pH-responsive and biodegradable polymeric micelles based on poly(β-amino ester)-*graft*-phosphorylcholine for doxorubicin delivery

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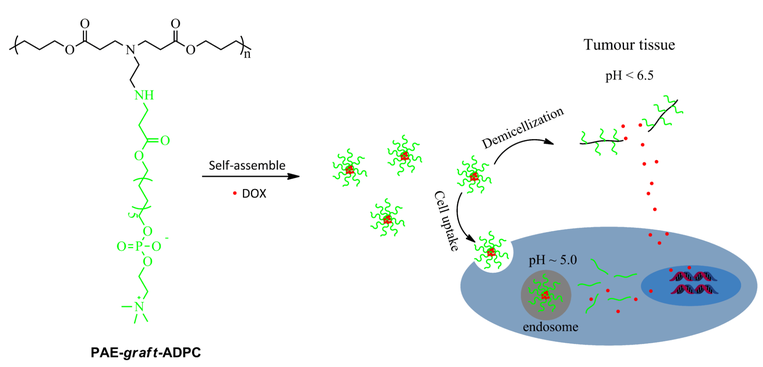
Introduction

Polymeric micelles self-assembled from amphiphilic block copolymers as drug delivery systems have been investigated for the past few decades, due to their advantages of hydrophobic cores to serve as drug reservoirs and hydrophilic shells to prevent micelle aggregation and ensure micelle solubility. micelles with stealth shells have a long circulation time in blood and could then accumulate in tumor tissue through an enhanced permeability and retention (EPR) effect.

However, the EPR effect can only enhance the nanocarriers accumulated in tumor tissues; the poor cellular internalization limits the utilization of anticancer drugs, which hampers the efficacy of cancer chemotherapy.

In order to design a drug delivery system with prolonged circulation time and rapid drug release into the tumor tissue, an acid-triggered anticancer drug delivery system based on poly(β-amino ester) and zwitterion was developed in this research.

Polymer Structure Design



Scheme 1. Illustration of DOX-loaded PAE-*graft*-ADPC micelles responding to the extracellular pH and free DOX internalization.

Characterizations

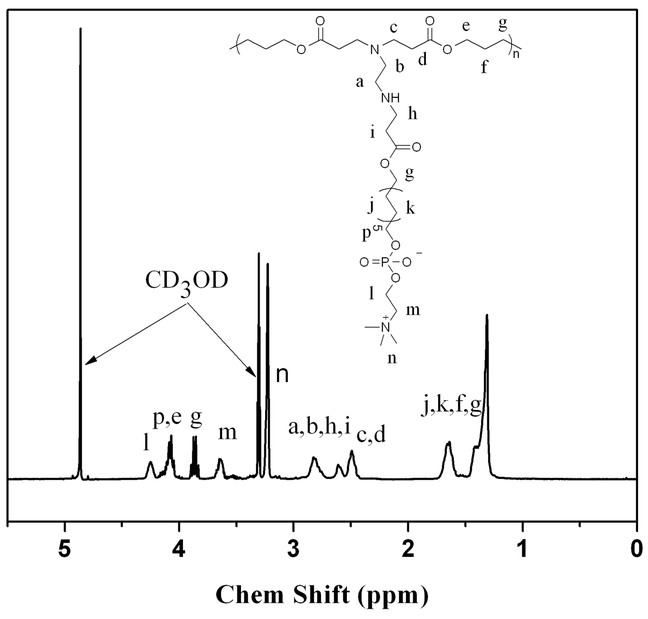


Fig. 1 ^{1}H NMR spectrum of PAE-*graft*-ADPC (CD_3OD).

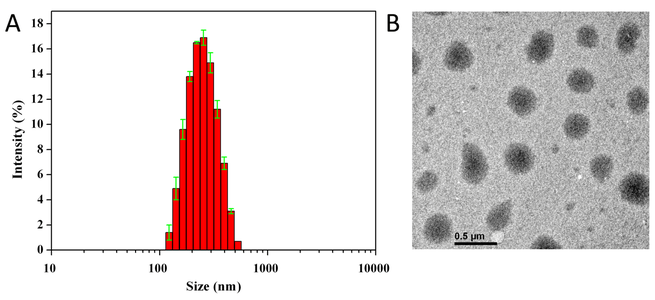


Fig. 2 DLS plots (A) and TEM image (B) of DOX-loaded PAE-*graft*-ADPC micelles.

