (RAFT)-dispersion polymerization is an effective polymerization method for the preparation of polymeric vesicles at relatively higher concentration with many kinds of monomers,2-3 and thermal initiation polymerization is the commonly used method.4-6

Redox-initiated polymerization, which could be done at much lower temperatures, is more valuable for the RAFT polymerization. Redox-initiated RAFT emulsion polymerization7 and redox-initiated RAFT miniemulsion polymerization8 have been reported, while for the redox-initiated RAFT dispersion polymerization, Liu et al.9 reported the polymerization of 2-methoxyethyl acrylate (MEA) in water solvent, and our group first reported the redox-initiated RAFT dispersion polymerization in ethanol/water mixtures to prepare polymeric vesicles10.

Herein, the copolymerization of 2-(diisopropylamino) ethyl methacrylate (DIPEMA) and glycidyl methacrylate (GlyMA) with poly(ethylene oxide)-4-(4-Cyanopentanoic acid) dithiobenzoate (mPEG-CPADB) as the macro-chain-transfer agent (macro-CTA) was studied in detail via the redox-initiated RAFT dispersion polymerization in ethanol/water mixtures, where potassium persulfate (KPS) and sodium bisulfite (SBS) were used as the redox initiator. The evolution of the particles, and the effect of the degree of polymerization (DP) of the hydrophobic block P(DIPEMA-co-GlyMA) were evaluated.

2. Experiment

2.1 Materials

The α-methoxy-ω-hydroxypoly(ethylene oxide) (mPEG) (number average molecular weight = 1900), 4-(dimethylamino)pyridine (DMAP), CPADB and dicyclohexylcarbodiimide (DCC) compounds were purchased from Aladdin. 2-(diisopropylamino)-ethyl methacrylate (DIPEMA) and glycidyl methacrylate (GlyMA) were purchased from Aladdin and purified by passing through the Al2O3 column to remove the inhibitor. KPS (United Initiators (Shanghai) Co., Ltd.) and SBS (Damao Chemical Reagent Factory) were used as received.

2.2 Preparation of polymeric vesicles

The preparation of the macro-CTA agent and the polymeric vesicles via the redox-initiated RAFT dispersion polymerization were done according to the previous reported method.10 Followed was a typical example for the vesicle preparation: DIPEMA (0.4266 g, 2.0000 mmol), GlyMA (0.0711 g, 0.5000 mmol), mPEG-CPADB (0.0550 g, 0.02500 mmol), KPS (0.00175 g, 0.00625 mmol), SBS (0.000625 g, 0.00625 mmol), and ethanol/water solvent (4.9957 g, with a mass ratio of 6:4)

---

were all added into a reaction tube with a magnetic bar. Three pump-N2 purge cycles were conducted to remove the oxygen, and then the reaction tube was sealed. After stirring for 7 h at 35°C in the oven, the reaction mixture was quickly cooled and then opened to air to stop the reaction.

2.3 Characterization

Transmission electron microscopy (TEM, JEM-2100Plus electron microscope) was used for the morphology characterization of the produced particles, and the samples were stained with phosphotungstic acid before observations. Gel permeation chromatograph (GPC, Waters 2695) was used for the the molecular weight (Mn) and molecular weight distribution (Mw/Mn) measurements, and THF was used as the solvent and monodispersed polystyrene as the standards. The average diameter of the particles were tested on a commercial dynamic light scattering (DLS) spectrometer (PPS Z3000, UK).

3. Results and discussion

3.1 Evolution of the particles prepared via redox-initiated RAFT dispersion polymerization

The evolution of the particles prepared via the RAFT dispersion polymerization of DIPEMA and GlyMA by using KPS/SBS as the redox initiator were studied. Seven reactions were done with same formulation, and at the predetermined reaction times, the reactions were stopped for the polymerization process evaluation. The conversion, particle diameter, number average molecular weight and particle morphology were characterized for each sample. Figure 1 illustrated the evolution of the conversion, particle diameter, number average molecular weight and molecular weight distributions versus the polymerization time, while Figure 2 showed the TEM images of the samples prepared at different polymerization times.

