

# Fabrication of Tens-micron-sized Functionalized Polystyrene Microspheres for Utilization in Chiral Drug Isolation

Wang Renjie, Ren Ying, Chen Qianqian, Cheng Qiaohuan\*, Wang Shun\*

School of Material Science and Engineering, Henan University of Technology, Lianhua Street NO.100, Zhengzhou, 450001, China

\*Corresponding author: E-mail: qiaohuan\_cheng@haut.edu.cn (C.Q.); shun\_wang@haut.edu.cn (W.S.); Tel: (+86) 0371-67758729, (+86) 0371-67758729

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Functionalized polystyrene (PS) microspheres are promising materials for the isolation of the chiral drugs due to their properties, such as a large surface area, high chemical stability and tunable morphology. Considering 10-100  $\mu\text{m}$  microspheres are suitable as the matrix materials of the chiral stationary phase, and there are few reports on this. Here we report a facile synthesis of the tens-micron-sized carboxylated PS microspheres by a technology between the dispersion and suspension polymerization. The relation between the reaction solutions and the size of the carboxylated PS microspheres were investigated. The study showed that, the more  $\text{H}_2\text{O}$  were used in the reaction solutions, which lead the principle of the reaction more close to the suspension polymerization, the larger size of the carboxylated PS microspheres. In addition, more acrylic acid would destroy the stability of the sphere morphology. Comparing the particle size distribution and morphology, it was revealed that tens-micron-sized carboxylated PS microspheres with narrow size distribution can be fabricated with the ratio of  $\text{H}_2\text{O}/\text{Ethanol}$  30/20 and the proportion of carboxyl groups reached to  $\sim 11\%$ .

## Introduction

In recent years, the isolation of the chiral drugs has received prominent attention [1,2]. HPLC based on chiral stationary phases (CSPs) has become one of the most attractive approaches to chiral separations due to its simplicity, speed and selectivity [3-5]. Due to the high column efficiency and column capacity, the Brush-type CSPs has been widely used in the field of medicine [6,7]. Silica, was always utilized as the carrier of the Brush-type CSPs. However, poor mechanical properties and solvent resistance limit its application. Functionalized polymer microspheres is a class of materials with excellent mechanical properties, controllable morphology and good solvent resistance, which makes it particularly attractive for the Brush-type CSPs applications [8].

Functional polymer particles with various reactive groups on the surface have extensive applications in a variety of fields that include chromatography [8], X-ray imaging [9], controlled drug delivery [10,11], biosensors [12] and so on. Functionalized polystyrene (PS) microspheres has always been the focus of research and development [13]. The carboxyl group is one of the most important surface functional groups for the particles that are intended for biomedical or budiagnostic applications [14]. Furthermore, the preparation of monodisperse particles in the 10-100  $\mu\text{m}$  range is particularly challenging because it is just between the limits of particle size by conventional dispersion polymerization [15] and suspension polymerization [16].

In dispersion polymerization, monomers, initiator, and stabilizer are firstly dissolved in the reaction medium and the polymer particles gradually precipitate out from the reaction medium [17]. Ha J.W. *et. al.*, [18] reported the preparation of carboxyl-functionalized PS microspheres based on one stage batch or two-stage semi-continuous dispersion polymerizations in fluorinated alcohol, the size of the particles is only  $\sim 1.4 \mu\text{m}$ . Beal *et al.* prepared the size of the crosslinked P(St-co-AA) microspheres around 0.8  $\mu\text{m}$  by using butan-1-ol as the medium [15]. In addition, no matter how to change the parameters in the polymerization, the size of the particles were no larger than 10  $\mu\text{m}$ .

Moreover, the medium of the suspension polymerization cannot dissolve the monomer and initiator, each droplet, just containing monomer and few initiator, is an individual reaction system which have more monomers than the same situation in dispersion polymerization. Therefore the particles prepared by traditional suspension polymerization always bigger than 100  $\mu\text{m}$ . Our earlier research work revealed this principle [19]. In this study, a simple method was proposed to prepare the tens-micron-sized carboxylated PS microspheres. It was synthesized through the method between dispersion and suspension polymerization by utilizing mixed reaction medium which can adjust the content of the monomers in each reactor in turn to adjust the particle size. The factors influencing on the size and the particle size distribution were discussed.

## Experimental

### Material details

In this work, in order to guarantee the progress of the polymerization, the styrene (St) and acrylic acid (AA) were used after distillation at reduced pressure. The polymerization initiator azodiisobutyronitrile (AIBN), stabilizers polyvinylpyrrolidone K90 (PVP K90) was used without further purification. Ethanol and distilled water were commercially available and used without purification.

