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Preparation and Characterization of Responsive Copolymer Nano-Micelles for Co-Delivery of Anticancer Drugs

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***Abstract*—Chemotherapy is still challenging by low solubility, poor bioavailability and systematic toxicity. Herein, a pH-responsive polymer nano-micelle for drug delivery for combination chemotherapy for cancer. In the microenvironment of tumor cells, the as prepared polymer nano micelle can achieve controlled drug release. Remarkably, the as prepared polymer nano micelle possessed negatively charged under normal physiological conditions while switching into positive charge under acidic tumoral environment to enhance the cell uptake and anti-tumor efficiency. Therefore, the novel block copolymer nano-micelles were synthesized by using PEG, PEI and PLA as the segments. The pH-sensitive structure can achieve the charge reversal. The as prepared drug delivery system exhibited charge switch and controlled drug release, which can be used as a promising candidate for combined treatment of tumor.**

***Index Terms*— polymer micelle, PEI, pH-sensitive, drug delivery.**

INTRODUCTION

Recently, polymer nano micelles (PNMs) have been widely investigated as a preferred drug vector for cancer therapy attributing to its good biosafety, easy modification, and long blood circulation time in human body.[1-3] Nevertheless, poor drug loading, target property, and inefficient drug delivery still impede the development of the PNMs in treatment of cancer.[4] Therefore, stimuli-responsive PNMs for microenvironment of tumor are supposed to be the preferred strategy to solve the poor drug loading, target property, and inefficient drug delivery of PNMs.[5,6] PEI, as a presentative cationic polymer, is widely used in the drug delivery due to its good affinity towards the negative cell membrane.[7-9] However, the toxicity of PEI will cause serious side effect, which hindered the further application o PEI in clinic.[10,11] Therefore, we designed a PEG and PLA modified PEI based PNMs with good biocompatibility and efficient dual-drug delivery for cancer treatment.

In the present work, a novel kind of pH-responsive copolymer nano-micelles was prepared for delivery of anticancer drugs. The chemo-physical properties of the as prepared PNMs were characterized. PEG was used as the biocompatible polymer to enhance the biosafety of the PNMs. In conclusion, this as prepared PNMs was demonstrated good stability, and trigged drug release property, which can be potentially used as a promising anti-cancer candidate for chemotherapy.

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EXPERIMENTAL

Materials

PEG (95%, A.R.), succinic anhydride (96%, A.R.), polyethylenimine (98%, A.R.), DOX (98%, A.R.), PTX (99%, A.R.), PLA-OH (A.R.), 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide hydrochloride (A.R.), N-hydroxysuccinimide (99%, A.R.), 2,3-dimethylmaleic anhydride (DMMA, A.R.), acryloyl chloride (96%, A.R.). The organic solvents were used after purified. The other chemicals were used as received.

Synthesis of copolymer

The process of *copolymer* is shown as following. Firstly, PEG and PLA were modified by SA to prepare PEG-SA and PLA-SA. Subsequently, a certain mole ratio of PEG-SA and PLA-SA were added into a 25 mL round bottom flask. DMF was added into the round bottom flask to dissolve the polymers. NHS and EDC were also added into the round bottom flask with stirring for several hours. PEI was dissolved in DMF, and slowly added into the above mixture solution at about 35 ℃ under the exclusion of light and protection of nitrogen for 48 hours. The reaction solution was transferred into the dialysis bag and dialyzed for 24 hours. The final product, PLA-PEI-PEG was lyophilized to obtain a white powder.

Preparation of drug loaded PNMs

The process of synthesizing drug loaded PNMs is as follows. The drugs were dissolved in 15 mL of DMF. The mix solution and the copolymer were added into a round bottom flask for 18 hours under exclusion of light and protection of nitrogen. The mixture solution was then transferred into the dialysis bag and dialyzed against water for 24 hours. Finally, the products were lyophilized to obtain a red powder.

RESULTS AND DISCUSSION

Synthesis and characterization of the copolymers

The FTIR spectra of the as prepared PEG-SA, PLA-SA, and PLA-PEI-PEG were used to identify the chemical structures of copolymers. The representative FTIR spectra of each sample was shown in Figure 1. The absorbance of the PLA-PEI-PEG at about 1100 cm^{-1} belongs to the C-O-C bond in the PEG segment. The absorbance at 1750 cm^{-1} can be assigned to the C=O groups in the PLA segments. Based on the experimental results, it was indicated that the PLA-PEI-PEG copolymer was successfully synthesized.

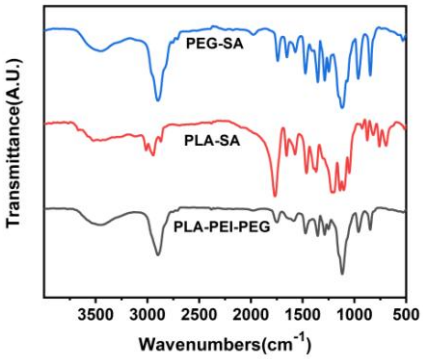

Figure 1. FI-IR spectrum of PLA-PEI-PEG, PLA-SA and PEG-SA.

The DLS was utilized to investigate the stability of the as prepared PNMs with disulfide. As shown in Figure 2, the nano-size of the PNMs was investigated at different time interval at pH 7.4. In general, the there is no obvious size charge of the PNMs at pH 7.4. It was indicated that the as prepared nanomicelles possessed a good structural stability in water, which can be potentially used as a drug carrier in clinic.