As shown in Figure 1 (a), for the reaction proceeded at 120 min, the conversion of the sample was 24.7%, the reaction mixture kept transparent, and only black dots were observed on the TEM photo (Figure 2 (a)). When the polymerization proceeded for 180 min, the reaction mixture became light turbid, and the nucleation stage started. The conversion increased to 44.8% and TEM photo (Figure 2 (b)) still showed small black dots, where DLS result showed the particle diameter was about 95 nm. When the reaction proceeded for 240 min, the conversion increased to 60.3%, and mixtures of vesicles and worms were observed (the particle diameter was bigger for the existing of the long shaped worms), as shown in Figure 2 (c). Then as the reaction proceeded for 300 min, pure vesicles with diameter of 430 nm were formed, and the conversion increased to 64.9%.

And then for the next two hours, the size of the vesicles kept at about 430 nm and did not change much, the conversion and the molecular weight showed similar trend and both increased slowly, seen from Figure 1. After the reaction proceeded for 420 min, the conversion was higher than 80%, and both the conversion and the

molecular weight did not change much later. The particle morphology evolution from sphere-to-worm-to-vesicle transitions was consistent with Armes' group11 for 2-Hydroxypropyl methacrylate (HPMA) RAFT polymerization with poly (glycerol monomethacrylate) (PGMA) as the chain transfer agent. During the polymerization, the hydrophilic macro-CTA agent was chain extended with DIPEMA and GlyMA to form an insoluble block segment, and when the amphiphilic block copolymer mPEG-b-P(DIPEMA-co-GlyMA) reached to a certain degree of polymerization, they would self-assemble to form nanoparticles, and then grew to higher order morphologies as the reaction proceeded. The molecular weight distributions (Mw/Mn) (in range of 1.16-1.23) were lower for the whole polymerization process, as shown in Figure 1 (b). The result of the low molecular weight distribution was consistent with the characterization of the RAFT polymerization and also indicated the advantages of the redox initiation.12
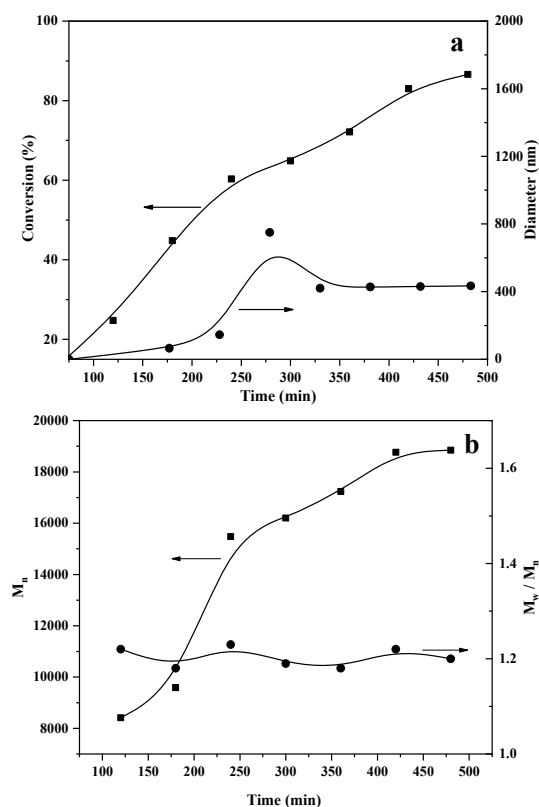

