



## Pharmacokinetics of a paclitaxel-loaded low molecular weight heparin-all-*trans*-retinoid acid conjugate ternary nanoparticulate drug delivery system

Lin Hou <sup>a,b,c,1</sup>, Jing Yao <sup>a,b,1</sup>, Jianping Zhou <sup>a,b,\*</sup>, Qiang Zhang <sup>d</sup>

<sup>a</sup> Department of Pharmaceutics, China Pharmaceutical University, 24 Tongjiaxiang, Nanjing 210009, China

<sup>b</sup> State Key Laboratory of Natural Medicines, China Pharmaceutical University, Nanjing 210009, China

<sup>c</sup> School of Pharmacy, Zhengzhou University, 100 Science Road, Zhengzhou 450001, China

<sup>d</sup> Pharmaceutical Sciences Department, Peking University, 38 Xueyuan Road, Haidian District, Beijing 100191, China

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### ABSTRACT

Amphiphilic low molecular weight heparin-all-*trans*-retinoid acid (LHR) conjugate, as a drug carrier for cancer therapy, was found to have markedly low toxicity and to form self-assembled nanoparticles for simultaneous delivery of paclitaxel (PTX) and all-*trans*-retinoid acid (ATRA) in our previous study. In the present study, PTX-loaded LHR nanoparticles were prepared and demonstrated a spherical shape with particle size of 108.9 nm. Cellular uptake analysis suggested rapid internalization and nuclear transport of LHR nanoparticles. In order to investigate the dynamic behaviors and targeting ability of LHR nanoparticles on tumor-bearing mice, near-infrared fluorescent (NIR) dye DiR was encapsulated into the nanoparticles for *ex vivo* optical imaging. The results indicated that LHR nanoparticles could enhance the targeting and residence time in tumor site. Furthermore, *in vivo* biodistribution study also showed that the area under the plasma concentration time curve (AUC (0→inf)) values of PTX and ATRA for PTX-loaded LHR nanoparticles in tumor were 1.56 and 1.62-fold higher than those for PTX plus ATRA solution. Finally, PTX-loaded LHR nanoparticles demonstrated greater tumor growth inhibition effect *in vivo* without unexpected side effects, compared to PTX solution and PTX plus ATRA solution. These results suggest that PTX-loaded LHR nanoparticles can be considered as promising targeted delivery system for combination cancer chemotherapy to improve therapeutic efficacy and minimize adverse effects.

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### 1. Introduction

Anticancer drugs are normally associated with severe side effects during therapy. Nowadays combination chemotherapy with multiple drugs, a basic chemotherapeutic protocol for cancer, has been widely used in the clinic to solve this problem [1]. However, the clinical applications of most anticancer drugs are extremely limited by their poor aqueous solubility and nonspecific systemic delivery. And when it comes to combination use of multiple drugs, mixed drugs are prone to aggregation and precipitation, losing respective pharmaceutical activity and raising a risk of embolisms [2]. Currently, these obstacles cannot be overcome by conventional drug formulations, necessitating sequential drug administration or a separate intravenous (i.v.) line. Consequently, there is

a tremendous incentive to develop drug delivery systems (DDS) for combination chemotherapy, to improve their water solubility and availability at tumor sites, and to maximize the therapeutic efficacy while minimize the adverse effects.

In the last few years, a number of pioneering studies have been carried out that highlight the suitability of polymer-drug conjugates to deliver drug combinations [3]. It has been shown to offer benefits of the passive tumor targeting by the enhanced permeability and retention (EPR) effect [4], decreased toxicity [5], and increased solubility as well as chemical stability [6]. Miller et al. conjugated two drugs with the same polymeric backbone resulting in a nano-conjugate at a size of ~100 nm [7]. A phase I study was carried out on forty-three patients with advanced solid tumors combining a fixed dose of cis-platin with escalating doses of PGA-PTX and showed increased efficacy. Therefore, using the polymer-drug conjugates is a potential delivery option, facilitating ease of entry into clinical trials in the combination cancer chemotherapy.

Nevertheless, the difficulties of obtaining polymers with suitable physicochemical and biopharmaceutical properties are

\* Corresponding author. Department of Pharmaceutics, China Pharmaceutical University, 24 Tongjiaxiang, Nanjing 210009, China. Tel.: +86 25 83271102; fax: +86 25 83301606.

E-mail address: [zhoujp@163.com](mailto:zhoujp@163.com) (J. Zhou).

<sup>1</sup> Lin Hou and Jing Yao contributed equally to this work.