Synthesis of Polymer Nanospheres for Drug Delivery

Jenna Rabadi, Pier F. Cirillo*, and Dequan Xiao*

Department of Chemistry and Chemical Engineering, Tagliatela College of Engineering
University of New Haven, West Haven, CT 06516

Abstract

Drug discovery aids the pharmacologists and ultimately pharmaceutical companies, and the health field in general. This experiment aims to form a molecular vehicle that can help the delivery of drugs. Due to the presence of cellular membranes, a drug cannot be too soluble, otherwise the drug will not be absorbed through the cellular membrane. This experiment aims to change the solubility of drugs by forming polymer nanospheres of the drugs *via* molecular self-assembly. To achieve this, we will focus on embedding the drug molecules inside polymer nanospheres in order to enhance the retention time. Stable polymer nanospheres consisting of small drug molecules were observed using an amphiphilic copolymer poly(4VP-*co*-AN).

Methods

The research were carried out in the following three steps: the preparation of the PAN-stat-PV4P polymers, fabrication of hollow polymer nanospheres, and the characterization of the hollow polymer nanospheres.

Preparation of the PAN-stat-PV4P polymers
Polymerization of 4-vinylpyridine and acrylonitrile was performed using cumyl dithiobenzoate (CDB) as a macro-RAFT agent and 2, 20-azobisisobutyronitrile (AIBN) as initiator. The molar ratio is [CDB-RAFT] : [AIBN] 1⁄4 4 : 1. A dry Schlenk flask will be charged with CDB macro-RAFT agent, 4-vinylpyridine, acrylonitrile, dimethylformamide (DMF), and AIBN. After three freeze– pump–thaw cycles, the reaction mixture was immersed in a thermostat oil bath at 70 °C. After the polymerization was carried out for 40 h, the reaction mixture was cooled to 40 °C. The polymer was precipitated by pouring the polymer solution into excess water while stirring. The precipitate was collected by filtration, and then dried in a vacuum oven at 60 °C overnight.

Fabrication of hollow polymer nanospheres
poly(4VP-*co*-AN) was neutralized with concentrated hydrochloric acid. An aqueous solution of 1.0 g/L copolymer was prepared. A drug molecule (DM) aqueous solution of 1.0 g L was prepared. The titration of the polymer solution by the DM was then conducted slowly with a speed of about 2–3 drops per second. The PAN-stat-P4VP/DM precipitates were filtered out, washed twice with copious amounts of hot water for removing any unbound DM from the complex, and dried under vacuum at 60 °C for 2 days. The polymer/DM self-assembly was dissolved in DMF, and then mixed with water to form polymer nanospheres.

Characterization of the hollow polymer nanospheres
The morphology of the hollow polymer nanospheres was characterized by transmission electron micrograph (TEM).

Synthesis of cumyl dithiobenzoate
Benzyl chloride, andhydrous methanol, sodium methodixde solution, and powerdered sulfur were added to a short neck round-bottom flask and then immersed in an oil bath. Then the mixture was cooled, pressure was reduced and HCl was added until the mixture was a deep purple color.

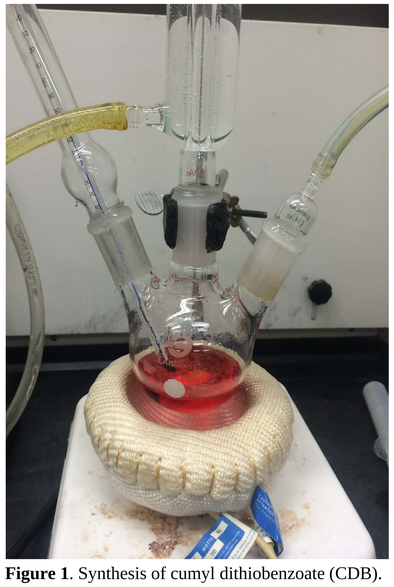
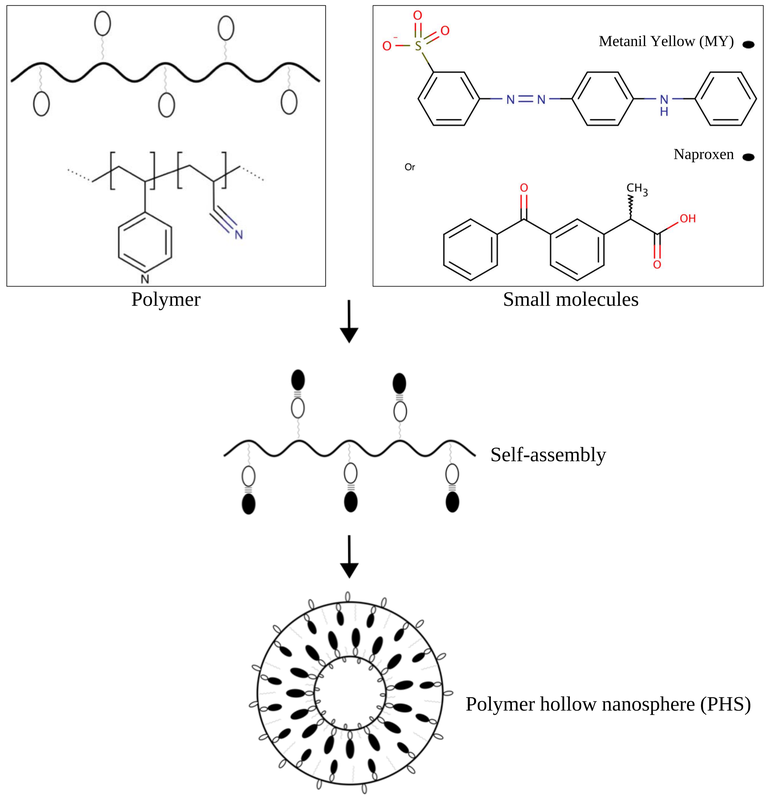


