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Full Length Article

# Delivery of paclitaxel using nanoparticles composed of poly(ethylene oxide)-b-poly(butylene oxide) (PEO-PBO)

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ABSTRACT

An amphiphilic block copolymer poly(ethylene oxide)-b-poly(butylene oxide) (PEO-PBO) was evaluated as a carrier for therapeutic delivery of paclitaxel (PTX). PEO-PBO and PTX form nanoparticles (NPs) by self-assembly upon hydration. The size of these NPs was about 92.71 nm and the zeta potential was −5.06 mV, which met the requirements for passive tumor targeting through the enhanced permeability and retention effect. Compared with a commonly used block copolymer poly(ethylene glycol)-b-poly-D,L-(lactic acid) (PEG-PDLLA), PEO-PBO forms nanoparticles with superior pharmacokinetic, biodistribution, and tumor inhibitory properties. Meanwhile, results of hemolysis study and CMC determination showed that PEO-PBO had better biocompatibility and stability than PEG-PDLLA. These data suggest that PEO-PBO has potential for application in drug delivery and warrant further evaluation.



## 1. Introduction

Polymeric nanoparticles (NPs) are emerging as carriers for hydrophobic drugs [1–3]. NP delivery can be used to overcome low solubility of a drug, prolong its residence time in the body, improve its biodistribution, and reduce its systemic toxicity. PLA/PLGA are commonly used for their biocompatibility and biodegradability [4–8].

Most solid tumors had unique patho physiological characteristics as extensive vessel formation and defective vascular structure, compared with normal tissues, to provide enough nutrients and oxygen that required by rapid tumor growth [9,10]. Vascular permeability factor (vascular endothelial growth factor) was the trigger of this phenomenon and is over expressed in many types of tumor [11,12]. Enhanced vascular permeability leaded to extravasation of plasma proteins macromolecules and lipid particles into the interstitial space so they accumulate in solid tumors, resulting in the enhanced permeability and retention (EPR) effect. As a result, macromolecular drug delivery system can improve the drug uptake and distribution in tumor site without using targeting ligand [9,10]. The EPR effect is influenced by many factors including explicit molecular size (≥40 kDa), enough circulation time,and suitable surface charge. High positive charge can leadto rapid clearance from the blood circulation because of non specifically adsorption to the luminal surface of vascular walls mean while particles with high negative charges are easily to be trapped in the liver. Prolong circulation time may also increase the drug distribution in liver. Because the majority of the NPs can be cleared by the interception/metabolism of reticular endothelial system (RES)after intravenous administration [13], primarily by Kupffer cells of the liver [14]. These obstacles hinder the application of polymer nanoparticles. These are commonly addressed through the use of PEGylated copolymer [15]. Because thehydrophilic property of PEG, it can be combined with ahydrophobicpolymerto form amphiphilic polymers. These form NPs with prolonged blood circulation time [16–18]. For example, PEG-PLA was widely studied as nanoparticles or hydrogels for delivery of hydrophobic drugs [19–22]. Besides, synthesis of new biodegradable materials would be a feasible way to develop the drug formulations [23].

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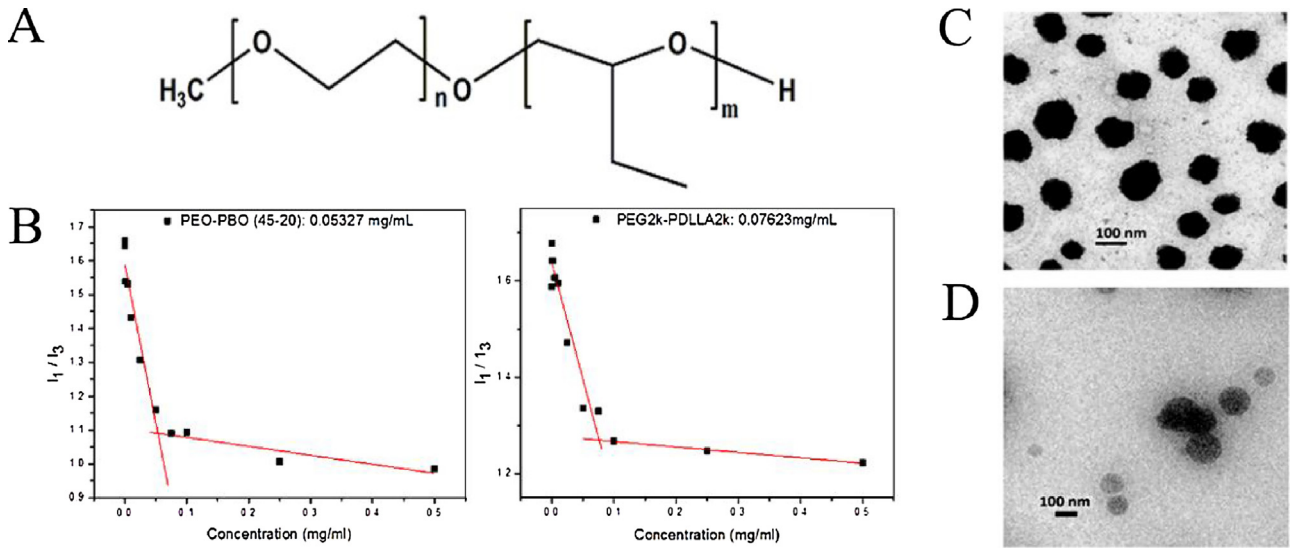