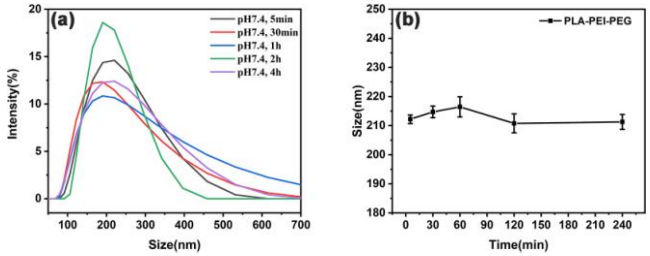

Figure 2 The particle size distribution of the as prepared PNMs at pH 7.4.

The DLS was also utilized to investigate the stability of the as prepared PNMs at pH 5.0. As shown in Figure 3, the nano-size of the PNMs was investigated for 4 hours at pH pH 5.5. It was indicated that the nano-size of the as prepared PNMs increased from about 200 nm to 270 nm at pH 5.5, which can be attributed to the pH-triggered protonation of amino groups in the PEI segment.

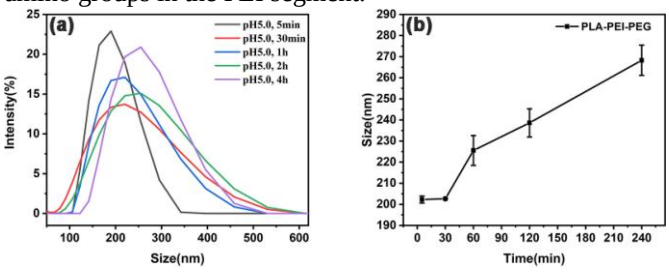

Figure 3 The particle size distribution of the as prepared PNMs at pH 5.5.

The zeta potentials of the as prepared PMNs were investigated at different pH values. In Figure 4, the zeta potential of the as prepared PMNs was of about 2.5 mV at pH 8.0, however the zeta potential increased to about 20 mV at pH 5.0. It can be explained by the acid-sensitive structure of PEI and the protonation of the amino-groups in the as prepared PLA-PEI-PEG copolymer.

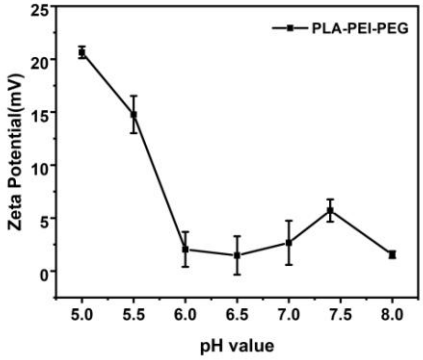

Figure 4 The zeta potential of the as prepared PMNs at different pH values.

CONCLUSION

In conclusion, a novel kind of pH-responsive copolymer nano-micelles was prepared for anticancer drugs. The as prepared PNMs exhibited good stability in water, while an obvious size charge under different pHs with or without GSH. The zeta value of the as prepared PNMs was investigated at different pHs to simulate the in vivo chemical condition. Based on the above experimental results, the as prepared PNMs were considered as a potential drug carrier for anti-cancer therapy.

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REFERENCES

[1] Wang Y, Zhang H, Jing H, et al. Lung cancer combination therapy: co-delivery of paclitaxel and doxorubicin by nanostructured lipid carriers for synergistic effect[J]. Drug Delivery, 2016, 23(4):1398-1404.

[2] Huang Z, Xie X, Wang C, et al. PTX encapsulated by an XG–DOX conjugate for combination therapy against multi-drug resistance[J]. Rsc Advances, 2016, 21(3):956-961.

[3] Ma X, Zhang Y, Pan G, et al. Fabrication of redox-responsive doxorubicin and paclitaxel prodrug nanoparticles with microfluidics for selective cancer therapy[J]. Biomaterials Science, 2019, 7(2):634-644.

[4] Ivana M, Blazic, Gordana B, et al. Quantitative assessment of rectal cancer response to neoadjuvant combined chemotherapy and radiation therapy[J]. Radiology, 2017, 17(7):2489-2501.

[5] Liu Y, Qiao L, Zhang S, et al. Dual pH-responsive multifunctional nanoparticles for targeted treatment of breast cancer by combining immunotherapy and chemotherapy[J]. Acta Biomaterialia, 2017, 5(24):12911-12920.

[6] Qian J, Yao Y, Wang H, et al. Folate-decorated hydrophilic three-arm star-block terpolymer as a novel nanovehicle for targeted co-delivery of doxorubicin and Bcl-2 siRNA in breast cancer therapy[J]. Acta Biomaterialia, 2015, 15:102-116.

[7] Xu W, Qian J, Hou G, et al. Hyaluronic acid-functionalized gold nanorods with pH/NIR dual-responsive drug release for synergetic targeted photothermal chemotherapy of breast cancer[J]. ACS Applied Materials & Interfaces, 2017, 9 (42):36533–36547.

[8] Chung JW, Lee KA, Neikirk C, et al. Photoresponsive coumarin‐stabilized polymeric nanoparticles as a detectable drug carrier[J]. Small, 2012, 8(11):1693-1700.

[9] Liu P, Hui Y, Ying S, et al. A mPEG-PLGA-b-PLL copolymer carrier for adriamycin and siRNA delivery[J]. Biomaterials, 2012, 33(17):4403-4412.

[10] Miao Q, Xu D, Zhi W, Xu L, Wang T, Yan W, Lovejoy DB, Kalinowski DS, Richardson DR, Nie G: Amphiphilic hyper-branched co-polymer nanoparticles for the controlled delivery of anti-tumor agents. Biomaterials, 2010, 31(28):7364-7375.

[11] Hou Q, Yi X, Yan X, et al. Co-delivery of paclitaxel and doxorubicin using mixed micelles based on the redox sensitive prodrugs[J]. Colloids and Surfaces B, 2018, 10:17283-17292.