Preparation and characterization of chitosan–poly(acrylic acid)
polymer magnetic microspheres

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Abstract

A modified method to prepare chitosan–poly(acrylic acid)(CS–PAA) polymer magnetic microspheres was reported in this paper. First, via self-assembly of positively charged CS and negatively charged Fe₃O₄ nanoparticles, magnetic CS cores with a large amount of Fe₃O₄ nanoparticles were successfully prepared. Subsequently, the AA monomers were polymerized on the magnetic CS cores based on the reaction system of water-soluble polymer–monomer pairs. These polymer magnetic microspheres had a high Fe₃O₄ loading content, and showed unique pH-dependent behaviors on the size and zeta potential. From the magnetometer measurements data, the CS–PAA polymer magnetic microspheres also had superparamagnetic property as well as fast magnetic response. A continuous release of the entrapped ammonium glycyrrhizinate in such polymer magnetic microspheres occurred, which confirmed the potential applications of these microspheres for the targeted delivery of drugs.

Keywords: Chitosan–poly(acrylic acid); Polymer magnetic microspheres; Controlled drug delivery

1. Introduction

In the recent years, due to requirements of the clinical therapy, the development of appropriate carriers for controlled drug delivery is a challenge for researchers. Some of proteins, peptides, drugs, and oligonucleotides are unstable compounds that need to be protected from degradation in the biological environment. As such, the future of these molecules as therapeutic agents clearly depends on the design of an appropriate carrier for their delivery to the body. Several studies have been reported so far in the development of these carriers, among which the design of biodegradable nanoparticles has drawn considerable attentions. In particular, chitosan (CS), which is the second abundant polysaccharide present in nature, has come to be an interesting polymer. Due to the nontoxic, biocompatible and slower biodegradable characteristics, CS has been widely used as a drug delivery carrier and biomedical material [1]. In our group, it has been demonstrated that CS-based nanoparticles had shown an excellent capacity for the association of ammonium glycyrrhizinate [2].

The release profile of ammonium glycyrrhizinate from nanoparticles has a slowly continuous release phase, and thus the oral absorption of ammonium glycyrrhizinate may be improved using CS carriers. However, for most localized diseases, site-directed drug targeting is currently one of the most efficient treatments compared with others. Targeted drug delivery systems can allow the maximum fraction and preferential distribution of the delivered drug to focus cells. Yet, few of researches related to targeted drug deliver of CS-based microparticles (<1 μm) have been reported.

Magnetically controlled drug targeting is one of the various possibilities of drug targeting. This technology is based on binding targeted drugs with magnetic nanoparticles, which concentrate drugs in the area of interest by means of magnetic fields. Recently, the development of magnetically responsive microspheres has brought an important driving force into play [3–9]. Different inorganic or polymeric materials have been proposed as carriers of magnetic materials. A considerable advantage of the polymeric carriers is the presence of a variety of functional groups, which is able to modulate the carrier properties for the desired applications. Also, the use of natural polymers attracts much interest not only because of their availability from abundant renewable resources, but also due to their biocompatibility and biodegradability. Therefore, based on the previous work [2,10], we presented a developing strategy to obtain stable CS–PAA polymer magnetic...
microspheres with high Fe₃O₄ loading content. These nanoparticles were prepared by cationic CS coating negatively charged Fe₃O₄ nanoparticles by electrostatic adsorption and subsequent polymerization of acrylic acid (AA) onto the CS-coated Fe₃O₄ cores. The physicochemical properties of CS–PAA polymer magnetic microspheres were analyzed, and the controlled release of ammonium glycyrrhizinate loaded in the micorspheres was also examined carefully.

2. Experimental section

2.1. Materials

Chitosan with the deacetylation degree (DD) of 90% and the molecular weight (Mₙ) of 200 kD was purchased from Kabo Biochemical Company (Shanghai, China). Acrylic acid (AA) (Shanghai Chemical Reagents Company) (Shanghai, China) was distilled under reduced pressure in nitrogen atmosphere. Potassium persulfate (K₂S₂O₈) was recrystallized from distilled water. Ammonium glycyrrhizinate was purchased from Tianshan Pharmaceutical Limited Company (China) as a model of glycyrrhetic acid drug. All other reagents were of analytical grade and used without further purification.

