Synthesis of small polymeric nanoparticles sized below 10 nm via polymerization of a cross-linker in a glassy polymer matrix†

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Small polymeric nanoparticles sized below 10 nm were effectively synthesized via free radical polymerization of a cross-linker in a glassy polymer matrix, owing to the successful prohibition of aggregation between the primary nanoparticles by the matrix.

Small polymeric nanoparticles with a size of several nm are very important from both practical and theoretical viewpoints. For example, when used as drug carriers, polymeric nanoparticles sized below 5 nm can be excreted in urine because they are below the threshold of renal filtration; they do not have to be biodegradable to prevent bioaccumulation. 1,2 Polymeric nanoparticles sized below 10 nm are usually smaller than the size of unperturbed linear polymer chains. This remarkably enhances miscibility between such small polymeric nanoparticles and polymers. 3 Recently, in a mixture of a polymer and such small polymeric nanoparticles, a unique non-Einstein-like decrease in the viscosity was observed. 4 However, the synthesis of polymeric nanoparticles sized below 10 nm is still challenging. Microemulsion polymerizations are well developed for preparing polymeric nanoparticles sized from 20 to 50 nm. 5-7 Only in a few special cases are polymeric nanoparticles of several nm prepared by this method in presence of a large amount of metallosurfactants, which makes the purification of products difficult. 8 Dendrimer synthesis provides a precise way to produce well-defined branched polymeric particles with a layered structure whose sizes range from 2 to 15 nm, but the step-by-step synthesis processes are lengthy and tedious. 9-11 Hawker et al. prepared single polymer chain nanoparticles sized between 3-15 nm by the intra-chain crosslinking of macromolecules in an ultradilute solution. 12 Only in one special case, to the best of our knowledge, was the preparation efficiency of this method improved remarkably by combining a continuous addition strategy and thermally activated benzocyclobutene coupling chemistry; 13 the chemistry made the polymer chains inactive immediately at the reaction temperature, meaning that the total amount of reactive polymer chains in the reaction system was always extremely low.

Herein, we report a new and effective method for the preparation of polymeric nanoparticles sized below 10 nm by simply radically-polymerizing a cross-linker in a glassy polymer matrix. Before polymerization, the cross-linker and a radical initiator were molecularly dispersed in the matrix. During polymerization, the cross-linker molecules were able to diffuse in the glassy polymer matrix to participate in the polymerization to form primary nanoparticles, but diffusion and further aggregation of the primary nanoparticles were prevented by the glassy polymer matrix. Thus, the primary polymeric nanoparticles of several nm were the final product. After being separated from the matrix, polymeric nanoparticles of several nm can be prepared. The sizes can be further changed, simply by altering the weight ratio of the cross-linker, initiator and matrix. Additionally, the polymer matrix can be recovered and reused.

In the present study, the glassy polymer matrix, cross-linker and initiator used were poly(4-vinylpyridine) (P4VP; M n = 60.0 kDa, M w/M n = 2.27, T g = 150 °C; S1, ESI†), divinyl benzene (DVB) and 2,2'-azobis(isobutyronitrile) (AIBN), respectively. DVB, AIBN and P4VP were mixed together in different weight ratios (Table 1) in methanol under stirring for 48 h before use. DVB/AIBN/P4VP mixture films were prepared by film casting of the mixture solutions in methanol onto Teflon dishes. After having been dried at room temperature for 4 d, the films containing DVB and AIBN were polymerized at 65 °C for 24 h to form PDVB nanoparticles in the P4VP matrix. As expected, some DVB evaporated during the process of drying the films and in the polymerization. However, a large amount of DVB still remained in the films and finally transferred to PDVB small nanoparticles (S2, ESI†). The dried mixture films before the polymerization were transparent (S3, ESI†). According to Rayleigh’s law, the transparency of the DVB/AIBN/P4VP films indicated that they didn’t contain considerable numbers of DVB/AIBN domains larger than l/20 (l is the wavelength of visible light). We think that DVB and AIBN are miscible with, and thus molecularly dispersed in, the P4VP matrix, otherwise the mixture films would have been opaque (S3, ESI†).