### Material synthesis

A four-neck round-bottom flask was used as the container for the polymerization, with the solvent mixture of ethanol/H<sub>2</sub>O used as the dispersion medium, PVP K90 as the steric stabilizers, AIBN as the initiator. Under a nitrogen atmosphere, the copolymerization of St and AA was performed by a new method between the suspension and dispersion polymerization.

Firstly, the given amount of PVP K90 was dissolved into the dispersion medium, stirring at a constant rate, and then the initiator AIBN was dissolved into the mixture of the monomers, then the St, AA and AIBN mixtures was poured into the flask. At last, the flask was suspended in a temperature controlled water bath at 75°C. The reaction continued for 12 h totally. The resulting particles were dispersed by ultrasound wave, isolated by filtration and washed with distilled water and ethanol sequentially, finally dried at 60°C for 24 h.

### Characterizations

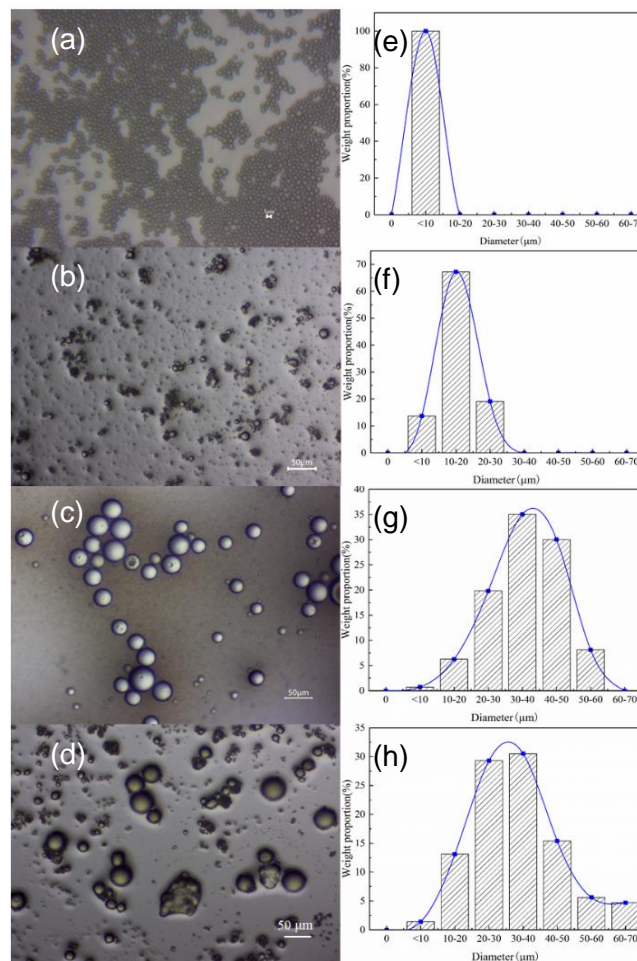
The chemical structure of the products was analyzed by Fourier transform infrared spectrometer (FTIR, Nicolet 460) with KBr wafer method. The particle size, size distribution and morphology of the particles were analyzed using an optical microscope (XSP-2CA).

## Results and discussion

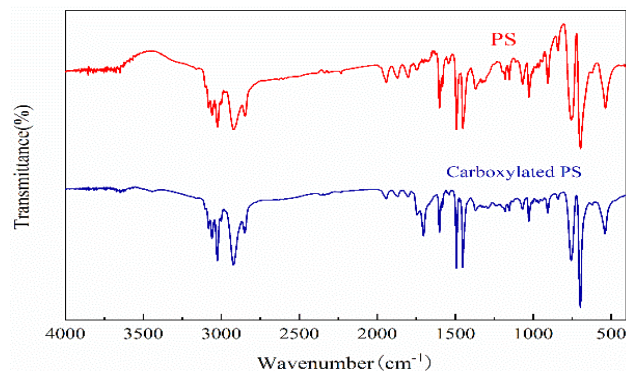
Extensively literature demonstrating that moderately monodisperse polymer particles ranging from 1 to 10 μm can be synthesized via simple dispersion polymerization. In addition, the traditional suspension polymerization can be used to prepare particles larger than 100 μm. Therefore, we considered to seek one method which between the dispersion and suspension polymerization to prepare tens-micron-sized carboxylated PS microspheres.