2.2. Preparation of CS polymer magnetic microspheres

Colloidal magnetite nanoparticles (Fe₃O₄ magnetic fluid) was prepared using the method described previous work [11], based on the coprecipitation of a molar Fe³⁺/Fe²⁺ ratio of 2:1 under the aqueous solution of sodium hydroxide. The resulting solution was treated with hydrogen nitrate followed by adding trisodium citrate solution (0.3 mol/L). The obtained magnetite nanoparticles were redispersed in water, and the dispersion was adjusted to 5.0 wt% for further use.

CS–PAA polymer magnetic microspheres were synthesized by polymerization of AA onto CS-coated Fe₃O₄ cores, which were prepared by interaction between cationic CS and Fe₃O₄ nanoparticles with citrate groups. First, 0.6 g Fe₃O₄ magnetic fluid was dispersed in CS solution (25 mL, 2.0 wt% acetic acid solution, 0.5 g CS). The reaction mixture was then sonicated for 15 min. Acrylic acid solution with stoichiometric molar ratio of 1.5:1 ([AA]: [glucosamine unit], except when otherwise stated) was added in the mixture solution mentioned above. Finally, the polymerization was initiated by K₂S₂O₈ at 80 °C under a nitrogen atmosphere for 2 h. The content of K₂S₂O₈ in the reaction system is about 4.0 × 10⁻³ mol/L. At the end of polymerization, 0.4 mL glutaraldehyde was added to the reaction system at 40 °C and crosslinking occurred for 1 h. The obtained polymer magnetic microspheres were enriched with the help of magnet (its magnetic field strength was 2000 G), and washed using distilled water repeatedly.

2.3. Characterization of CS–PAA polymer magnetic microspheres

The mean size and size distribution (polydispersity index, PDI=(σ₃²)/⟨μ₃⟩) [12] of the CS–PAA polymer magnetic microspheres were measured by dynamic light scattering (DLS) (Malvern, Autosizer 4700) in aqueous solution with pH 4. All DLS measurements were carried out with a wavelength of 532 nm at 25 °C and an angle detection of 90°.

The zeta potential of polymer magnetic microspheres was measured on a Zeta Potential Analyzer (Brookhaven, USA). For zeta potential measurements, the samples were diluted with 0.1 mmol/L NaCl solution at a pH value of 4 (except when otherwise stated) and measured in the automatic mode. All measurements were performed in triplicate.

Transmission electron microscopy (TEM) images were obtained on a Hitachi H-600 transmission electron microscope, and the samples for TEM measurements were prepared by placing one drop of sample on copper grids coated with carbon.

FT-IR spectra were measured on a Nicolet, Magna-550 spectrometer. The CS-coated magnetite nanoparticles and CS–PAA polymer magnetic microspheres were dried, and the powders were mixed with KBr and pressed to a plate for measurement.

Thermal gravimetric analysis of microspheres was measured on Pyris 1 TGA instrument with a heating rate of 10 °C/min in the nitrogen flow.

A vibrating-sample magnetometer (VSM) (EG & G Princeton Applied Research Vibrating Sample Magnetometer, Model 155, USA) was used at room temperature to characterize the magnetic properties of Fe₃O₄ nanoparticles and CS–PAA polymer magnetic microspheres.

2.4. In vitro ammonium glycyrrhizinate releasing from CS–PAA polymer magnetic microspheres

The ammonium glycyrrhizinate loaded inside CS–PAA polymer magnetic microspheres was prepared by adding 50 mg of ammonium glycyrrhizinate in 50 ml dispersion of CS–PAA polymer magnetic microspheres and incubated for 48 h. The ammonium glycyrrhizinate-loaded CS–PAA polymer magnetic microspheres were ultracentrifuged at 35,000 rpm, 16 °C for 30 min. The deposit was then redispersed in saline solution (20 mL; 0.9 wt% NaCl). Finally, 5 mL of this solution was placed in a dialysis membrane bag (molecular weight cutoff 10 kDa) and immersed into 250 mL of PBS solution (pH 7.4). The entire system was kept at 37 °C in a constant temperature vibrator. At appropriate time intervals, 3 mL of the release medium was removed and 3 mL of fresh medium PBS solution was added into the system. The amount of ammonium glycyrrhizinate in the release medium was evaluated by HPLC (Shimadzu LC-4A, Kyoto, Japan; reversed phase column (Inertsil ODS-3, 4.6 × 250 mm² GLSciences), and the mobile phase was a mixture of methanol:H₂O=4:1. The wavelength was set at 254 nm and the column operated at 25 °C and using a calibration curve. The percentage released was calculated relative to the initial amount of ammonium glycyrrhizinate in the CS–PAA polymer magnetic microspheres. The ammonium glycyrrhizinate encapsulation efficiency (AE) and the ammonium glycyrrhizinate loading capacity (LC) of CS polymer magnetic microspheres were
calculated according to the equation reported previous work [2]. All measurements were performed in triplicate.

