A Facile Method to Construct a pH-Responsive Drug Delivery System Using Chitosan-Based Polymers

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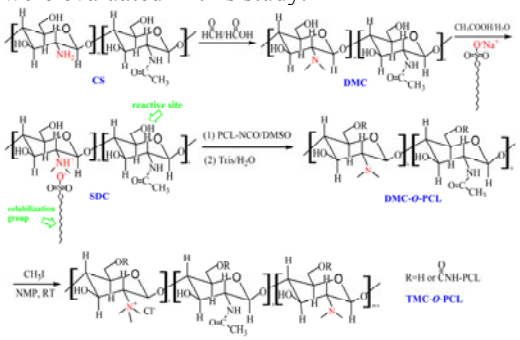
Introduction: Multifunctional drug carriers, such as pH-responsive polymeric micelles, for tumor-specific uptake and intracellular delivery have been received a lot of attentions in the past decades.[1] Most of researches are focused on the development of new acid-sensitive covalent systems. In this paper, biodegradable micelles with poly(ethylene glycol)(PEG) shells were prepared based on the electrostatic interaction between two chitosan-based copolymers: cationic trimethylated chitosan-O-Poly(ε-caprolacton)(TMC-O-PCL) and ampholytic N-carboxyethyl chitosan-g-PEG (CEC-g-PEG). The micelle system is highly promising for the efficient intracellular delivery of various anti-cancer drugs.

Methods: A novel method was developed to synthesize TMC-O-PCL. N,N-dimethylated chitosan (DMC) was first synthesized following the procedures described by Verheul et al.[2] And then sodium dodecyl sulfate (SDS)-DMC complex (SDC) was prepared simply by mixing acidic solutions of DMC and SDS.[3] Using the organo-soluble SDC as an intermediate, isocyanate-ended PCL was introduced onto SDC. SDS was removed by precipitating the copolymer into Tris solution. After reacting with iodomethane, TMC-O-PCL was obtained. CEC was synthesized by grafting acrylic acid (AA) on chitosan utilizing Michael's reaction and then PEG was introduced onto chitosan through esterification. TMC-O-PCL micelle solution was prepared by a dialysis method and then solution of CEC-g-PEG was added to form three-layered micelles with a pH-responsive shell through electrostatic interaction. The decomplexation behavior was studied by changing the pH of solution. The structure of the copolymers was characterized using ^{1}H-NMR (AVANCE DMX 500MHZ). The hydrodynamic diameters (D_h) and Zeta-potential of the micelles were measured with a dynamic light scattering instrument (Malven Nano ZS).

Results: TMC-O-PCL with a well-defined structure was synthesized by a novel and mild way. The synthetic route of TMC-O-PCL was shown in Scheme 1. The precursor SDC complex had excellent solubility in dimethylsulfoxide (DMSO), and SDS was dissociated from SDC-O-PCL simply by precipitating the SDC-O-PCL solution in DMSO into aqueous Tris Solution. It is worth noting that the unique characteristics of SDC, such as easy preparation, excellent solubility in common organic solvents, the presence of abundant reactive hydroxyl groups along chitosan backbone and the convenience of removing SDS from the products, should make it very useful as a precursor for preparing cationic copolymers with versatile functionalities. The PCL grafting level and trimethylation degree of TMC-O-PCL can be modulated by altering the feed ratio and the reaction time with iodomethane. CEC-g-PEG with AA substitution degree at 43.5% and PEG grafting level at 23.6% was prepared and the pH-responsive properties were evaluated in this study.



Scheme 1. Synthetic route to well-defined TMC-O-PCL

The complexation behavior between TMC-O-PCL micelle and CEC-g-PEG was monitored by a dynamic light scattering instrument. The increase of the D_h and the decrease of zeta-potential demonstrated that a complex micelle was constructed through electrostatic interaction in PBS. When lowering the pH of the solution, the decrease of D_h suggests that the dissociation of the micelle occurred (Figure 1).

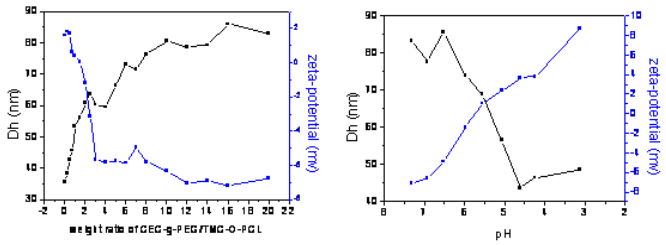


Figure 1. (a) The dependence of D_h and zeta-potential of complex micelle on the weight ratio of CEC-g-PEG/TMC-O-PCL. (b) Effect of pH on the D_h and zeta-potential of complex micelle.

Conclusions: A novel pH-responsive polymeric micelle system was constructed via electrostatic interaction. Using SDC as an organo-soluble intermediate, TMC-O-PCL with well-defined structure could be synthesized under homogeneous and very mild reaction condition. The copolymers self-assembling into spherical micelle with cationic surface enables further constructing of three layer micelles with the interaction of anionic CEC-g-PEG. The pH responsive range falls in 4.6 to 6.5, suggesting that the system can be used potentially as an anti-cancer drug carrier.

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