**Fig. 1** shows the micrograph and the size distribution of the microspheres fabricated by varying the ratio of the dispersion medium of the polymerization. It was found that with the ratio of ethanol to H<sub>2</sub>O decreased from 45/5 to 10/40, the average particle diameter increased. When the ratio of ethanol to H<sub>2</sub>O was 45/5, the mechanism of the polymerization was much close to the dispersion polymerization, so the size of the microspheres were all <10 μm and most of the particles were around 2.5 μm. Then we tried to increase the ratio of the H<sub>2</sub>O in the medium, then the bigger microspheres were obtained and

the particle size was concentrated in 20-30 μm. The tens-micron-sized microspheres were fabricated when we increased the ratio of the H<sub>2</sub>O to 60% and almost 85% microspheres were among 20-50 μm. Although the size of the microspheres became bigger with the continuous increase of the H<sub>2</sub>O in the medium, there were some non-spherical particles generated. In addition, the size distribution also became bigger and bigger with the increase of the H<sub>2</sub>O.



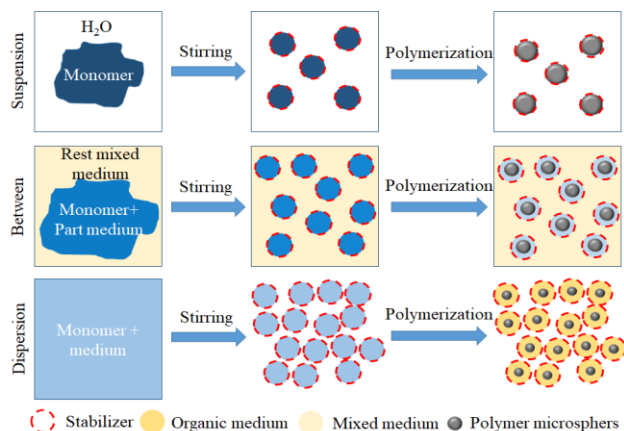
**Fig. 1.** The micrograph and the size distribution of the microspheres fabricated by using different volume ratio of ethanol and H<sub>2</sub>O: (a, e) 45/5; (b, f) 30/20; (c, g) 20/30; (d, h) 10/40.



**Fig. 2.** The infrared spectrum graph of the PS and carboxylated PS microspheres.

**Fig. 2** shows the infrared spectrogram of PS and carboxylated PS microspheres. The absorption peak at  $1452\text{ cm}^{-1}$ ,  $1490\text{ cm}^{-1}$ , and  $1599\text{ cm}^{-1}$  represent the stretching vibration of the C=C in the benzene ring, peaks at  $3026\text{ cm}^{-1}$ ,  $3056\text{ cm}^{-1}$ , and  $3082\text{ cm}^{-1}$  point to the stretching vibration of the =C-H in the benzene ring. All of these peaks illustrated the major structure of the PS. Compared with PS, carboxylated PS particles has strong peaks at  $1704\text{ cm}^{-1}$  which stands for the stretching vibration of the C=O in the monomer acrylic acid (AA). Furthermore, the content of the carboxyl in microspheres by calculated was around 11% based on the baseline quantitative analysis.

Based on these results, we proposed the principle of the polymerization used in this research can be explained by the mechanism between dispersion and suspension polymerization. **Fig. 3** showed the theory of the polymerization we suggested. Because of the shear force from the stirring process, the monomers were dispersed into many small droplets, each droplet was one reaction unit which would generate the polymer microspheres. This unit contained the homogenous mixture of the monomer and the medium for dispersion polymerization, so the monomer content of each droplets is less than the suspension polymerization, this would lead to the smaller particles. Therefore, adjust the solubility of the monomer in the mixed medium could acquire the tens-micron-sized polymer particles between the suspension and dispersion polymerization.



**Fig. 3.** Schematic representation of the synthesis of the carboxylated PS microspheres by different polymerization technology.

## Conclusion

We confirmed a method to obtain the tens-micron-sized carboxylated PS microspheres by using mixed dispersion medium of ethanol and H<sub>2</sub>O. When the ratio of the ethanol to H<sub>2</sub>O reached 20/30, 85% particles of the products were between 20-50  $\mu\text{m}$ .

Our research proposed the theory of the polymerization which was used to fabricate tens-micron-sized carboxylated PS microspheres. The essential of this theory is the control of the solubility of the monomer in the mixed medium. Actually this technology also can be

used to synthesize different functionalized polymer microspheres, such as the chloromethylated PS microspheres what we have prepared.

As the results showed, the size distribution of the particles was broader with the principle close to the suspension polymerization. Actually, this was also caused by the different monomer contents in each droplets. It is necessary for the full assessment of the theory to check the relation of the monomer solubility with the size and the size distribution.

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## Conflicts of interest

There are no conflicts to declare

## Supporting information

Supporting informations are available online at journal website.

## Keywords

PS microspheres, carboxylated, chiral stationary phase, dispersion polymerization, suspension polymerization.

