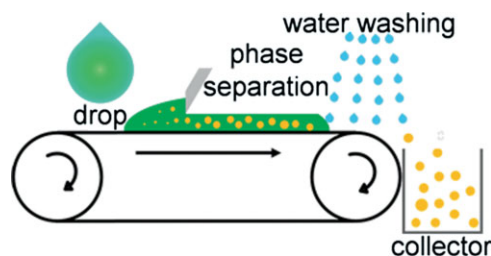


Continuous Production of Functionalized Polymer Particles Employing the Phase Separation in Polymer Blend Films^a

ChooJin Park, Dong Choon Hyun, Min-Cheol Lim, Su-Jeong Kim, Young-Rok Kim, Hyun-Jong Paik, Unyong Jeong*

This study reports a continuous preparation of spherical or hemispherical polymer particles simply utilizing the phase separation in polymer blend films during the coating process. We took an advantage of the strong phase separation between a water-soluble crystalline polymer as a matrix and hydrophobic polymers as minor components. We demonstrated the preparation of water-soluble polystyrene (PS) particles, nitrilotriacetic acid (NTA)-functionalized PS particles for protein separation, and semiconducting poly(3-hexylthiophene) (P3HT) particles. The sizes of the particles could be controlled by adjusting the film thickness and weight fraction of the minor component polymers in the blend film. It provides a simple facile way to prepare polymer particles in a continuous process.



Introduction

Polymer particles have been of great interest owing to their diverse applications such as cosmetics, pharmaceutical industries, food industries, paints, and toners in reproducing systems.^[1] Enormous efforts have been devoted to produce functional polymer particles in a large scale.

Microemulsion polymerization and suspension polymerization are conventional solution processes to prepare polymeric particles with uniform size via *in-situ* polymerization.^[2] In spite of large quantity production, the approach has a limitation in the polymer species available as well as the existence of residual monomer in the resulting particles. Non-polymerization methods have been also investigated, including spray-drying,^[3] coacervation,^[4] porous glass emulsification,^[5] and electro-spraying.^[6] Preparation of diverse species of particles is allowed through those approaches, but it is difficult to obtain uniform-sized particles. Very recently, our group developed an electro-spraying process to generate uniform microcapsules,^[7] but the size was limited to microscale. Polymer particle preparation still needs a simple route to meet a massive production, diverse species, and size control down to nanometer scale.

It has been well known that immiscible polymer blends experience phase separation when the polymer chains are mobile under thermal annealing or solvent treatment.^[8] A minor component polymer evolves into spherical particles

C. J. Park, D. C. Hyun, U. Jeong
Department of Materials Science and Engineering, Yonsei
University, 134 Shinchon-dong, Seoul 120-749, Korea
E-mail: ujeong@yonsei.ac.kr

M. C. Lim, Y. R. Kim
Institute of Life Sciences and Resources & Department of Food
Science and Biotechnology, College of Life Sciences, Kyung Hee
University, Yongin, Korea
S. J. Kim, H. J. Paik
Department of Polymer Science and Engineering, Pusan
University, Busan, Korea

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in a major component matrix. The particle size is governed by the chain mobility of the polymers, the volume fraction of the minor component, and interfacial tension between the polymers.^[8] This study employed the polymer phase separation in blend films during the drying process so that we can achieve continuous production of relatively uniform-sized polymer particles. This new approach enabled the preparation of various functional particles. As a proof-of-concept, we prepared size-controlled polystyrene (PS) particles, water-soluble PS particles, superparamagnetic PS particles functionalized with nitrilotriacetic acid (NTA), and poly(3-hexylthiophene) (P3HT) particles.

