Synthesis of Polymer Nanospheres for Drug Delivery

Jenna Rabadi
Department of Chemistry and Chemical Engineering
Dequan Xiao and Pier Cirillo

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).
Molecular self-assembly is a process that molecules will self-organize to form particularaggregation structures or morphology without direct interference by external forces. The driving force for molecular self-assembly is the non-covalent interaction, such as hydrogen bonding, metal coordination, hydrophobic forces, van der Waals forces, π-π interactions, and electrostatic interactions. Recently functional polymers with ionic groups were used to form hollow polymer nanospheres via the self-assembly of polymers with small organic molecules. The formation mechanism of the polymer nanospheres has been suggested by Xiao et al.[1] They made a polymer (PAN-stat-PV4P) composed of 4-vinylpyridine and acrylonitrile units, and then they obtained the self-assembly of PAN-stat-PV4P with organic dye molecules metanil yellow (MY). The self-assembly was then dissolved into a good organic solvent and then water was added into the self-assembly solution to form hollow polymer nanospheres via a bilayer intermediate. However hollow polymer nanospheres containing drug molecules have never been made.In my proposal, I will perform the self-assembly of the polymer with drug molecules via the electrostatic interactions. Once the drug molecule is transformed into the nanospheres, the solubility of the drug molecules will be reduced dramatically because the ionic functional groups such as carboxylic acids will be embedded inside the nanosphere. In this way, we can facilitate the drug delivery by reducing solubility of the drugs and thus enhance the drug's retention time on cellular membranes.

Introduction

Molecular self-assembly is a process that molecules will self-organize to form particular aggregation structures or morphology without direct interference by external forces. The driving force for molecular self-assembly is the non-covalent interaction, such as hydrogen bonding, metal coordination, hydrophobic forces, van der Waals forces, π-π interactions, and electrostatic interactions.

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The self-assembly was then dissolved into a good organic solvent and then water was added into the self-assembly solution to form hollow polymer via a bilayer intermediate.

However hollow polymer nanospheres containing drug molecules have never been made. The self-assembly of the polymer with drug molecules via the electrostatic interactions was formed. Once the drug molecule is transformed into the nanospheres, the solubility of the drug molecules will be reduced dramatically because the ionic functional groups such as carboxylic acids will be embedded inside the nanosphere. In this way, we can facilitate the drug delivery by reducing solubility of the drugs and thus enhance the drug's retention time on cellular membranes.

Methods

The research was 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.

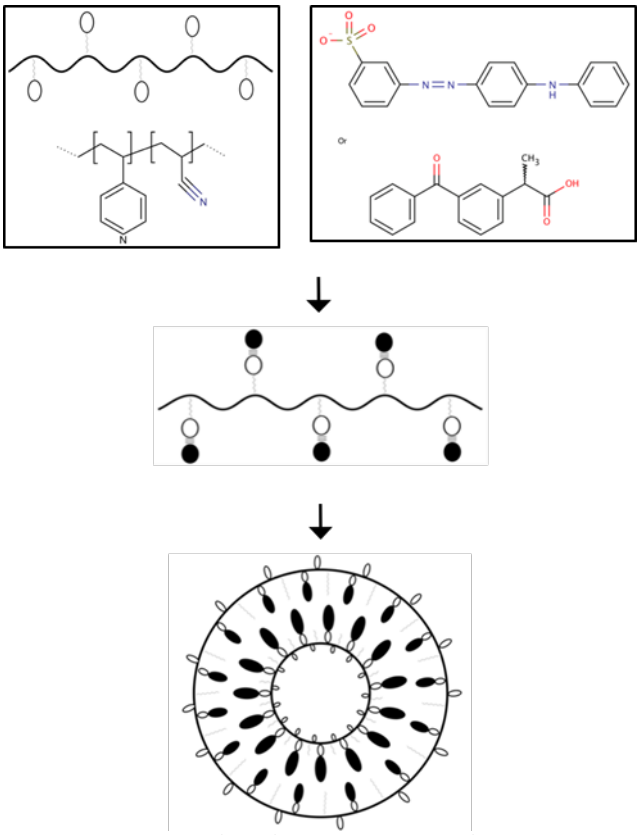
Characterization of the hollow polymer nanospheres

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

Synthesis of cumyl dithiobenzoate

Benzly chloride, andhydrous methanol, sodium methodixde solution, and powdered 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 Discussion

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 attaches to the hydrophilic layer on the outside of the nanosphere, and the second possibility is that the drug attaches to the center of the nanosphere that is hydrophilic.