Figure 1. Synthesis of cumyl dithiobenzoate (CDB).



Scheme 1. Illustration of the fabrication procedure for polymer hollow nanospheres.

Results and Disucssion

1. Possible Structure of the Polymeric Hollow Nanospheres

The nanospheres containing drug molecules were observed. The drug molecules are located in the nanospheres in two possible ways: The first possibility is that the drug either attachs to the hydrophilic layer on the outside of the nanosphere, and the second possiblity is that the drug attachs to the center of the nanosphere that is hydrophilic.

The two possiblities should both influence the solubility of the drug. The ideal case is to localize the drug in the center of the hollow nanosphere. However, the drug can be located on the outer surface, its solubility can be reduced significantly as its negatively charged ionic groups are chelating with the positively charged ionic groups on the polymer backbone.

Figure 2. Synthesized poly(4VP-*co*-AN) with the ratio 100% 4VP to 0% AN.

Figure 3. Self-assembly of poly(4VP-*co*-AN) with Metanil Yellow (left) and Naproxen (right), respectively.

Figure 4. PHS of poly(4VP-*co*-AN)/Naproxen

Table 1. Synthesized poly(4VP-*co*-AN) with different ratios of 4VP:AN.

Reaction Number	**1**	**2**	**3**	**4**	**5**
4VP:AN Ratio	100:0	90:10	80:20	70:30	60:40
Reaction Number	**6**	**7**	**8**	**9**	**10**
4VP:AN Ratio	50:50	40:60	30:70	20:80	10:90

2. Characterization of Molecular Interactions

FTIR

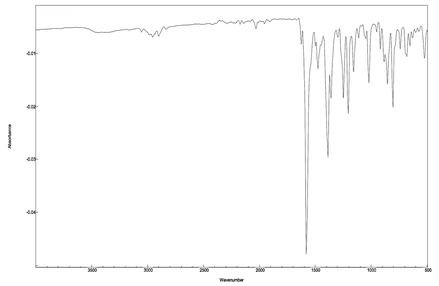


Figure 5. FTIR spectrum of poly(4VP-*co*-AN)/Naproxen.

NMR

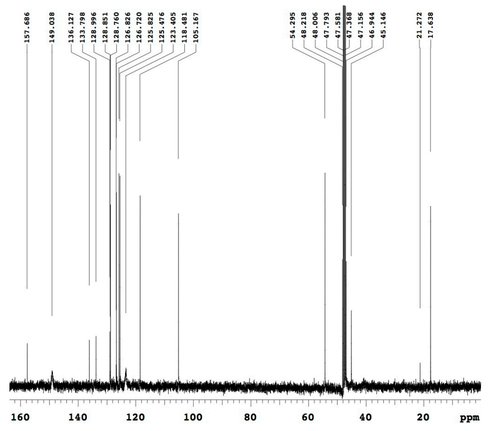


Figure 6. ^{13}C-NMR spectrum of poly(4VP-*co*-AN)/Naproxen.

3. Morphology Characterization by TEM

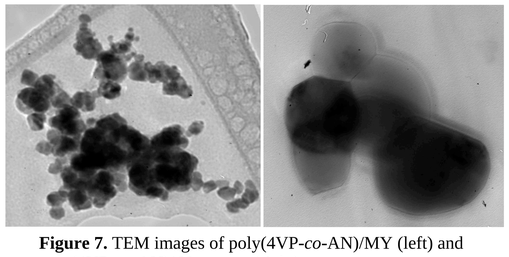


Figure 7. TEM images of poly(4VP-*co*-AN)/MY (left) and poly(4VP-*co*-AN)/ Naproxen (right).

Conclusion

We synthesized ten different poly(4VP-*co*-AN) polymers with different monomer ratios. We fabricated the self-assemblies of the poly(4VP-*co*-AN) polymers with the small molecules: metanil yellow and naproxen, respectively.

We observed the nanospheres of poly(4VP-*co*-AN)/MY and poly(4VP-*co*-AN)/Naproxen. This is the first observation of PHS for drug molecules using the poly(4VP-*co*-AN) polymers.

By FTIR and ^{13}C-NMR spectra, we proved that the self-assemblies between the copolymer and the small molecules here are formed through ionic interactions.

Acknowledgements

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