Experimental Section

Poly(ethylene oxide) (PEO, $\bar{M}_w = 10\,000$ Da), two polystyrenes (PS) with different molecular weight ($\bar{M}_w = 11\,000$ Da and $\bar{M}_w = 44\,000$ Da), and poly(3-hexylthiophene) (P3HT, $\bar{M}_w = 87\,000$ Da, regioregularity = 95%) were purchased from Aldrich. Superparamagnetic iron oxide nanoparticles dispersed in toluene (EMG 911) were purchased from Ferrofluids. PS-*b*-PEO-*b*-PS triblockcopolymer (19,400-*b*-10,000-*b*-19,400) was purchased from Polymer Science Co. PS with a nitrilotriacetic acid (NTA) end group (PS-NTA, $\bar{M}_w = 16\,000$ Da) was synthesized by atom transfer radical polymerization by using *N,N'*-bis[(*tert*-butyloxycarbonyl)methyl]-*N''*-bromoisobutyryl-L-lysine *tert*-butyl ester^[9] as an initiator which was transformed into NTA later.^[10]

Mixture solution of PEO and PS were prepared in chloroform (Mallinckrodt Baker, 99.9%) at a predetermined PS weight fraction as a minor phase. Total concentration of the polymers was varied from 0.4 wt% to 8 wt% in order to control the thickness of the polymer blend films. The polymer solutions were drop-casted on a rolling belt through a syringe and bladed to make the films uniform. After dried in air at room temperature the PEO matrix was dissolved by spraying water on the blend film or making the belt passing through a water bath. Because evaporation rate of the solvent is highly dependent on film thickness, spin-coating was used to study the morphologies in thin blend films with high evaporation rate. Spin-coating has been carried out at 3 000 rpm for 30 sec. Crystallization of PEO was completed during spin-coating.

In order to produce water-soluble PS particles, PS-*b*-PEO-*b*-PS triblock copolymer (0.01 wt% in the mixture solution) was added in the PEO/PS mixture solution. P3HT particles were prepared at a low weight fraction of P3HT versus PEO ($\phi_{P3HT} = 0.167$). PS-NTA particles including iron oxide nanoparticles were produced at $\phi_{PS-NTA} = 0.25$. The as-purchased iron oxide nanoparticle suspension was completely dried in vacuum and added into a PS-NTA/PEO chloroform solution. Polymer was 4 wt% and the magnetic nanoparticle was 0.5 wt% in the mixture solution. The produced PS-NTA particles could be dispersed in water. For the preparation of his-tagged green fluorescence protein (GFP), *E. coli* BL21 containing pET28a-gfp was cultured for overexpression of GFP. We followed the reported process.^[10]

The polymer particles were observed by a field emission scanning electron microscopy (FE-SEM, S-4200, Hitachi) and a transmission electron microscopy (TEM, 2100F, Jeol). Photolumi-

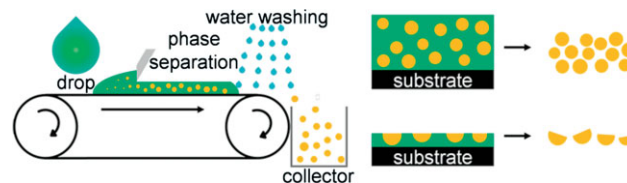


Figure 1. Schematic illustration describing the production of polymeric particles in the form of spheres or hemispheres. A mixture solution of two polymers is dropped on a belt and bladed for uniform thickness. During the solvent evaporation, the two polymers are phase separated. The minor component polymer separates into spherical particles in a thick matrix, while it generates hemispheres in a thin matrix.

nescence of the P3HT particles was obtained by a fluorescence spectrophotometer (Varian, Cary Eclipse).

Results and Discussion

Figure 1 illustrates the continuous process to produce polymeric particles by employing the *in-situ* phase separation in a polymer blend film during the drying process. A mixture solution of two polymers was casted on a rolling belt. The thickness of the blend film was controlled by a blade. When the two polymers were incompatible, the minor component polymer should be phase separated into droplets in a matrix of the major component polymer. A water-soluble crystalline polymer was an appropriate matrix polymer for this approach because the crystallization strongly repels the minor component polymers. Once the crystallization started, the solidified crystallites played as a physical block restricting translation of the small domains even when considerable amount of solvent still remained in the mixture film. Such physical entrapment led to relatively uniform-sized particles. Removing the matrix could produce particles of the minor component polymer. The shape of the particles was dependent on the thickness of the polymer blend. When the blend was thick enough for multiple stacking of the particles, spherical particles were embedded in the matrix polymer. For thin blend films that cannot accommodate one or two layers of the particles, hemispherical particles were prepared. The hemispherical shape was readily obtained with hydrophobic polymers as a minor component because the polymers are selectively located at the air surface. We often observed hemispherical particles at the top surface of thick films as well.