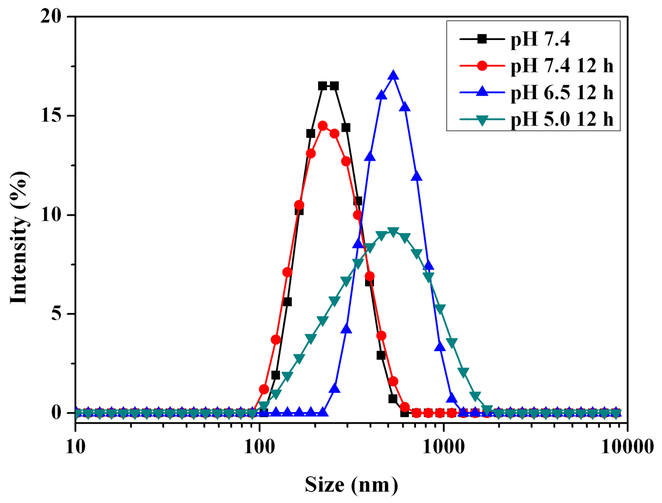


Fig. 3 Changes of size distributions of DOX-loaded PAE-*graft*-ADPC micelles at 37 °C and different pH monitored by DLS.

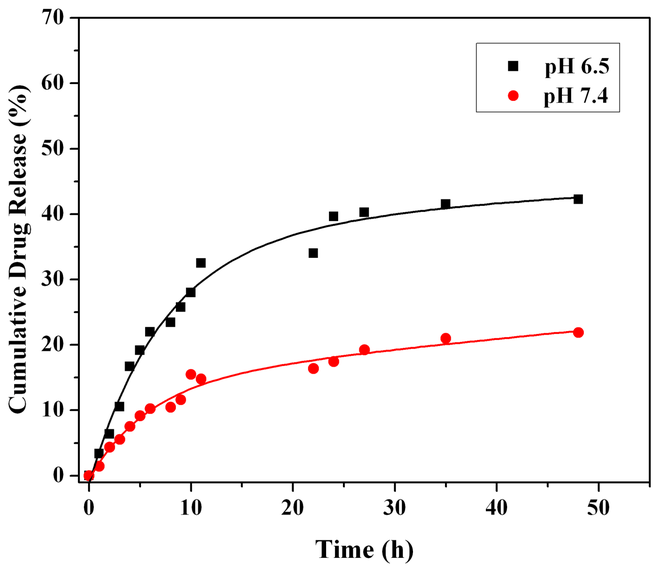


Fig. 4 In vitro release of DOX from PAE-*graft*-ADPC micelles in PBS under different pH conditions.

