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pH-sensitive degradable chimaeric polymersomes for the intracellular release of doxorubicin hydrochloride

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ABSTRACT

pH-sensitive degradable chimaeric polymersomes were developed based on asymmetric poly(ethylene glycol)-*b*-poly(2,4,6-trimethoxybenzylidene-1,1,1-tris(hydroxymethyl)ethane methacrylate)-*b*-poly(-acrylic acid) (PEG-PTTMA-PAA) triblock copolymers for active loading as well as triggered intracellular release of hydrophilic doxorubicin hydrochloride (DOX·HCl). PEG-PTTMA-PAA copolymers were readily prepared with $M_{n\ PAA}$ ranging from 1.5, 2.1 to 2.7 kg/mol by sequential reversible addition-fragmentation chain transfer (RAFT) copolymerization of 2,4,6-trimethoxybenzylidene-1,1,1-tris(hydroxymethyl)ethane methacrylate (TTMA) and acrylic acid (AA) using PEG-CPADN ($M_{n\ PEG}$ = 5.0 kg/mol; CPADN: 4-cyanopentanoic acid dithionaphthalenoate) as a macro-RAFT agent. PEG-PTTMA-PAA copolymers formed mono-disperse polymersomes with average sizes of 63.9–112.1 nm, which decreased with increasing $M_{n\ PAA}$. The polymersomal structure was confirmed by transmission electron microscopy (TEM) and confocal laser scanning microscopy (CLSM). Notably, the acetals in polymersomes while sufficiently stable at pH 7.4 were prone to rapid hydrolysis at mildly acidic pHs of 4.0 and 5.0, which resulted in swelling and eventually disassembly of polymersomes. These chimaeric polymersomes could actively load DOX·HCl resulting in remarkably high drug loading contents (up to 15.9 wt.%) and loading efficiencies (up to 88.8%). The *in vitro* release studies showed that DOX·HCl was released from chimaeric polymersomes in a controlled and pH-dependent manner. CLSM observations revealed that these chimaeric polymersomes could efficiently deliver and release DOX·HCl into the nuclei of HeLa cells. MTT assays in HeLa cells demonstrated that DOX·HCl-loaded PEG-PTTMA-PAA polymersomes exhibited high anti-tumor activity with IC_{50} (inhibitory concentration to produce 50% cell death) of 1.48–1.67 μg/mL, close to that of free DOX·HCl, while blank polymersomes were practically non-toxic up to a tested concentration of 2.0 mg/mL. These pH-sensitive degradable chimaeric polymersomes have appeared to be a promising alternative to liposomes for tumor-targeted delivery of DOX·HCl.

1. Introduction

The development in tumor-targeting nano delivery systems such as liposomes, micelles and nanoparticles has revived the therapeutic uses of numerous potent chemotherapeutics that are too toxic to be applied otherwise [1–3]. In the past decade, vastly different approaches have been designed for targeted delivery of hydrophobic drugs including paclitaxel (PTX) and doxorubicin (DOX) [4,5]. In comparison, few systems among which are macromolecular prodrugs [6], liposomes [7,8] and more recently polymersomes [9,10] have been developed for controlled release of hydrophilic small molecule anti-cancer drugs such as doxorubicin hydrochloride (DOX·HCl) and mitoxantrone hydrochloride. Liposomes and polymersomes that possess large aqueous interiors to accommodate water-soluble entities and hydrophobic membranes to control drug diffusion are the most ideal nano-carriers for hydrophilic small molecule anti-cancer agents. Unlike the macromolecular prodrug approach, drugs are physically encapsulated into liposomes and polymersomes (no chemical alternation of drug). It is interesting to note that liposomal doxorubicin (Doxil®, Caelyx® and Myocet®) is one of the very few nano drugs that are routinely used in the clinical settings for treating various forms of cancers including advanced ovarian cancer, breast cancer, multiple myeloma and Kaposi's sarcoma [11,12].

Polymersomes (also known as polymeric vesicles) have recently emerged as an improved alternative to liposomes [13,14]. As compared to liposomes, polymersomes usually exhibit better colloidal stability, higher mechanical strength, and lower chemical

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