3. Results and discussion

3.1. Synthesis of CS–PAA polymer magnetic microspheres

More recently, Jiang group [13] also developed an approach to prepare CS–PAA magnetic hollow nanospheres. The PVA-stabilized Fe₃O₄ nanoparticles were interacted with AA (or PAA) by hydrogen bonds, leading to the existence of a minor amount of Fe₃O₄ nanoparticles in the inner shell of CS–PAA complexes. However, the molecule of CS is present in solutions in a cationic polyelectrolyte form, which tends to ease of formation of specific structures via the electrostatic assembly, compared with the interactions of hydrogen-bond donor and acceptor groups. As a result, based on the electrostatic interaction of cationic CS and negatively charged Fe₃O₄, it is more possible that the magnetic CS nanoparticles would be prepared with a high loading of Fe₃O₄ nanoparticles inside. Herein, this type of magnetic microspheres was studied in detail in our research. The significantly improved magnetic properties may shed new light on the development of the targeted drug delivery for CS-based carriers. Also, the systematic experiments were conducted, such as superparamagnetic property, colloidal stability and controlled drug release attempt. Meanwhile, the pH sensitive property based on the CS–PAA shells was paid more attention to because of the important factor for the drugs’ loading and releasing.

The preparation procedure was illustrated in Scheme 1. Firstly, a stable dispersion of magnetite nanoparticles modified by citrate groups was dispersed in CS solution. By the electrostatic interaction between cationic CS and negatively charged Fe₃O₄ nanoparticles, the CS-coated nanoparticles could be obtained in favor of improvement of the stability of magnetite nanoparticles in the acid solution [14]. Secondly, to prepare CS polymer magnetic particles with regular shape, the AA solution was added in the above solution to form the polymer–monomer pair. Finally, the monomers, AA, were polymerized by the initiation of KPS [15] with CS-coated Fe₃O₄ cores, resulting in the formation of the CS–PAA polymer magnetic microspheres.

Fig. 1 showed FTIR spectra of CS (A), CS–PAA-polymer magnetic particles (B) and CS-coated magnetite nanoparticles (C). In the IR spectrum of CS (Fig. 1(A)), the characteristic absorption bands appeared at 1646 cm⁻¹ (amide I), 1610 cm⁻¹ (amide II) and 1386 cm⁻¹ (amide III). In the spectrum of CS-coated magnetic nanoparticles (Fig. 1(C)), compared with the spectrum of CS, the 1646 cm⁻¹ peak of –NH₂ bending vibration shifted to 1556 cm⁻¹, and a new sharp peak 1406 cm⁻¹ appeared. It could be attributed to the linkage between citrate group and ammonium ion [16]. The results indicated that the presence of the electrostatic interactions between citrate groups of magnetite nanoparticles and amino groups of chitosan in CS-coated magnetite nanoparticles. In the IR spectrum of CS–PAA polymer magnetic particles (Fig. 1(B)), the characteristic absorption bands at 1720 and 1626 cm⁻¹, which can be assigned to the absorption peaks of the carboxyl groups of PAA, and the NH₃⁺ absorption of CS, respectively, were observed [15]. Furthermore, the absorption peaks at 1538 and 1406 cm⁻¹ could be assigned to asymmetric and symmetric stretching vibrations of COO⁻ anion groups. These results indicated that the carboxylic groups of PAA were dissociated into COO⁻ groups, which complexed with protonated amino groups of CS through electrostatic interaction to form the polyelectrolyte complex during the polymerization.

