ACS OMEGA

http://pubs.acs.org/journal/acsodf

Article

# Construction of a Drug Delivery System via pH-Responsive Polymeric Nanomicelles Containing Ferrocene for DOX Release and Enhancement of Therapeutic Effects

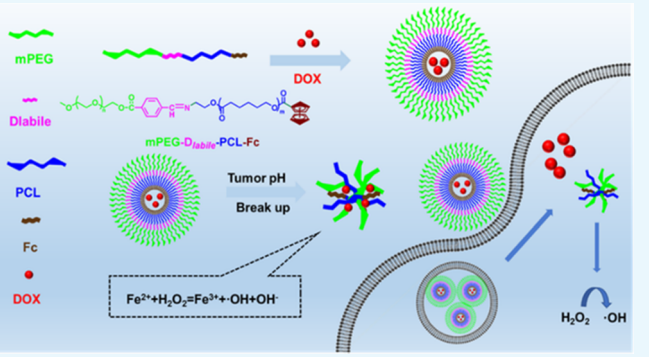
Chenggang Song, Fan Yang, Ruixuan Ji, Yin Lv,* and Zhong Wei*

Cite This: *ACS Omega* 2021, 6, 28242−28253

Read Online

ACCESS | Metrics & More | Article Recommendations

**ABSTRACT:** We report an amphiphilic block copolymer via poly(ethylene glycol) methyl ether-$D_{labile}$-poly(caprolactone)-ferrocene (mPEG-$D_{labile}$-PCL-Fc) to deliver anticancer drug doxorubicin (DOX). Lipase Novozyme-435 was used as a catalyst for ring-opening polymerization with $\varepsilon$-caprolactone, and an acid-sensitive Schiff base was used to connect the hydrophilic and hydrophobic parts; the ferrocene provided ferrous ions and was introduced at the end of the amphiphilic copolymer. The resulting copolymers were characterized by $^{1}$H NMR/$^{13}$C NMR and could be self-assembled in an aqueous solution to form nanomicelles with PCL-Fc as a hydrophobic core and mPEG as a hydrophilic shell. Transmission electron microscopy showed that the micelles were spherical and nanosized before and after DOX loading. The blank micelles also showed good biocompatibility. The drug-loaded polymeric nanomicelles exhibited a positive anticancer effect relative to the copolymers without ferrocene; the therapeutic effect of drug-loaded micelles containing ferrocene was more obvious. In vitro drug release results also showed that the polymer had a good pH response. Confocal microscopy also showed that polymeric micelles can effectively deliver and release the drug; the polymer containing ferrocene also leads to significantly improved ROS levels in tumor cells. Ferrocene can effectively and synergistically inhibit tumor cells with DOX.






## 1. INTRODUCTION

Cancer remains one of the leading causes of death.[1−3] Chemotherapy remains one of the most commonly used methods for the treatment of cancer, but it has many side effects[4] and can have limited bioavailability. Therefore, improving the utilization rate and selectivity of drugs to cancer cells is essential for improving the effect of antitumor drugs. Here, a smart nanodrug delivery system can respond to different environmental stimuli and release drugs under specific conditions to achieve targeted and controlled release of drugs; this can reduce the toxic and side effects of drugs and reduce the damage of drugs to the human body. Therefore, to address the shortcomings of traditional treatments, it is necessary to develop an intelligent response nanodrug carrier system.

There are significant differences in the microenvironment between tumor cells and normal cells, and this difference can be used to design drug delivery systems with different response types to overcome these difficulties.[5] The tumor microenvironment (TME) has characteristics of hypoxia, microacid, enzyme overexpression (such as protease, phospholipase, or glycosidase),[6] and high concentration of reactive oxygen.[7−10] The acidic microenvironment in tumor cells is the most obvious and most commonly used.[11−14] The pH of the extracellular environment of tumor cells is about 6.5, which is usually lower than that of normal tissue cells (pH 7.4); the pH of lysosomes is low (about 5.0−5.5). Based on these properties, scientists have developed various pH-sensitive drug carriers, including hydrazone bonds, aldehyde bonds, and imide bonds.

Programmed death is critical to disease research and normal development of the body.[15−17] Ferroptosis is a new type of programmed cell death proposed by Brent R. Stockwell in 2012. Ferroptosis depends on intracellular ferrous iron and is distinct from apoptosis as well as necrosis and autophagy in morphology, biochemistry, and genetics. In general, ferrous ions react with hydrogen peroxide in tumor cells to produce hydroxyl radicals to increase the oxidative stress of tumor cells. Research on ferroptosis caused by nanomedicine has only recently started, and most studies still use nanoiron to cause ferroptosis. However, there are some problems in the

Received: August 11, 2021
Accepted: September 30, 2021
Published: October 11, 2021