Figure 1. (a) Conversion and particle diameter versus polymerization time, and (b) the number average molecular weight (Mn) and Mw/Mn versus polymerization time in the ethanol-water mixture with 40 wt% of water.
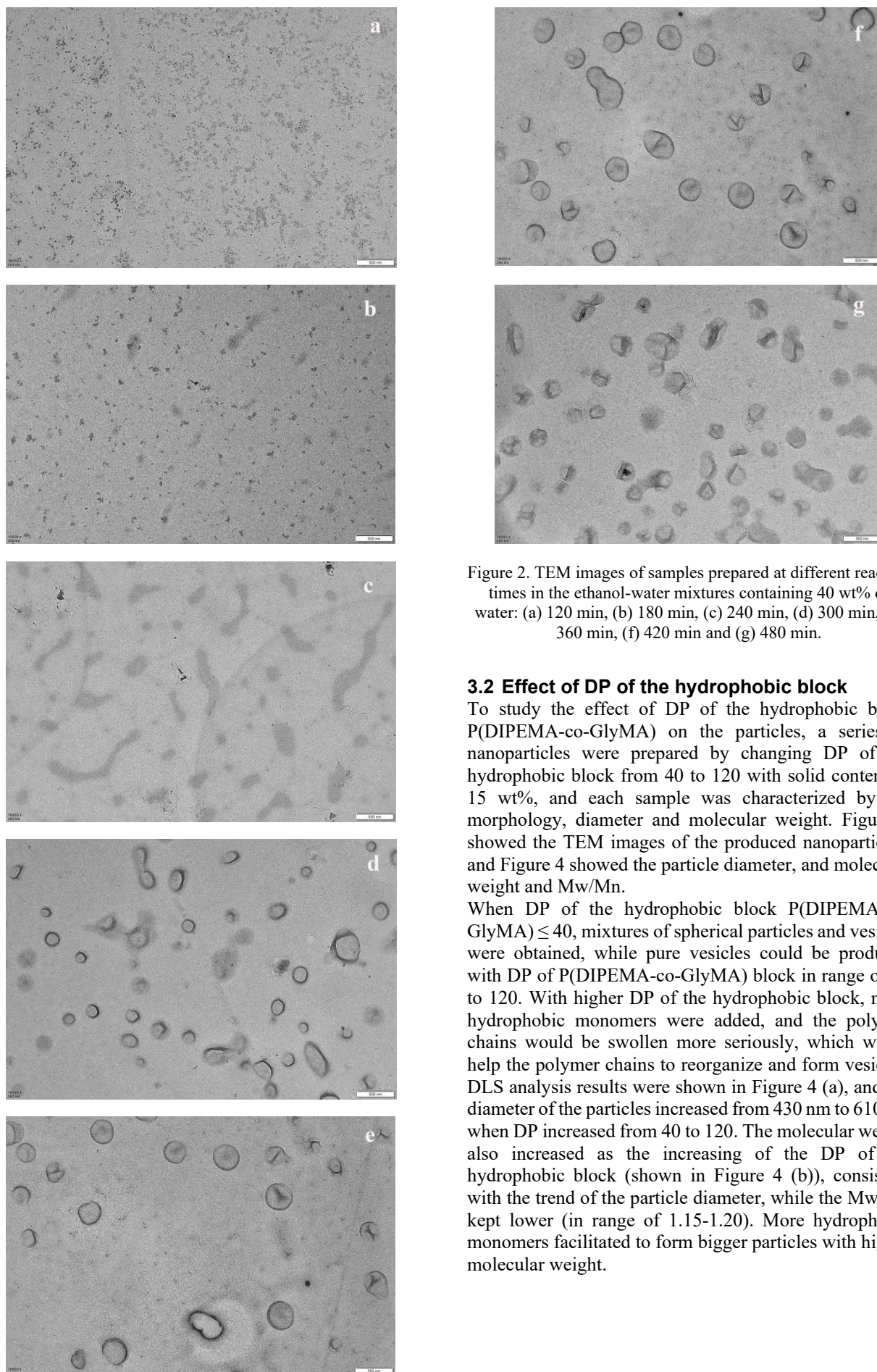
Figure 2. TEM images of samples prepared at different reaction times in the ethanol-water mixtures containing 40 wt% of water: (a) 120 min, (b) 180 min, (c) 240 min, (d) 300 min, (e) 360 min, (f) 420 min and (g) 480 min.

3.2 Effect of DP of the hydrophobic block

To study the effect of DP of the hydrophobic block P(DIPEMA-co-GlyMA) on the particles, a series of nanoparticles were prepared by changing DP of the hydrophobic block from 40 to 120 with solid content of 15 wt%, and each sample was characterized by the morphology, diameter and molecular weight. Figure 3 showed the TEM images of the produced nanoparticles, and Figure 4 showed the particle diameter, and molecular weight and M_w/M_n.