To obtain quick respond to magnetic field, the effect of improvement of magnetic content on the formation of CS-coated magnetite particles was also studied. As shown in Fig. 2, when the magnetic content was increased from 0.1 to 1.0 g, the particle size of CS-coated Fe₃O₄ nanoparticles increased and the zeta potentials decreased. It has been previously reported that the presence of the electrostatic
interactions between citrate groups and amino groups of chitosan in inionically crosslinked chitosan beads [16]. Although the interaction between the negatively charged citrate groups of magnetite nanoparticles and amino groups of chitosan was weak, it can lead to formation of the CS-coated magnetite nanoparticles. Herein, it was also demonstrated that due to multiple citrate groups of the colloidal magnetite nanoparticles, some of them were linked with amino groups of CS by electrostatic interactions in CS-coated magnetite nanoparticles, which resulted in an increase of the particle size and decrease of the zeta potential. These results were very close to the result from the FT-IR analysis.

Fig. 3(a) showed the transmission electron microscopy (TEM) image of magnetite nanoparticles. These particles with nanometer size were successfully prepared as shown in the figure. Because the surface of iron oxide with negative charges has an affinity toward CS, protonated CS could coat the magnetite nanoparticles by the electrostatic interaction. The TEM image of CS-coated magnetite particles was shown in Fig. 3(b). This illustrated that the thin CS layer was formed around the small aggregates of several magnetite nanoparticles, which was not observed in the simple of single colloidal magnetite nanoparticles. The structure of CS-coated magnetite nanoparticles was looser, leading to the bigger size. The average diameter of such a structure was 300 ± 50 nm, which was smaller than that determined by DLS (>500 nm) in aqueous solution, presumably arising from the dry state of the TEM measurement. Fig. 3(c) shown the TEM image of CS–PAA polymer magnetic microspheres. Due to the requirement of minimizing the surface free energy, the PAA chains precipitated at the surface of the CS-coated magnetite templates, leading to formation of the regular spherical shape. It was visible that black aggregates of multiple magnetite nanoparticles were encapsulated within the crosslinked CS–PAA polymer microspheres (Fig. 3(c), inset). The loading content of magnetite was determined to be about 38% by thermogravimetric analysis. Upon selectively crosslinking the CS shell layer, the size became more uniform and the diameter decreased further, to 80 ± 10 nm (Fig. 3(d)).

Table 1 presented the change of hydrodynamic sizes, size distributions and zeta potentials of the CS–PAA polymer magnetic microspheres with decrease of the molar ratio of CS and AA. This showed CS polymer magnetic microspheres could be obtained at a different ratio of CS to AA. It was observed that when the [CS]:[AA] equaled to 1:1.5, these particles had the smallest size (250 nm). Also, from Fig. 4, the size distribution was more uniform than others. This result suggested that the molar ratio of CS and AA had an influence on the particle size, and as [CS]:[AA] = 1:1.5, it should be regarded as the optimum condition. In Table 1, it was found that the surfaces of CS–PAA polymer magnetic microspheres have positive charges of about 25–35 mV at pH 4.0. When the colloidal magnetite nanoparticles content 0.6 g.

<table>
<thead>
<tr>
<th>Sample</th>
<th>CS:AA (molar ratio)</th>
<th>Particle size (nm)</th>
<th>Polydispersity ((\mu_3/\mu_2^2))</th>
<th>Zeta potential (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:0.5</td>
<td>270</td>
<td>0.15</td>
<td>34.8 (1.9)</td>
</tr>
<tr>
<td>2</td>
<td>1:1</td>
<td>300</td>
<td>0.20</td>
<td>33.0 (2.5)</td>
</tr>
<tr>
<td>3</td>
<td>1:1.5</td>
<td>250</td>
<td>0.11</td>
<td>31.8 (1.2)</td>
</tr>
<tr>
<td>4</td>
<td>1:2</td>
<td>365</td>
<td>0.25</td>
<td>26.1 (0.9)</td>
</tr>
</tbody>
</table>

The colloidal magnetite nanoparticles content 0.6 g.