As a model system, we first employed the phase separation between PS ($\bar{M}_w = 11\,000$ Da) and PEO ($\bar{M}_w = 10\,000$ Da). The two polymers have been known to be strongly immiscible each other.^[8] Figure 2A,B show the PS particles obtained from a thick film of the polymer blend. The same volume of PEO solution (3 wt%) and PS solution

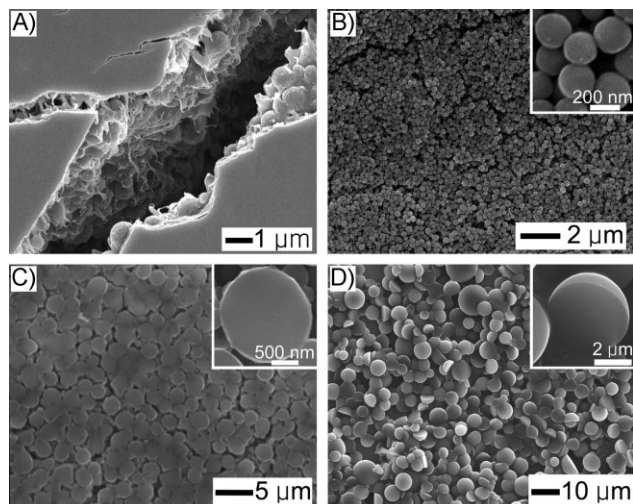


Figure 2. (A,B) SEM images of a thick mixture film consisting of polystyrene (PS) and poly(ethylene oxide) (PEO). The film was made by drop casting. (A) Spherical PS particles are embedded in the thick PEO matrix film. (B) PS particles obtained by washing the PEO matrix with water. (C,D) SEM images of a thin mixture film (approximately $3\ \mu\text{m}$) consisting of PS and PEO. The film was made by drop casting. (C) The minor component (PS) was exposed to air, giving lotus leaf-like features from top view. (D) PS hemispherical particles collected by washing the PEO matrix with water. The insets are blow-up images.

(1 wt%) in chloroform were mixed and the mixture solution was dropped on the substrate. After waiting for 10 min, the dense solution was bladed for uniform film thickness. The solvent was allowed to evaporate in air. As the solvent evaporated, the solubility of polymers decreased and PEO started to be crystallized. The phase-separated PS chains evolved to small domains in the PEO crystalline matrix. Figure 2A shows the PS spheres embedded in the PEO matrix, observed through a crack in the mixture film. After washing out the PEO matrix with water, PS particles with relatively uniform size could be retrieved (Figure 2B). The average diameter of the particles was $218 \pm 43\ \text{nm}$. When the polymer film was thin and slowly evaporated, hemispherical PS particles were obtained. The film was prepared by drop-casting a diluted polymer solution at the same weight fraction of PS versus PEO ($\phi_{\text{PS}} = 0.25$). The hydrophobic PS chains moved to the surface due to the lower surface energy and maintained a flat topology, thereby hemispheres were generated. The top view of the PS domains in Figure 2C looks like a collection of lotus leaves. The inset image clearly shows the flat top surface of the particles. Figure 2D is the hemispherical PS particles collected on a Si wafer after dissolving the PEO matrix. The inset clearly verifies the hemispherical shape of the particles. Because the solvent continuously moved to the surface during the evaporation process, the movement of the PS chains at the air surface should be much easier

relative to those inside a thick film, which led to large particles with broad size distribution. It is noticeable that a blend pair with a weak interfacial tension such as PEO/PMMA led to a bicontinuous film, producing porous PMMA after removing the PEO (see Figure S1 in the Supporting Information).