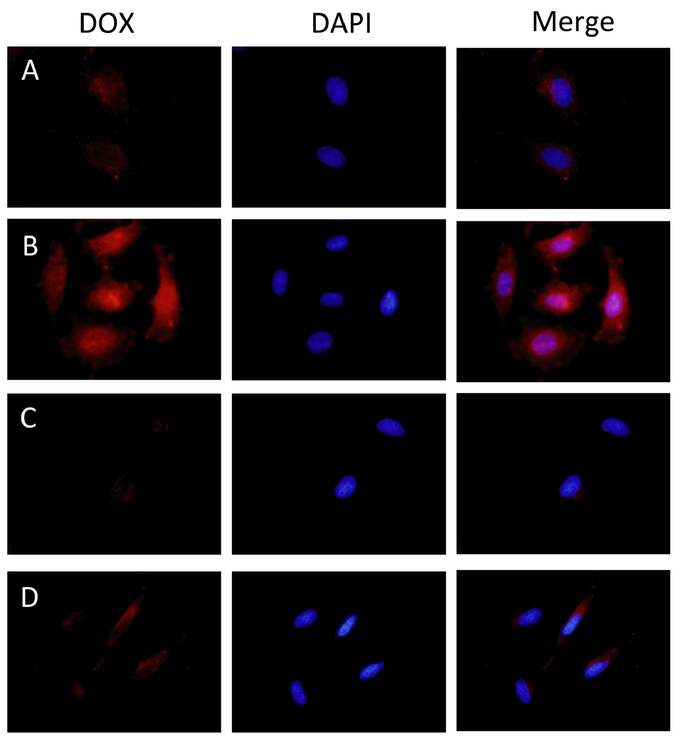


Fig. 5 Fluorescence microscopy images of HepG2 incubated with DOX-loaded micelles at pH 6.5 and 7.4 for different times. From left to right DOX (red), DAPI (blue) and the two images merged. (A) pH 6.5, 1 h; (B) pH 6.5, 2 h; (C) pH 7.4, 1 h; and (D) pH 7.4, 2 h.

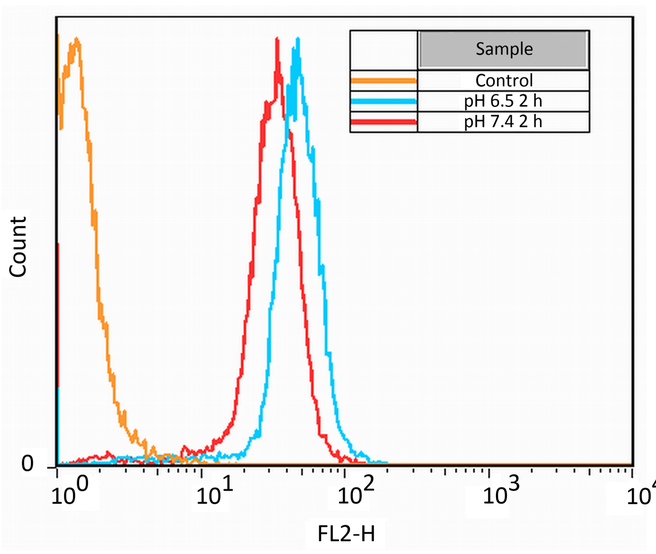


Fig. 6 Flow cytometric profiles of HepG2 cells incubated with DOX-loaded micelles at pH 6.5 or 7.4 for 2 h.

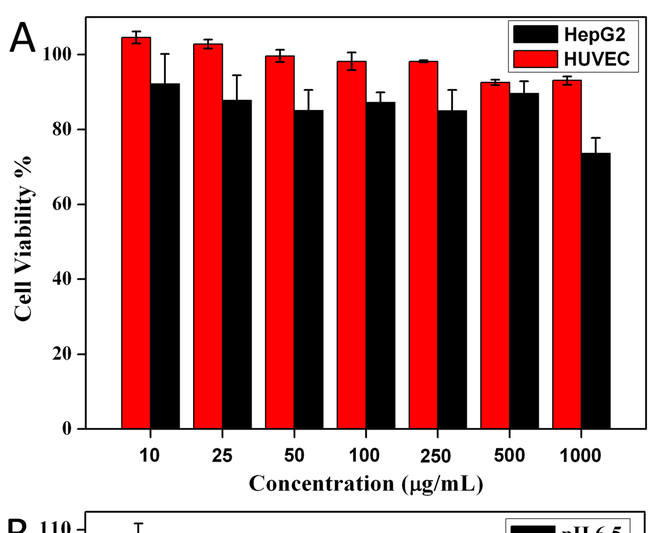


Fig. 7 Cell viabilities of HepG2 and HUVEC cells incubated with various concentrations of PAE-*graft*-ADPC micelles (A) and cell viabilities of HepG2 preincubated with DOX-loaded micelles at pH 6.5 and 7.4 (B).

Conclusion

In this paper, we have demonstrated that a novel pH responsive and biodegradable polymer PAE-*graft*-ADPC can be explored as an effective drug delivery system for cancer therapy. In vitro drug release showed that DOX was rapidly released from micelles at pH 6.5 and insinuated drugs can be released effectively at the site of extracellular tumor cells. Fluorescence images and flow cytometric analysis indicated that DOX easily traversed into the cells after the cells were incubated with DOX-loaded Micelles at pH 6.5. Furthermore, in vitro cytotoxicity studies indicated that the growth of HepG2 cells was inhibited remarkably when the cells were pre-treated with DOX-loaded micelles at pH 6.5.

Acknowledgements

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