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Poly(ω-pentadecalactone-*co*-butylene-*co*-succinate) nanoparticles as biodegradable carriers for camptothecin delivery

Jie Liu [a,b], Zhaozhong Jiang [a], Shengmin Zhang [b], W. Mark Saltzman [a,*]

[a] *Department of Biomedical Engineering, Yale University, 55 Prospect Street, MEC 414, New Haven, CT 06511-8260, USA*
[b] *Advanced Biomaterials and Tissue Engineering Center, Huazhong University of Science and Technology, Wuhan 430074, China*

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ABSTRACT

In this study, we show that degradable particles of a hydrophobic polymer can effectively deliver drugs to tumors after i.v. administration. Free-standing nanoparticles with diameters of 100–300 nm were successfully fabricated from highly hydrophobic, biodegradable poly(ω-pentadecalactone-*co*-butylene-*co*-succinate) (PPBS) copolyesters. PPBS copolymers with various compositions (20–80 mol% PDL unit contents) were synthesized via copolymerization of ω-pentadecalactone (PDL), diethyl succinate (DES), and 1,4-butanediol (BD) using *Candida antarctica* lipase B (CALB) as the catalyst. Camptothecin (CPT, 12–22%) was loaded into PPBS nanoparticles with high encapsulation efficiency (up to 96%) using a modified oil-in-water single emulsion technique. The CPT-loaded nanoparticles had a zeta potential of about −10 mV. PPBS particles were non-toxic in cell culture. Upon encapsulation, the active lactone form of CPT was remarkably stabilized and no lactone-to-carboxylate structural conversion was observed for CPT-loaded PPBS nanoparticles incubated in both phosphate-buffered saline (PBS, pH = 7.4) and DMEM medium for at least 24 h. In PBS at 37 °C, CPT-loaded PPBS nanoparticles showed a low burst CPT release (20–30%) within the first 24 h followed by a sustained, essentially complete, release of the remaining drug over the subsequent 40 days. Compared to free CPT, CPT-loaded PPBS nanoparticles showed a significant enhancement of cellular uptake, higher cytotoxicity against Lewis lung carcinoma and 9L cell lines *in vitro*, a longer circulation time, and substantially better antitumor efficacy *in vivo*. These results demonstrate the potential of PPBS nanoparticles as long-term stable and effective drug delivery systems in cancer therapy.

1. Introduction

Current chemotherapy is far from satisfactory: drug treatments often have limited effectiveness and patients suffer from serious side effects. Drug delivery devices have been studied extensively over the past few decades, including degradable polymer matrices, polymeric nanoparticles, liposomes, and micelles [1,2].The use of nano-sized particles in cancer therapy is particularly exciting, as these materials can increase drug solubility and stability, as well as improve pharmacological effect by passively delivering chemotherapeutic agents to tumor sites via enhanced permeability and retention (EPR) effect [3–5].

Camptothecin (CPT) is a natural plant alkaloid extracted from *Camptotheca acuminate* (a tree grown in China), which has shown a broad spectrum of antitumor activity against various types of solid tumors [6]. However, effective delivery of CPT to tumor targets is extremely challenging due to its insolubility in water, structural instability, and high toxicity to normal tissue cells. Under physiological conditions, i.e. at pH equal to or above 7, CPT undergoes lactone ring-opening hydrolysis to form the inactive carboxylate form as shown in Scheme 1 [7].

Additionally, human serum albumin in the blood has a high affinity for binding to the carboxylate form of CPT, thus driving the above lactone–carboxylate equilibrium toward the formation of the inactive carboxylate form [8]. As a result, the potency of the drug is reduced substantially when administrated to humans. Because of its toxic side effects, CPT, like most other antitumor drugs, needs to be frequently administered with limited doses to achieve desirable drug efficacy. Effective drug delivery methods providing sustained release of controllable amount of drugs over a prolonged period of time would be obviously advantageous for administration of these kinds of drugs [9].

To address these problems in CPT delivery, several different approaches have been taken to improve drug delivery efficiency

* Corresponding author. Tel.: +1 203 432 4262; fax: +1 203 432 0030.
E-mail address: mark.saltzman@yale.edu (W.M. Saltzman).

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