The two possibilities 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.

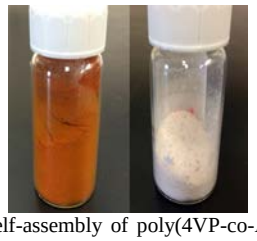


Figure 3. Self-assembly of poly(4VP-co-AN) with Metanil Yellow (left) and Naproxen (right), respectively.

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

Characterization of Molecular Interactions

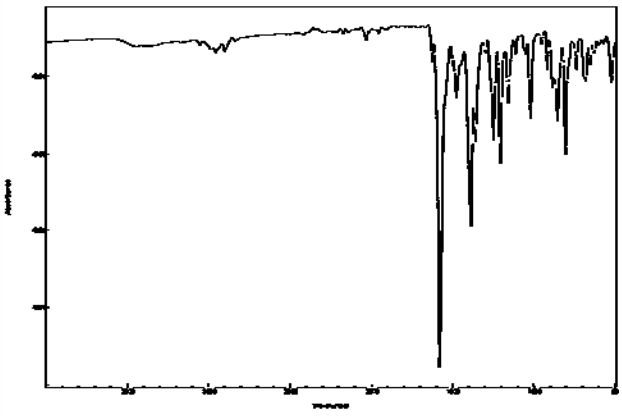


Figure 5. FTIR spectrum of poly(4VP-co-AN)/Naproxen.

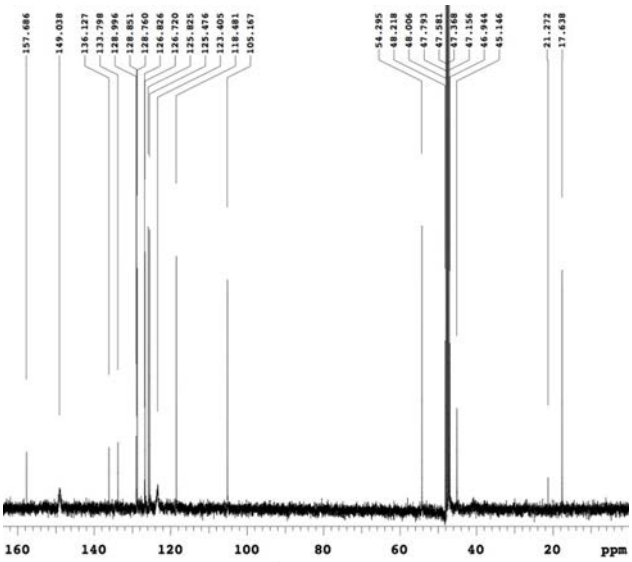


Figure 6. 13C-NMR spectrum of poly(4VP-co-AN)/Naproxen.

Morphology Characterization by TEM

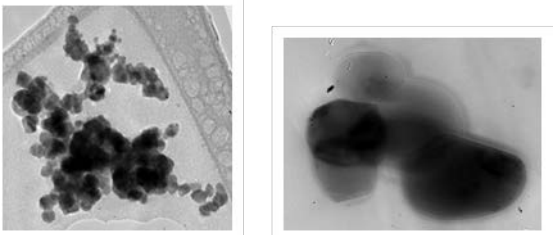


Figure 7. TEM images of poly(4VP-co-AN)/MY (left) and poly(4VP-co-AN)/ Naproxen (right).

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.

References

[1] Jin, Cheng, Taoran Zhang, Fangzhuan Liu, Lingyu Wang, Qinjian Yin, and Dequan Xiao. "Fabrication of Size Controllable Polymeric Hollow Nanospheres Containing Azo Functional Groups via Ionic Self-assembly." *RSC Advances* 4.16 (2014): 8216. Print.

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Biography

Jenna Rabadi is currently a junior at the University of New Haven majoring in Nutrition and Dietetics. She hopes to go to graduate school to obtain a Master's in Nutrition and attend a Physician Assistant program.

Jenna spends her spare time participating in clubs and organizations on campus. She is a Resident Assistant, Academy Liaison of the student chapter of the Academy of Nutrition and Dietetics, Mentor of the Dream Team, and a volunteer with Cooking Corps and Yale-New Haven Hospital.