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## References

- Xu, G. F.; Du, Y. X.; Chen, B.; Chen, J. Q., *Chromatographia*, **2010**, *72*, 289.
- Gandhi, K.; Shah, U.; Patel, S., *Curr Drug Discov Technol*, **2019**.
- Yu, J.; Tang, J.; Yuan, X.; Guo, X.; Zhao, L., *Chirality*, **2017**, *29*, 147.
- Ishidate, R.; Sato, T.; Ikai, T.; Kanoh, S.; Yashima, E.; Maeda, K., *Polym Chem-Uk*, **2019**, *10*, 6260.
- Asnin, L. D.; Vasyanin, A. N.; Stepanova, M. V., *Russ Chem B+*, **2019**, *68*, 2232.
- Knezevic, A.; Novak, J.; Vinkovic, V., *Molecules*, **2019**, *24*.
- Asnin, L. D.; Boteva, A. A.; Krasnykh, O. P.; Stepanova, M. V.; Ali, I., *J Chromatogr A*, **2019**, *1592*, 112.
- Huang, Z.; Yao, P.; Zhu, Q.; Wang, L.; Zhu, Y., *Talanta*, **2018**, *185*, 8.
- Skjongsfjell, E. T. B.; Kleiven, D.; Patil, N.; Chushkin, Y.; Zontone, F.; Gibaud, A.; Breiby, D. W., *J Opt Soc Am A*, **2018**, *35*, 7.
- Yang, X.; Chen, L.; Huang, B.; Bai, F.; Yang, X., *Polymer*, **2009**, *50*, 8.
- Franca, M. T.; Nicolay Pereira, R.; Klüppel Riekes, M.; Munari Oliveira Pinto, J.; Stulzer, H. K., *European Journal of Pharmaceutical Sciences*, **2018**, *111*, 10.
- Wang, J.; Wang, X.; Tang, H.; Gao, Z.; He, S.; Li, J.; Han, S., *Biosens Bioelectron*, **2018**, *100*, 1.
- Lü, S.; Jiang, W.; Li, J., *Colloid and Polymer Science* **2018**, *297*, 10.
- Chaleawlert-umpon, S.; Pimpha, N., *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, **2012**, *414*, 9.
- Beal, J. H. L.; Xu, Y.; Al-Samlim, N.; Arnold, W. M., *Journal of Applied Polymer Science*, **2016**, *133*.
- Okubo, M.; Konishi, Y.; Minami, H., *Colloid & Polymer Science*, **1998**, *276*, 5.
- Zhang, B.; Lu, J.; Liu, X.; Jin, H.; He, G.; Guo, X., *International Journal of Polymer Science*, **2018**, *2018*, 8.

18. Lee, S. G.; Ha, J. W., *Macromol Res.* **2016**, *24*, 675.  
19. Duan, R.; Chen, J.; Hou, G.; Ke, J. *Applied Sciences in Graphic Communication and Packaging*, Springer, Singapore, **2018**, pp. 927-933.

### Authors biography



Dr. Renjie Wang is currently an assistant professor in School of Materials Science and Engineering in Henan University of Technology. He has been actively involved in the research of the preparation and application of functionalized polymer microspheres since 2010. He also actively involved in the research of the chromosome conformation based on Rouse polymer model since 2013. His current research interests focus on the preparation of PI aerogel materials and the study of the chromosome conformation in living budding yeast cells



Dr. Ying Ren has been actively involved in the research of the preparation and application of diamond-like carbon coatings, especially in the biomedical field since 2009. She has been committed to construct diamond-like coated artificial joint heterostructure to solve the problem of short life expectancy of traditional artificial joints under the combined action of high-load friction and corrosion in the complex physiological and mechanical environment of the human body.



Dr. Qianqian Chen received her PhD degree in science from Université Libre de Bruxelles in 2018. She is currently an assistant professor in the faculty of Material Science and Engineering at Henan University of Technology (China). Her current research interests focus on plasma-surface interaction, design and synthesis of photocatalysts, and surface modification of photocatalysts.



Dr. Qiaohuan Cheng received her PhD degree in science from Technological University Dublin in 2010. She is currently a lecturer in the faculty of Material Science and Engineering at Henan University of Technology (China). Her current research interests focus on the dispersion of nanoparticles, modification and application of nanomaterials.



Dr. Shun Wang is currently an assistant professor in School of Materials Science and Engineering in Henan University of Technology. His research efforts have been mainly devoted to two areas: 1) the design and synthesis of low-dimensional nanomaterials for energy storage and 2) the electronic, elastic and optical properties of MXene by the first-principles method based on density functional theory.