When DP of the hydrophobic block P(DIPEMA-co-GlyMA) ≤ 40, mixtures of spherical particles and vesicles were obtained, while pure vesicles could be produced with DP of P(DIPEMA-co-GlyMA) block in range of 60 to 120. With higher DP of the hydrophobic block, more hydrophobic monomers were added, and the polymer chains would be swollen more seriously, which would help the polymer chains to reorganize and form vesicles. DLS analysis results were shown in Figure 4 (a), and the diameter of the particles increased from 430 nm to 610 nm when DP increased from 40 to 120. The molecular weight also increased as the increasing of the DP of the hydrophobic block (shown in Figure 4 (b)), consistent with the trend of the particle diameter, while the M_w/M_n kept lower (in range of 1.15-1.20). More hydrophobic monomers facilitated to form bigger particles with higher molecular weight.
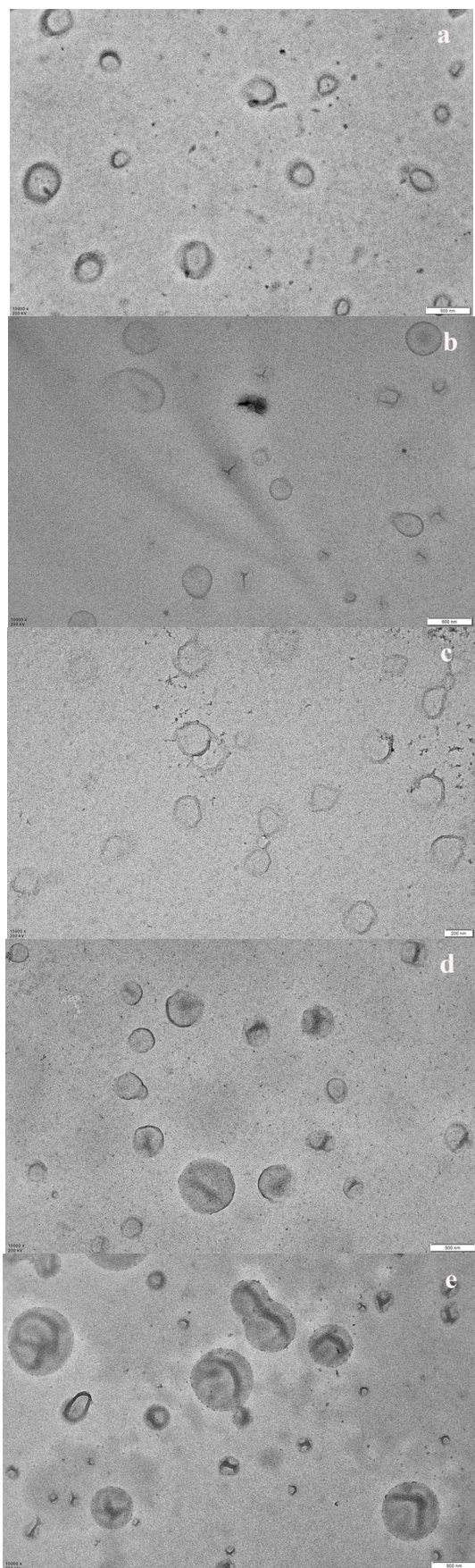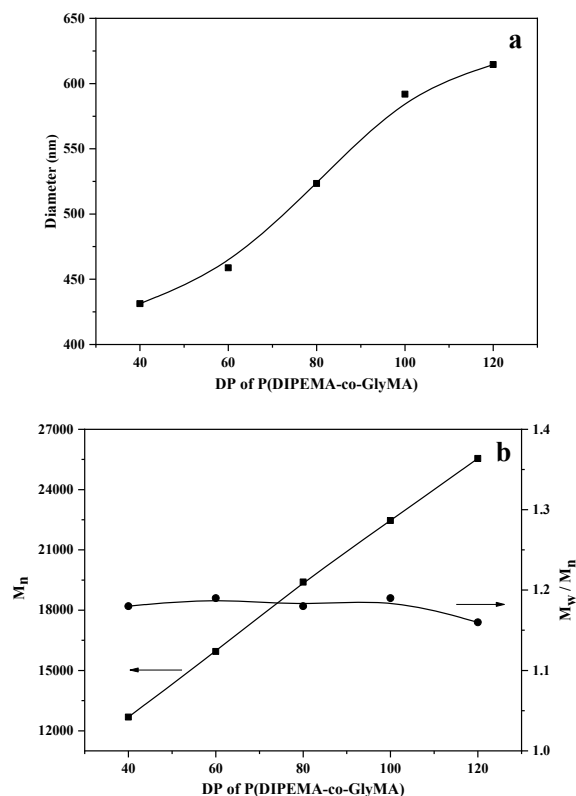
Figure 4. (a) Diameter of particles prepared under different DP of P(DIPEMA-co-GlyMA) block; (b) the number average molecular weight (Mn) and Mw/Mn versus different DP of P(DIPEMA-co-GlyMA) block.