The polymerized films were also transparent (S3, ESI†), which suggests that the resultant PDVB nanoparticles were individually dispersed in the P4VP matrix, with their size being less than l/20 according to Rayleigh’s law. P4VP can be protonated and become water soluble at pH < 4.5, whereas PDVB is hydrophobic. By dissolving the polymerized mixture

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† Electronic supplementary information (ESI) available: Materials and instruments; DVB evaporation during drying and polymerization; digital photographs of the films with P4VP as the matrix; size distributions of PDVB nanoparticles determined by software; TEM images of the microtomed films; reason for using number averaged curves; ratio of (R g)/(R h) determined by DLS and SLS; TEM and AFM observation of PDVB nanoparticle films; hydrophobic domains within PDVB nanoparticles probed by pyrene; nanoparticles smaller than 10 nm as drug carriers. See DOI: 10.1039/b911574a
films in acidic water at pH 1. PDVB nanoparticles were released from the films and coalesced into turbidities due to their hydrophobic nature. After centrifugation at 10,000 rpm for 30 min, the white PDVB turbidities floated on the surface rather than sank to the bottom of the solution. When the container was gently vibrated, the PDVB solid originally floating on the surface of water dispersed quickly into the solution, like the dissipation of clouds into air. Both phenomena imply that the white solid was a collection of small nanoparticles; there should be no chain entanglement among the nanoparticles, which makes the solid quite different from normal polymer precipitates. The PDVB solids floating on the surface were collected carefully by syringe. An additional five cycles of dispersion of the PDVB solid in acidic water (pH = 4), centrifugation and collection were applied to obtain purified PDVB solid, with a yield of ca. 10%.

After being dried under vacuum, the as-obtained PDVB solid could not be re-dispersed in water or any organic solvent, such as chloroform, tetrahydrofuran, DMF etc. However, to characterize the size of the PDVB nanoparticles, it was necessary to obtain a stable suspension of the nanoparticles. We noted that after polymerization, the residue of AIBN connected to the PDVB nanoparticles contained CN groups. As indicated in Table 1, the weight ratio of AIBN/P4VP in each of the films was fixed at 0.05%. The molar ratio of the CN groups to the benzene groups of PDVB were calculated (according to the data in Table S1 and with an assumption that all the AIBN molecules were decomposed to initiate the polymerization of DVB) to be 0.09, 0.07, 0.05, 0.03 for P1, P2, P3 and P4, respectively. Hence, in order to increase the water dispersibility of the PDVB nanoparticles, we conducted their hydrolysis in acidic water (pH 4) for 4 d at room temperature. It is interesting that the as-hydrolyzed PDVB nanoparticles are dispersible in water. FT-IR characterization of the hydrolyzed PDVB nanoparticles confirmed that the CN groups had been changed into both carboxyl groups (1711 cm\(^{-1}\)) and amide groups (1658 cm\(^{-1}\)) (Fig. 1). The FT-IR characterization did not detect any signals from P4VP (1537 and 1416 cm\(^{-1}\)), indicating the success in separating the PDVB nanoparticles from the P4VP matrix. Therefore, the nanoparticles may have a loose nanostructure (S7, ESI†) resulting from the diffusion-limited mechanism of particle formation (Fig. 4). This mechanism takes place due to the fact that the diffusion of DVB molecules in the glassy matrix is relatively slow, while the polymerization takes place once the DVB molecules come into contact with the active center.

In the TEM images, we also observed the existence of large nanoparticles with sizes of several tens of nm (data not shown). However, the number ratio of these large nanoparticles to the smaller ones was almost negligible, which is consistent with the DLS results. Perhaps these large nanoparticles were formed in defects of the films or in aqueous suspensions due to secondary aggregation of some of the nanoparticles.

The hydrolyzed PDVB nanoparticles dispersed in water were measured by DLS. In a number-averaged DLS curve (Fig. 2 and S6, ESI†), the PDVB nanoparticles gave nearly a single peak in the Contin Model, with an average hydrodynamic radius, \(<R_h>\), between 3.3 and 17.1 nm, depending on the weight ratio of DVB/P4VP in the original mixture solution.