- Particle size was measured at pH 4.0.
- Zeta potential was measured at pH 4.0.
- Standard deviation.
molar ratio of CS and AA increased, the zeta potential also increased. As the ratio of CS and AA equalled to 1:2, compared with the content of CS, it was possible that the excessive PAA would be absorbed onto the surface of magnetic microspheres, which may decrease the surface charges of CS–PAA polymer magnetic microspheres, leading to the decrease of zeta potential [15]. With increase of ratios, especially as $[\text{CS}]:[\text{AA}] = 1:0.5$, the CS–PAA magnetic nanoparticles had a high zeta potential, which was significantly increased by 7 mV in comparison with it as $[\text{CS}]:[\text{AA}] = 1:2$. It was one possible reason that some of negatively-charged Fe$_3$O$_4$ nanoparticles loaded on the surface of microspheres (it was suggested by observation in Fig. 3(c)) was involved in adsorption of the excessive CS, leading to a sharp increase of the zeta potential.

### 3.2. Effect of pH on CS–PAA polymer magnetic microspheres

The effect of pH values on the particle size of the CS–PAA polymer magnetic microspheres was shown in Fig. 5(A), in which particle size increased from 250 to 980 nm with increasing the pH value from 2.6 to 6.4, and then decreased from 400 to 240 nm with changing the pH value from 7.0 to 11.0. Correspondingly, the effect of pH values on the zeta potential of the CS–PAA polymer magnetic microspheres was plotted in Fig. 5(B). The zeta potential of CS–PAA polymer magnetic microspheres had a negative zeta potential. These facts can be explained by the following. The intrinsic $pK_a$ of the CS has been reported as 6.5 [17], and the carboxylic groups of the PAA became ionized as the pH values are above its $pK_a$ of 4.7 [18]. Citric acid is also a kind of weak acid, and the $pK_a$ value of citrate is 3.2. When pH<6.4, CS, citric acid and PAA are partly ionized. These CS–PAA polymer magnetic microspheres were formed by ionic interaction between negatively charged PAA, colloidal magnetite nanoparticles with citrate groups and positively charged CS. The changes in the zeta potential measurements with pH change of the medium reflected the charge density of the particles. When pH increase (<6.4), the zeta potential decrease from 46.6 to 30.1 mV because of the decrease of CS ionization and increase of citric acid and PAA ionization, resulting in the increase of the particle size from 250 to 380 nm.

A sharp increase in the average particle size (980 nm) was observed for pH 6.4. There existed a bimodal size distribution with mean particle size of 690 and 2130 nm (the result was not shown here). At the pH value (6.4), near the CS $pK_a$ values (6.5), the zeta potential of the CS–PAA polymer magnetic microspheres is near zero. The low zeta potential would result in the aggregation of particles so as to the sharp increase of the particle size.

Worthy of mention is that, when pH>6.4, CS–PAA polymer magnetic microspheres showed no precipitate formation, and have a small size, relatively narrow size distribution, and negative zeta potential. This fact might be explained by the following. When pH>6.4, CS was a neutral molecule and
there were some ionized PAA chain around the particle surface. Thus, the negative zeta potential can be formed for the particles. The electrostatic repulsive forces of inter-PAA molecules resulted in a small size and no undergoing aggregation were observed in this pH range. The negative zeta potential of CS–PAA polymer magnetic microspheres increased as the pH value increased from 7.0 to 11.0, which would result in the stability and the decreased particle size of polymer magnetic microspheres.

From these results as mentioned above, it could be seen that these CS–PAA polymer magnetic microspheres were pH sensitive. By controlling the pH value of the medium, the surfaces of the polymer magnetic microspheres could have positive or negative charges.

### 3.3. Effect of ionic strength on the stability of CS–PAA polymer magnetic microspheres

Since, CS is a cationic polyelectrolyte, the effect of ionic strength of the medium on nanoparticles is important. The effect of salt concentration on the properties of CS–PAA polymer magnetic microspheres was determined by measuring the mean size of microspheres after the addition of NaCl solution at varying concentrations (0.05–1 mol/L). The results in Table 2 indicated clearly that an increase in the salt concentration increased the size of the CS–PAA polymer magnetic microspheres. When the ionic strength was higher than 1 mol/L NaCl, some aggregations would form and the particle size distribution became wide. It is well known that an increase in salt concentration leads to an increase in the size of microspheres because of the electrostatic shielding leading to destabilization of colloids. A practical conclusion was that the CS–PAA polymer magnetic microspheres were stable in physiological saline (0.15 mol/L NaCl) within 48 h (data not shown), which was important for the potential use of the polymer magnetic microspheres in pharmaceutics.

