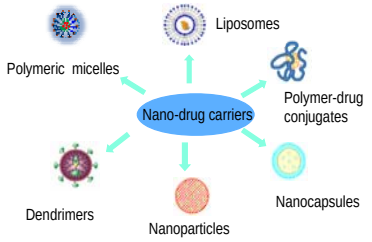
Targeted Drug delivery using Stimuli-Responsive Fullerene Polymeric Systems

Zhaoling Yao and Kam C. Tam*

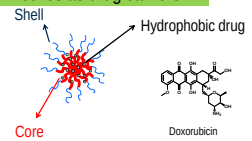
Department of Chemical Engineering, Waterloo Institute for Nanotechnology, University of Waterloo, 200 University Avenue West, Waterloo, Ontario, CANADA N2L 3G1, *mkctam@uwaterloo.ca

Introduction

Various types of nano-sized drug carriers



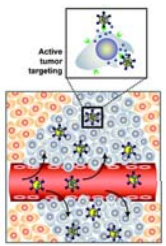
Polymeric micelles as drug carriers



- Solubilizing poorly water soluble drugs
- Higher stability and uniform nano-size (<150nm)
- Hydrophilic corona prevents interaction with blood serum
- The polymer architecture can be tailored to meet specific requirement

Research Objectives

- Prepare PDMAEMA-b-C_{60} with targeting moieties.
- Investigate the self-assembly behavior of PDMAEMA-b-C_{60} at various pH and temperature conditions.
- Investigate the interaction of micelles and drug molecules.
- Explore the use of PDMAEMA-b-C_{60} polymeric micelles as targeted drug carriers.

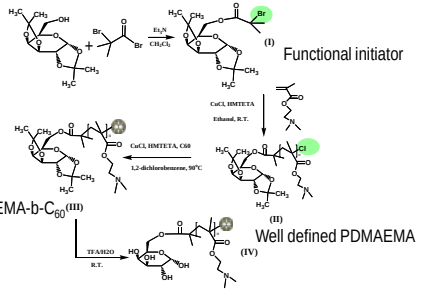


- Active targeting: Certain kinds of targeting moieties are attached to the drug carriers
- Recognize the receptors on cell membrane surfaces through interactions, such as antigen-antibody and ligand-receptor bindings
- Specific targeting can be achieved

Omid C. Farokhzad and Robert Langer Impact of Nanotechnology on Drug Delivery, ACS Nano, 2009, 3 (1), 16-20

Synthesis

ATRP was used to synthesize well-defined PDMAEMA-C_{60}

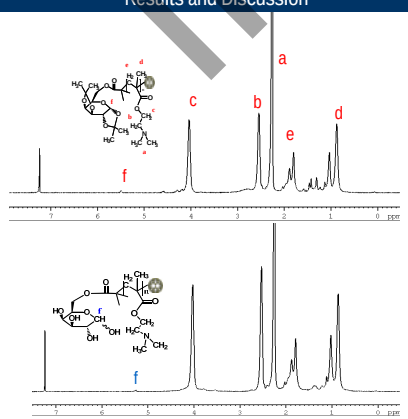


PDMAEMA-b-C_{60} with targeting ligand

Instrumentation and characterization

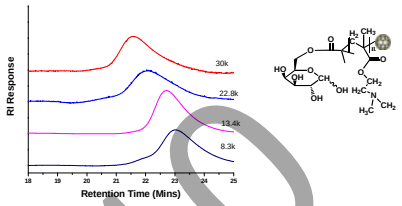
- GPC to measure the molecular weight and PDI of the polymers
- ^{1}H NMR and ^{13}C NMR to analyze chemical structure
- UV-vis to detect C_{60}
- Dynamic light scattering to study the self-assembly behavior of PDMAEMA-b-C_{60} systems
- DSC to measure the LCST of the PDMAEMA-b-C_{60} system.

Results and Discussion

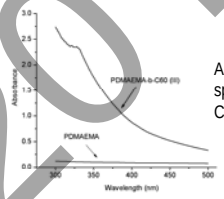


Isopropylidene groups were removed using TFA/Water (8/2) at room temperature . The peak at 5.5ppm disappeared and another peak at 5.2 ppm appeared, which confirmed that deprotection was successful.

GPC and UV results

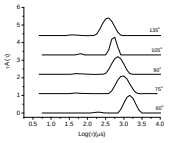


Well defined PDMAEMA-C_{60} containing galactose targeting ligands were synthesized. PDI of all the copolymers are less than 1.13.



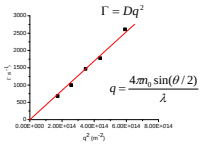
Absorption at 330nm from the UV spectrum indicated the presence of C_{60} in the PDMAEMA-C_{60}

Effect of Mw on R_h

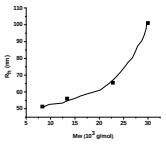


Decay time distribution

$$R_{h,a} = \frac{kT}{6\pi\eta D}$$

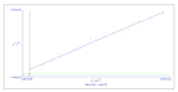


Angular dependence graph



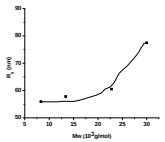
Dynamic light scattering (DLS) was used to measure the hydrodynamic radius (R_h). It was found that R_h increases when the M_w of PDMAEMA increases.

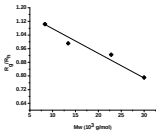
Effect of M_w on R_g



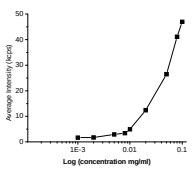
Static light scattering (SLS) was used to measure the z-average radius gyration (R_g).

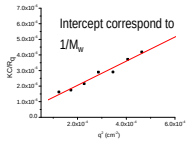
It was found that R_g increases when the M_w of PDMAEMA increases. However, the R_g/R_h decrease with increasing M_w.





Effect of M_w on CMC and N_{agg}





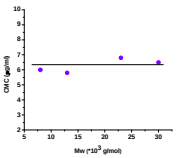
SLS was used to measure the apparent N_{agg} of the aggregates using the following equations:

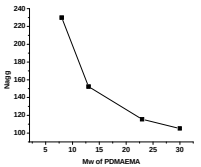
Critical micelle concentration (CMC) was obtained from DLS data.

$$\frac{KC}{R(q)} = \frac{1}{M_w}(1 + \frac{1}{3}R_g^2 q^2) + 2A_2 C$$

Where: $R(q) = R_{tol,90}(\frac{n}{n_{tol}})^2 \frac{I - I_0}{I_{tol}} \sin\theta$

$$K = [4\pi^2 n_{tol}^2 (dn/dc)^2] / N_A \lambda^4$$





Results showed that CMC remained constant at about 6.5 μg/ml when the M_w of PDMAEMA was varied.

The aggregation number decreased when the M_w of PDMAEMA was increased.

Conclusions and Future work

Conclusions

1. PDMAEMA-b-C_{60} containing galactose targeting moieties with well-defined molecular weights, low polydispersity were successfully synthesized via the ATRP process.

2. Self assembly behaviors were investigated using DLS and SLS. Result showed that R_h and R_g increased with increasing M_w of PDMAEMA.

3. When the M_w of PDMAEMA was increased, CMC reamined essentially constant , however the aggregation number of the micelles decreased.

Future work

1) Investigates pH responsive properties of the resulting PDMAEMA-C_{60} systems.
2) Measure the LCST of the PDMAEMA-C_{60} at pH 7 and 10 under different conditions, such as in the presence of sugar or other molecules.
3) Investigate the targeting efficiency of drug loaded micelles.
4) Use TEM and AFM to study the morphology and size of the polymeric micelles.