Size of the particles should be affected by several factors such as evaporation rate of the solvent, thickness of the film, mixing ratio between the polymers, and molecular weight of the polymers. Unfortunately, solvent evaporation and film thickness are not independently controllable because overall evaporation is faster in thin films. Drop casting in air is a slow evaporation process producing relatively thick films. Extreme opposite case is a thin film generated by spin-coating. The size of the resultant particles must be between those prepared by the two extreme cases. Figure 3A exhibits the dependence of the particle size on the thickness of the spin-coated films. The weight fraction of PS was fixed at $\phi_{\text{PS}} = 0.25$. The solid circles and the hollow circles in Figure 3A indicate diameters of the particles

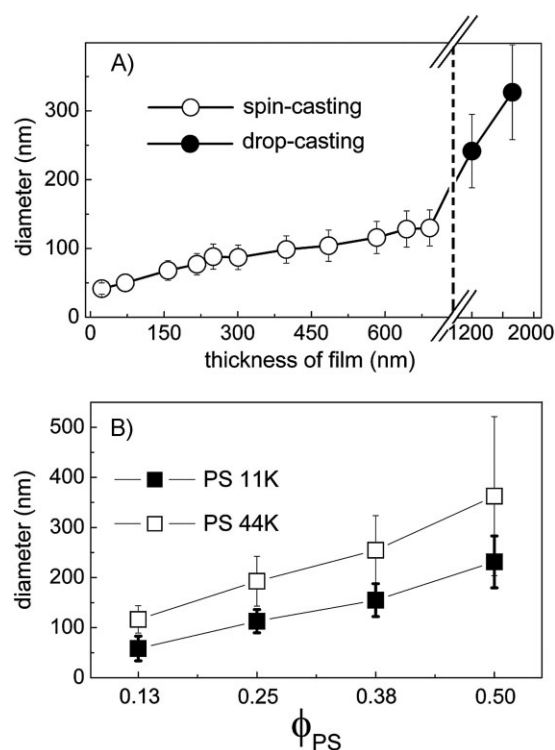


Figure 3. (A) Diameter change of the spherical PS particles by changing thickness of the blend films. The hollow symbols were obtained from thin films prepared by spin-coating. The fast solvent evaporation produced spherical particles. The solid symbols obtained from thick films prepared by drop casting. (B) Effect of PS weight fraction (ϕ_{PS}) in the blend film on the spherical particle size. The films were prepared by spin-coating with a fixed thickness ($\sim 600\ \text{nm}$). PS with a higher molecular weight (44k) produced larger particles than PS with a lower molecular weight (11k) did.

obtained by drop-casting and spin-coating, respectively. Slow evaporation produced bigger particles than fast evaporation. Hemispherical particles were not observed in spin-coated thin films, which is contrast to the thin films with slow evaporation exhibited in Figure 2C. This difference is attributed to the fast crystallization of PEO chains in the spin-coated films, which restricts the movement of PS chains to the air surface. The diameter of the PS particles decreased as the film thickness was reduced in the spin-coated films. 700 nm-thick films produced particles of 130 nm, while 80 nm-thick films generated particles of ~ 50 nm in diameter. Interestingly, 23 nm-thick films gave particles of 42 nm. This size is considered as the minimum achievable with the PEO(10K)/PS(11K) pair. Figure 3B exhibits the dependence of particle size on weight fraction of PS. The mixture films were prepared by spin-coating and their thickness was fixed at ~ 600 nm. The particle diameter was linearly proportional to the weight fraction of PS. At $\phi_{PS} > 0.5$, the PS formed a continuous phase instead of separated particles. Another variable for the particle formation is the molecular weight of the polymers. As seen in Figure 3B, PS (44K) produced much larger particles than PS (11K) did at the same weight fraction of PS. The increased segregation power with the larger-molecular-weight PS is considered to cause early phase separation so that larger particles can be generated.