4. Conclusion

Polymeric vesicles in range of 450-610 nm were fabricated via the redox-initiated RAFT dispersion polymerization approach. The study of the evolution of the particles indicated that the particles experienced from sphere-to-worm-to-vesicle transitions, and the particle diameter and molecular weight increased faster at the first 240 min, and then the growth rate became slower. DP of the hydrophobic block P(DIPEMA-co-GlyMA) had significant effect on the produced particles. Good shaped vesicles could be produced when DP of the hydrophobic block P(DIPEMA-co-GlyMA) increased to 60, and the diameter and the molecular weight of the particles both increased as the increasing of the DP of the hydrophobic block.

Acknowledgements

Figure 3. TEM images of nanoparticles prepared under different DP of P(DIPEMA-co-GlyMA) block, (a) DP=40, (b) DP=60, (c) DP=80, (d) DP=100 and (e) DP=120.

References

1. S. L. Canning, G. N. Smith, S. P. Armes, A critical appraisal of RAFT-mediated polymerization-induced selfassembly, Macromolecules, 2016, 49, 1985-2001.

2. N. J. W. Penfold, J. R. Whatley, S. P. Armes, Thermoreversible block copolymer worm gels using binary mixtures of PEG stabilizer blocks, Macromolecules, 2019, 52, 1653-1662.

3. W. Zhang, C. Hong, C. Pan, Artificially smart vesicles with superior structural stability: fabrication, characterizations, and transmembrane traffic, ACS Appl. Mater. Interfaces, 2017, 9, 15086-15095.

4. C. Gonzato, M. Semsarilar, E. R. Jones, F. Li, G. J. P. Krooshof, P. Wyman, O. O. Mykhaylyk, R. Tuinier, S. P. Armes, Rational synthesis of low-polydispersity block copolymer vesicles in concentrated solution via polymerization-induced self-assembly, J. Am. Chem. Soc., 2014, 136, 11100−11106.

5. L. Qiu, C. Xu, F. Zhong, C. Hong, C. Pan, Fabrication of functional nano-objects through RAFT dispersion polymerization and influence of morphology on drug delivery, ACS Appl. Mater. Interfaces, 2016, 8, 18347-18359.

6. A. Zhu, X. Lv, L. Shen, B. Zhang, Z. An, Polymerization-induced cooperative assembly of block copolymer and homopolymer via RAFT dispersion polymerization, ACS Macro Lett. 2017, 6, 304-309.

7. X. Dai, L. Yu, Y. Zhang, L. Zhang, J. Tan, Polymerization-induced self-assembly via RAFT-mediated emulsion polymerization of methacrylic monomers. Macromolecules, 2019, 52,7468-7476.

8. M. Park, K. Kim, A. K. Mohanty, H. Y. Cho, H. Lee, Y. Kang, B. Seo, W. Lee, H. B. Jeon, H. Paik, Redox-initiated reversible addition-fragmentation chain transfer (RAFT) miniemulsion polymerization of styrene using PPEGMA-based macro-RAFT agent, Macromol. Rapid Commun., 2020, 2000399.

9. G. Liu, Q. Qiu, W. Shen, Z. An, Aqueous dispersion polymerization of 2-methoxyethyl acrylate for the synthesis of biocompatible nanoparticles using a hydrophilic RAFT polymer and a redox initiator. Macromolecules, 2011, 44, 5237-5245.

10. F. Zhang, Q. Yao, X. Chen, H. Zhou, M. Zhou, Y. Li, H. Cheng, In-depth study of anticancer drug diffusion through a cross-linked pH-responsive polymeric vesicle membrane, Drug Delivery, 2023, 30, 2162626.

11. A. Blanazs, J. Madsen, G. Battaglia, A. J. Ryan, S. P. Armes, Mechanistic insights for block copolymer morphologies: how do worms form vesicles?, J. Am. Chem. Soc., 2011, 133, 16581-16587.

12. X. Tian, J. Ding, B. Zhang, F. Qiu, X. Zhuang, Y. Chen, Recent advances in RAFT polymerization: novel initiation mechanisms and optoelectronic applications, Polymers, 2018, 10, 318.