**Fig. 1.** Characterization of PEO-PBO nanoparticles.
A: Structure of PEO-PBO. B: Pyrene $I_1$:$I_3$ ratio versus polymer concentration plot for determination of critical micelle concentration (CMC). C and D: TEM images of PEO-PBO/PEG-PDLLA nanoparticles. **C**: PEO-PBO nanoparticles, **D**: PEG-PDLLA nanoparticles (The scale bar is 100 nm).

In this study, we intend to develop a new polymer formulation to lower the drug accumulation in liver. Poly(oxyethylene)-b-poly(oxybutylene)(PEO-PBO)(Fig. 1A) is a new amphiphilicpolymer synthesized by oxacyclopropane and epoxybutane, which showed good biocompatibility and biodegradable capabilityas a potential drug carrier material. As anamphiphilic polymer, it can improve the solubility of water-insoluble drug, for example taxanes, which are widely used anticancer drugs in clinical treatment. Because of these advantages, we used PEO-PBO (45-20) to prepare single material nanoparticles while compared with the similar molecular mass polymer, PEG(2 K)–PDLLA(2 K). The characterization of drug loading PEO-PBO nanoparticles showed the uniform particle size and, what's more, the excellent tumor targeting ability while loaded with fluorescent dye as a tracer.

The present research included the preparation of PEO-PBO nanoparticle loaded with paclitaxel (PTX) as the model drug and its characterization had been determined. The *in vitro* test including release study and cytotoxicity had been taken then, the pharmacokinetics was investigated in rats, *in vivo* antitumor activity and *in vivo* imaging experiment were detected in tumor-bearing nude mice.

## 2. Materials and methods

### 2.1. Materials

PTXwas purchased from Yew Biotechnology Co. (Jiangsu,China). Penicillin-streptomycin, RPMI-1640, fetal bovine serum (FBS), 0.25% (w/v) trypsin, and 0.03%(w/v) EDTA solution were purchased from Hyclone (USA). Acetonitrile (HPLC grade) was obtained from Nanjing Xinhuayuan Chemical Agents Co. (Nanjing, China). PEG(2 K)-PDLLA(2 K) was purchased from Jinan Daigang Biomaterial Co. (Shandong, China). 1,1-dioctadecyl-3,3,3,3-tetramethylindotricarbocyanine iodide (DiRiodide) (D12731) probe was purchased from Life Technologies (Shanghai,China).

BEL-7402 cells (human hepatocellular carcinoma cells) and A549 cells (human lung adenocarcinoma cell lines) were obtained from the Institute of Biochemistry and Cell Biology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences (Shanghai, China). Culture plates and dishes were purchased from Corning Inc. (NY,USA).

Male Sprague-Dawley (SD) rats (250 ± 20 g), male BALB/c nude mice (20 ± 2 g), SPF male ICR mice were supplied by Animal Experiment Center of Zhejiang Academy of Medical Sciences (Hangzhou, China) and kept under SPF conditions.

All the animals we used in the study are complying with the NIH Guide for Care and Use of Laboratory Animals.

### 2.2. PEO-PBO

In this study, poly(oxyethylene)-b-poly(oxybutylene)(PEO-PBO, 45-20) was prepared and provided by Advanced Polymer Materials Inc. (Montreal, Canada).

### 2.3. Thecritical micelle concentration (CMC) assay

Critical micelle concentrations of PEO-PBO (45-20) and PEG(2 K)-PDLLA(2 K) were detected by the pyrene 1:3 ratio method through fluorescence spectrophotometer [24]. The concentrations of each polymer used ranged from 0.0001 ~ 0.5 mg/mL. The excitation wave length of fluorescence measurement was 334 nm, excitation slit width was 5.0 nm, emission slit width was 2.5 nm and all the samples were measured at room temperature.

### 2.4. Preparation of drug loadednanoparticle

Nanoparticle was prepared through titration hydration method: 20 mg polymer and 1 mg PTX were dissolved in 2 mL acetonitrile. The organic solvent was dropped into a 30 mL water phase ($H_2O$/ethanol, v/v = 6:5) to form the emulsion and then the organic solution was removed by rotary evaporation (vacuum, 60 °C, 20 rpm/min, 30 min). After the solvent was removed and the whole solution was concentrated in 2 mL, the rotary evaporation was stopped and the production was obtained.

PEG-PDLLA NP was prepared in the same way.

### 2.5. Characterization of PTX loaded NP

The characterization of the PEO-PBO/PEG-PDLLANP including volume-average diameters and zeta potential (ξ) were measured by a Malvern Zetasizer (Nano-ZS, Malvern, Worcestershire, UK) at room temperature (25 °C). Its morphology was observed through a