The size of the spherical domains in the polymer-polymer melt blends in bulk under mechanical mixing has been long-time studied. The size distribution from the melt blending was relatively broad, typically with more than 20% standard deviation. The poor uniformity is caused by the coalescence of the particles generated from the elongated minor phase. In contrast, the precipitation of polymers from a solution can give uniform-sized particles in the presence of a surfactant. The system in this study is a combination of the phase separation from a bulk blend and precipitation from a solution. The particles obtained by this approach usually showed $\sim 10\%$ standard deviation which is poor relative to the well-known batch-type procedures. We consider that the use of low-molecular-weight surfactants or adjusting the rate of solvent evaporation and matrix crystallization may improve the size uniformity, which is left for future study in an optimized setup.

Because industrial polymers can be used in this approach, instead of expensive monomers, the process can be cheap. The use of pre-synthesized polymers allows production of particles that are not obtainable in the batch-type solution processes. In addition, the process can minimize the possible existence of small molecules in the particles which is problematic in the particles produced from monomers. Figure 4 demonstrates a few applications from the approach described above. Since the PS particles produced above contained no surfactant, they could not be dispersed in aqueous solvents. We added a small amount of

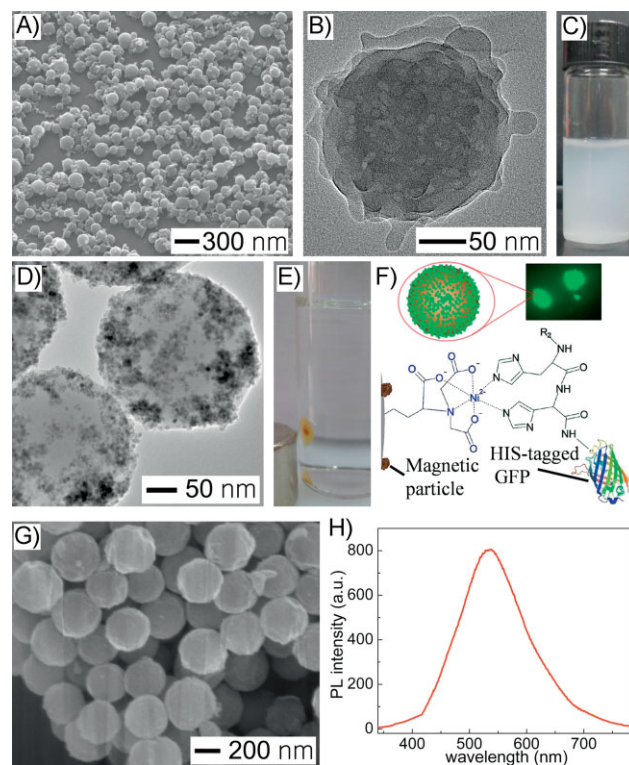


Figure 4. TEM and camera images of various particles prepared by the phase separation in polymer blend films. (A–C) Water-soluble PS particles obtained from the phase separation of PS in a thick PEO film containing small amount of PS-*b*-PEO-*b*-PS triblock copolymer. (D–F) Superparamagnetic particles of nitrilotriacetic acid (NTA) end-functionalized PS produced from the phase separation in a thick PEO matrix including iron oxide nanoparticles. The magnetic nanoparticles were selectively deposited on the surface of the PS particles. The NTA surface groups were utilized to purify histidine-tagged green fluorescence proteins (GFPs). (G) Poly(3-hexylthiophene) (P3HT) particles prepared in a thick PEO film. Their size could be controlled by adjusting the thickness of the films. (H) The emission spectrum of P3HT particles upon excitation at 390 nm.

PEO-*b*-PS-*b*-PEO triblock copolymer (0.25 wt% versus the total polymer) to the mixture solution of PS and PEO. Figure 4A–C exhibit the water-soluble PS particles obtained after drop-casting the mixture film, followed by dissolving the PEO matrix. As shown in the SEM image in Figure 4A, the retrieved particles had a rough surface. The TEM image in Figure 4B indicates the triblock copolymer chains played as a compatibilizer at the PS/PEO interface. The reduced interfacial tension increased the thickness of the PS/PEO interface during the phase separation, resulting in the rough surface on the PS particles. Owing to the hydrophilic PEO block of the triblock copolymer, the particles obtained were well suspended in water as seen in Figure 4C.