**3.4. Magnetic properties of CS–PAA polymer magnetic microspheres**

Fig. 6 showed a typical magnetization curve of CS–PAA polymer magnetic microspheres. The saturation magnetization ($\sigma_s$) of the CS–PAA polymer magnetic microspheres was about 23.1 emu/g, which represented a magnetic content of 36 wt% by comparing the reference value for the pure magnetite nanoparticles of $\sigma_s$ to be 64.3 emu/g. The result was very close to the result from the thermogravimetric analysis. As could be seen from Fig. 6, the hysteresis loop showed superparamagnetic property (i.e. no remanence effect), indicating that the single-domain magnetic nanoparticles remained in these polymer nanoparticles.

![Fig. 6. Magnetization curve of CS–PAA polymer magnetic microspheres.](image-url)
The superparamagnetic property of polymer magnetic microspheres is critical for their application in biomedical and bioengineering fields, which prevents polymer magnetic microspheres from aggregation and enables them to redisperse rapidly when the magnetic field is removed [19]. The variation of the magnetization with the applied magnetic field provides the information on the magnetic properties of the polymer magnetic microspheres. Fig. 7 illustrated the separation and redispersion process of the CS–PAA polymer magnetic microspheres. In the absence of an external magnetic field, the dispersion of the CS–PAA polymer magnetic microspheres was dark yellow and homogeneous (Fig. 7(A)). When the external magnetic field was applied, the polymer magnetic microspheres were enriched, leading to transparence of the dispersion (Fig. 7(B)).

3.5. In vitro release of ammonium glycyrrhizinate from CS–PAA polymer magnetic microspheres

In order to investigate the drug-loading capacity and the drug release behavior of such CS–PAA polymer magnetic microspheres, the anti-inflammatory, antitumorigenic and anti-hepatotoxic drug ammonium glycyrrhizinate was loaded into the polymer magnetic microspheres with an encapsulation efficiency of 70%. Fig. 8 displayed the ammonium glycyrrhizinate release profile (at 37 \(^\circ\)C) of the CS–PAA polymer magnetic microspheres. The percentage released was calculated based on the initial ammonium glycyrrhizinate amount in the CS–PAA polymer magnetic microspheres. A small burst release about 24% of the total loaded ammonium glycyrrhizinate occurred in the initial two hours, followed by a very slow drug release. Zhou et al. [20] reported about the drug release in microspheres and revealed that the release involved two different mechanisms of drug molecules diffusion and polymer matrix degradation. The burst release of drug was associated with those drug molecules dispersing close to the microsphere surface, which easily diffused in the initial incubation time. The hypothesis was also suitable for ammonium glycyrrhizinate release from polymer magnetic microspheres. Since, the size of ammonium glycyrrhizinate molecule was much smaller than that of polymer magnetic microspheres, ammonium glycyrrhizinate molecules diffused easily through the surface or the pore of polymer magnetic microspheres in a short time. Therefore, the rapid dissolution process suggested that the release medium penetrated into the microspheres, and dissolved the entrapped ammonium glycyrrhizinate. In addition, the polymer magnetic microspheres with huge specific surface area can adsorb ammonium glycyrrhizinate, so the first burst release was also possibly due to the part of ammonium glycyrrhizinate desorbed from magnetic polymer nanoparticle surface. After this initial release burst, the CS–PAA polymer magnetic microspheres continuously released the entrapped ammonium glycyrrhizinate. These results indicated that these CS–PAA polymer magnetic microspheres would be good candidates for drug carriers for hydrophilic glycyrrhetic acid (or its salt).
4. Conclusions

CS–PAA polymer magnetic microspheres with a high Fe₃O₄ loading content have been readily prepared by polymerization of AA onto the CS–Fe₃O₄ cores, which were self assembled by the electrostatic interaction between protonated CS and negatively charged Fe₃O₄ nanoparticles. The obtained CS–PAA polymer magnetic microspheres showed pH-dependent behaviors and superparamagnetic properties. The Glycyrrhetin acid was also loaded in the magnetic particles. The release profile suggested that these microspheres were appropriate for the drug carriers. This approach would be extended to the other systems in which the different inorganic nanoparticles and polymer–monomer pairs are involved by the electrostatic interaction.

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