Cell Membrane-mimetic Polymeric Micelles as Carriers for Drug Delivery

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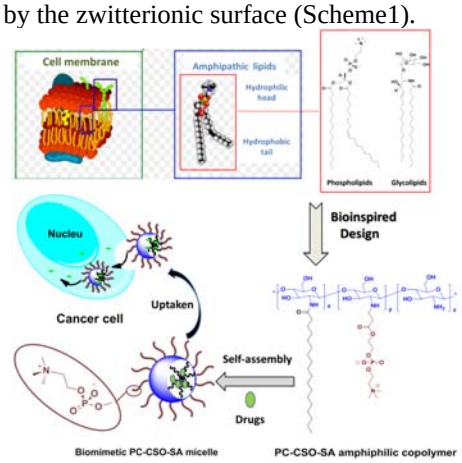
Introduction

Inspired by the external surface of natural cell membrane rich in phospholipids bearing zwitterion head groups, synthetic polymers with zwitterionic phosphorycholine (PC) have been developed and showed excellent properties on constructing ideal drug delivery system (DDS).[1] In this study, we demonstrated a novel zwitterionic biopolymer derivative (PC-CSO) by conjugating acryloyloxyethyl phosphorylcholine (APC) monomer to the chitosan oligosaccharide backbone for mimicking hydrophilic head groups of phospholipids and glycolipids. Hydrophobic stearic acid (SA) similar with fatty acid was typically selected to be grafted onto the hydrophilic PC-CSO and form PC-CSO-SA amphiphilic copolymers. Cell membrane-mimetic polymeric micelles with zwitterionic PC-CSO shells and SA cores were prepared by directly self-assembly of PC-CSO-SA in aqueous medium, exhibiting excellent stability and biocompatibility. In cancer therapy, such bimimetic polymeric micelles are promising drug delivery system and will possess longevity in blood circulation and achieve successful passive accumulation via EPR effect due to the good colloidal stability and nonadhesive properties provided by the zwitterionic surface (Scheme1).



Scheme 1. Bioinspired PC-CSO-SA micelles as drug carriers for cancer therapy.

Methods

Materials

Chitosan oligosaccharide (CSO, M_w~5000) and stearic acid were purchased from Aladdin Co., Ltd. zwitterionic APC monomer were prepared in our lab. All other reagents were purchased from the domestic suppliers and used as received.

Analytical Procedures

First, the synthesis and self-assemble of PC-CSO-SA amphiphilic copolymers were investigated by ^{1}H NMR, FTIR, TEM and DLS. Then, the stability of the biomimetic PC-CSO-SA micelles under various conditions including protein containing media, high salt or wide pH range conditions were tested. The cell uptaken and intracellular release behaviors of the drug-loaded micelles were further investigated by CLSM and Flow Cytometry.

Results

The amphiphilic PC-CSO-SA copolymers were synthesized by conjugating APC monomers and stearic acids onto the backbone of CSO. ^{1}H NMR result in Figure 1A demonstrated the synthesis was successful, and the substitution degree of PC and SA were 15.5% and 10.5%, respectively. Well-defined polymeric micelles were formed with PC-CSO as hydrophilic shell and hydrophobic SA as the core, evidenced by the TEM (Figure 1B). DLS results in Figure 1C indicated the excellent stability of PC-CSO-SA micelles in complex biological systems, which was attributed to the antifouling property of the zwitterionic PC-CSO surface that can bind water molecules strongly via electrostatically induced hydration.[2] Anti-cancer drugs, DOX, could be loaded into the micelle core, with high drug loading efficiency. The uptaken of drug-loaded micelles into cytoplasm were fast and the micelles then released the payload from cytoplasm to nucleus (Figure 1D).

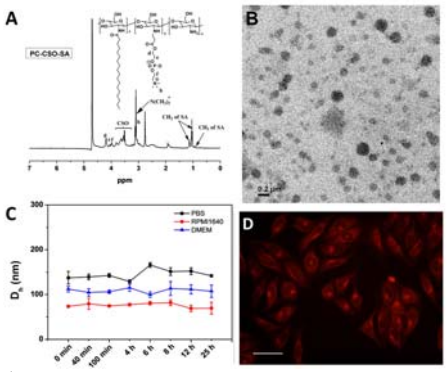


Figure 1. ^{1}H NMR (A) and TEM (B) results of PC-CSO-SA copolymer and the micelles; The stability of micelles in various medium (C) and the intracellular released of drug-loaded micelles (D).

Conclusion

Inspired by cell membrane, biomimetic PC-CSO-SA micelles were designed and prepared. The morphology and size of the micelles were studied by TEM and DLS. The biomimetic micelles showed excellent stability in complex biological systems, high salt concentration and extreme pH conditions due to its zwitterionic surface. The DOX-loaded micelles could be fast uptaken by cancer cells and efficiently deliver and release the drug to the cytoplasm as well as to the cell nucleus. With these properties, such biomimetic micelles are promising vehicles for pharmaceutical application.

References:

1. Liu GY, Soft Matter, 2012, 8, 8811-8821.
2. Liu XS, Nanoscale, 2013, 5, 3982-3991.