The same approach was utilized to prepare PS particles functionalized with nitrilotriacetic acid (NTA). A NTA-end functionalized PS was mixed with PEO and hydrophobic

iron oxide nanoparticles were added in the polymer blend solution (see Figure S2 in the Supporting Information). The total magnetic particles were 10 wt% versus PS. The samples were made by drop-casting, followed by drying in air. During the crystallization of the PEO phase, the iron oxide nanoparticles moved to the solvent-rich PS phase. Majority of the nanoparticles were found at the surface of the PS particles (Figure 4D). The NTA functional group has been well studied for their capability to form Ni complex that can bind histidine groups of biomolecules.^[11] Introduction of imidazole can replace the Ni-histidine binding so that the biomolecules can be released from the NTA group. We utilized the NTA-functionalized PS particles to purify histidine-tagged green fluorescent proteins (GFP). Because it is difficult to avoid nonspecific bindings of other proteins, we had treated the PS-NTA particles with bovine serum albumin (BSA) to block the non-specific bindings before the his-tagged proteins were introduced. The blocking process has been known as a general way of minimizing the non-specific binding of proteins to the surface. The fluorescent image in the inset of Figure 4E illustrates that GFP were successfully attached to the particle surface. The particles were quickly collected by a handy magnet thanks to the large amount of iron oxide nanoparticles loaded in the PS particles (Figure 4F). After decanting the solution and washing the particles with pure water, introduction of small amount of imidazole removed any fluorescence, which means that most GFP were eluted from the particle surface.

We tested the concept to prepare spherical particles of P3HT that are useful for optoelectronic applications.^[12] A mixture solution of P3HT and PEO in chloroform with $\phi_{\text{P3HT}} = 0.14$ was spin-coated. Figure 4G shows the P3HT particles retrieved from 130 nm-thick films. Figure 4H exhibits a luminescence peak from the particles at 390 nm excitation, which is typical in P3HT nanoparticles.^[12] When the weight fraction of P3HT was higher, each particle possessed long tails (see Figure S3 in the supporting information).

Discussion on the possibility of the process for practical production pathway is valuable. Because it is a continuous process, the overall production time is determined by the evaporation rate of the solvent which is the slowest process. The evaporation is slow for a diluted solution or thick films. In this study, the solvent was allowed to evaporate in air. As a typical process with a 3 wt% solution for a 20 μm -thick blend film, we waited for 10 min after dropping the solution on the belt to make the solution concentrated, and then the solution was slowly bladed. The time required for the coating and drying was about 20 min. If we use a concentrated solution, the coating time can be shortened. The produced amounts are directly proportional to the film thickness and dimension of the belt. If the film is about 20 μm -thick and the fraction of PS is 25 wt% in the PEO

matrix, 1 m² area (1 m · 1 m) can produce 4.5 g of PS particles. When the rolling speed of the belt is 0.1 m/min, the process will produce 4.5 g/10 min, which is 27 g/h. Air convection during the coating process can greatly enhance the evaporation rate, thus film thickness can be increased, which will effectively facilitate the production in large quantity. For example, a 1 mm-thick blend film with a rolling speed of 1 m/min will produce 15 kg/h. The costs from this approach should be cheap, because the process needs industrial polymers instead of expensive monomers. Most of all, the continuous process can guarantee the quality control of the particles in their size.

Conclusion

This study proposed a novel simple way to produce spherical or hemispherical polymer particles. We utilized the phase separation in a polymer blend consisting of a water-soluble crystalline polymer as a matrix and a hydrophobic polymer as a minor component. The crystallization-induced phase separation during the drying process led to isolated hydrophobic particles embedded in the matrix. Cycles of coating-evaporation-washing process enabled continuous production of functional particles. As proof-of-concept examples, we demonstrated the preparation of several functional particles of polystyrene (PS) and poly(3-hexylthiophene) (P3HT) in forms of spheres or hemisphere. The size of the particles could be controlled by adjusting the thickness of the films as well as the weight fraction of the minor polymer versus the matrix polymer. It provides a general facile way to prepare relatively uniform-sized polymer particles via a simple continuous process.

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