PDVB nanoparticles stained by ruthenium tetraoxide (RuO\(_4\)) were observed by TEM (Fig. 3). Most of the PDVB nanoparticles in the TEM images had a size of several nm. Although the \(<R_h>\) values of the PDVB nanoparticles were in the range 3.3 to 17.1 nm, the average sizes of the dried PDVB nanoparticles observed by TEM were from 2.6 to 7.2 nm.† The large differences between the sizes observed by TEM and the respective sizes measured by DLS indicate that the PDVB nanoparticles may have a loose nanostructure (S7, ESI†) and can be easily dispersed in water, which can be confirmed by our DLS results.

Table 1 Compositions of DVB/AIBN/P4VP mixtures and average sizes\(^i\) of the obtained PDVB nanoparticles

<table>
<thead>
<tr>
<th>Sample</th>
<th>Weight ratio of DVB/AIBN/P4VP</th>
<th>(&lt;R_h&gt;) by DLS/nm(^a)</th>
<th>Diameter by TEM/nm(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>0.91/0.05/100</td>
<td>3.3</td>
<td>2.6 ± 0.6</td>
</tr>
<tr>
<td>P2</td>
<td>1.82/0.05/100</td>
<td>9.0</td>
<td>3.4 ± 0.8</td>
</tr>
<tr>
<td>P3</td>
<td>3.64/0.05/100</td>
<td>15.1</td>
<td>6.2 ± 1.5</td>
</tr>
<tr>
<td>P4</td>
<td>5.46/0.05/100</td>
<td>17.1</td>
<td>7.2 ± 1.6</td>
</tr>
<tr>
<td>P5</td>
<td>7.28/0.05/100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}\) The average hydrodynamic radius, \(<R_h>\), measured by dynamic light scattering (DLS) after hydrolysing the nanoparticles. \(^{b}\) See S4, ESI. \(^{c}\) In the case of P5, the PDVB nanoparticles formed in the P4VP matrix were connected to each other at this high weight ratio of DVB/P4VP (see S5, ESI).

See S4, ESI. \(^{†}\) In the case of P5, the PDVB nanoparticles formed in the P4VP matrix were connected to each other at this high weight ratio of DVB/P4VP (see S5, ESI).
primary nanoparticles that had insufficient polar groups to stabilize them in water. It should be mentioned here that our TEM observations of the microtomed polymerized films revealed no such large nanoparticles (S5, ESI†). Therefore, we are inclined to think that the large PDVB nanoparticles are the result of aggregation among the nanoparticles of several nm in the aqueous suspensions.

As indicated by the signal at 1632 cm⁻¹ in Fig. 1, after the polymerization, some C=C double bonds remained in the nanoparticles; these can be used for the further modification of the nanoparticles.¹⁷ We have demonstrated that the PDVB nanoparticles could be further polymerized into nanoparticle films (see S8, ESI†). Besides, although the nanoparticles are very small in size, there are hydrophobic domains within them (S9, ESI†) that make them promising for use as drug carriers that are excretable in urine (S10, ESI†).¹⁸

In summary, small PDVB nanoparticles sized below 10 nm have been synthesized via the free radical polymerization of a cross-linker in a glassy polymer matrix. The glassy state of the polymer matrix permits diffusion of the cross-linker molecules but prohibits movement of the primary nanoparticles. Therefore, the secondary aggregation of the primary nanoparticles is prevented and the primary nanoparticles of several nm are the final product. After separation from the matrix, polymeric nanoparticles with a size below 10 nm were prepared. The size of the polymeric nanoparticles could be controlled easily by regulating the composition of the precursor mixture films. This method can be used as an efficient and low cost method for the preparation of small polymeric nanoparticles of several nm.

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Notes and references

In principle, the hydrodynamic radius of aggregates measured by DLS is that of the equivalent non-draining spheres. The average hydrodynamic radius is greatly affected by factors such as the structure, morphology and state of swelling of the aggregates. Usually, the average hydrodynamic radius of aggregates is remarkably different from the radius of the same aggregates in the dried state. In the present study, the PDVB nanoparticles were heavily stained by ruthenium tetroxide. TEM images should exhibit the outline of the dried PDVB nanoparticles. We prefer to use the diameters observed by TEM to describe the size of the nanoparticles. In most related studies, the sizes of small nanoparticles were determined by TEM or AFM.

Notes and references