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Original article

Construction and comparison of different nanocarriers for co-delivery of cisplatin and curcumin: A synergistic combination nanotherapy for cervical cancer

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ABSTRACT

Purpose: Co-delivery of two or more drugs into the same cancer cells or tissues in the same nanocarriers provides a new paradigm in cancer treatment. In this study, two kinds of nanocarriers: lipid-polymer hybrid nanoparticles (LPNs) and polymeric nanoparticles (PNPs) were constructed and compared for co-delivery of cisplatin (DDP) and curcumin (CUR).
Methods: DDP and CUR loaded LPNs (D/C/LPNs) and PNPs (D/C/PNPs) were prepared. Two kinds of nanocarriers were characterized in terms of particle size, zeta potential, drug encapsulation efficiency (EE), and drug release. Their *in vitro* cytotoxicity and *in vivo* anti-tumor efficacy was studied on human cervix adenocarcinoma cell line (HeLa cells) and mice bearing cervical cancer model.
Results: Compared with D/C/PNPs, D/C/LPNs showed significantly higher cytotoxicity *in vitro*. D/C/LPNs also displayed the best antitumor activity than other formulations tested *in vivo*.
Conclusions: The results demonstrated that LPNs could improve the anticancer efficacy of drugs to higher levels than PNPs and free drugs, thus could serve as an effective drug system for targeted and synergistic co-delivery nanomedicine for cervical cancer chemotherapy.

1. Introduction

Cervical cancer, with an incidence of 528,000 worldwide in 2012, is one of the most common cause of cancer-related deaths in females, with 85% of cases occurring in developing countries where cervical cancer is a leading cause of cancer death in females [1–4]. Based on the latest version of NCCN guidelines for cervical cancer (Version 1. 2015), cisplatin (DDP) alone or in combination with paclitaxel has been recommended as the first-line single-agent therapy or the first-line combination therapy for advanced stage, recurrent or metastatic cervical cancer [5,6] However, the dose limiting toxicities (nephrotoxicity and hepatotoxicity) and drug resistance associated with DDP has presented a serious concern in clinic [7–10]. Combination chemotherapy and nanocarrier-based delivery of DDP to the tumor sites are the most two areas of intense researches to solve the aforementioned problems [11–13].

Curcumin (CUR) is the natural compound extracted from the rhizome of turmeric (*Curcuma longa*) that allows suppression, retardation and inversion of carcinogenesis [14]. The molecular mechanism of CUR induced cytotoxicity in cervical cancer cells possess multiple targets including inhibition of telomerase; inhibition of cyclin D1 and CDK4 via acetylation and upregulation of p53, leading to cell cycle arrest at G1/S phase; induction of endoplasmic reticulum stress-mediated apoptosis, etc [15–17]. Furthermore, CUR can reverse the multi-drug resistance (MDR) of cancer cells [18]. DDP resistance in SiHaR due to over-expression of MRP1 and Pgp1 was overcome by CUR [19]; and the nephrotoxicity of DDP can be reduced by CUR, thereby enhancing the therapeutic window of DDP [10]. However, because of the hydrophobic properties of DDP and CUR, it is necessary to engineer ideal nanocarriers to co-delivery DDP and CUR to the tumor tissues at the same time.

Nanocarrier-based delivery of anticancer drugs has received much attention in recent years because of its potential for

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improving drug efficacy, reducing unwanted side effects and circumventing cellular accumulation mediated drug resistance. Of all the common nanoparticulate systems, liposomes and biodegradable polymeric nanoparticles (PNPs) have emerged as the two dominant classes of drug nanocarriers, as evidenced by increasing numbers of approved drug products, clinical trials, and research reports [20,21]. Lipid-polymer hybrid nanoparticles (LPNs), combing the mechanical advantages of biodegradable PNPs and biomimetic advantages of liposomes, are core-shell nanoparticles structures comprising polymer cores and lipid/lipid-PEG shells [22,23]. The hybrid architecture of LPNs can provide advantages such as entrapment of multiple therapeutic agents, high drug loading, controllable particle size, good serum stability, etc. Therefore, lipid-polymer hybrid nanoparticles (LPNs) were constructed for co-delivery of cisplatin (DDP) and curcumin (CUR), and compared with PNPs.

In the present study, DDP and CUR loaded LPNs (D/C/LPNs) and PNPs (D/C/PNPs) were prepared. The physicochemical properties of the two kinds of nanocarriers were characterized including particle size, zeta potential, drug encapsulation efficiency (EE), and drug release. *In vitro* cytotoxicity and *in vivo* anti-tumor efficacies were studied on human cervix adenocarcinoma cell line (HeLa cells) and mice bearing cervical cancer model. LNPs were anticipated to serve as an effective delivery platform for targeted and synergistic co-delivery DDP and CUR for cervical cancer chemotherapy.

2. Materials and methods

2.1. Materials

Cisplatin (DDP) was provided by Shandong Boyuan Pharmaceutical Co., Ltd (Ji'nan, China). Curcumin (CUR) was obtained from Ji'nan Guoshiweiye Chemical Co., Ltd (Ji'nan, China). Poly (lactic-co-glycolic acid) (PLGA, molar ratio of D, L-lactic to glycolic acid, 50: 50) was purchased from Ji'nan Daigang Biotechnology Co. Ltd. HeLa cells and human umbilical vein endothelial cells (HUVEC) were obtained from the American type culture collection (Manassas, VA). PEG-DSPE was purchased from Xi'an Ruixi Biological Technology Co., Ltd (Xi'an, China). Cholesterol, 3-(4,5-dimehyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT), and Pluronic F68 were purchased from Sigma-Aldrich Co., Ltd (St Louis, MO). All other chemicals were of analytical grade or higher.

BALB/c nude mice (18–22 g weight) were purchased from the Beijing Fuzhong Technology Development Co., Ltd (Beijing, China). All animal experiments complied with the Animal Management Rules of the Ministry of Health of the People's Republic of China.

2.2. Preparation of LPNs and PNPs

D/C/LPNs were prepared by the nanoprecipitation technology [24]. In detail, PLGA (100 mg), DDP (20 mg) and

Table 1
Characterization of LPNs and PNPs.

Characteristics	D/C/LPNs	D/LPNs	C/LPNs	D/C/PNPs	LPNs	PNPs
Particle size (nm)	163.4 ± 7.52	141.5 ± 5.13	151.4 ± 8.23	118.5 ± 4.62	110.3 ± 3.19	91.6 ± 2.94
PDI	0.16 ± 0.05	0.14 ± 0.03	0.19 ± 0.06	0.15 ± 0.04	0.12 ± 0.03	0.11 ± 0.02
Zeta potential (mV)	−19.6 ± 2.62	−11.9 ± 1.81	−25.8 ± 3.78	−13.7 ± 1.36	−21.3 ± 2.31	−15.6 ± 2.08
EE of DDP (%)	88.7 ± 6.81	89.5 ± 5.32	N/A	83.3 ± 3.89	N/A	N/A
EE of CUR (%)	85.2 ± 4.14	N/A	84.6 ± 3.72	81.5 ± 6.79	N/A	N/A
DL of DDP (%)	1.91 ± 0.31	1.96 ± 0.42	N/A	2.02 ± 0.56	N/A	N/A
DL of CUR (%)	9.1 ± 1.62	N/A	8.9 ± 1.34	8.7 ± 1.49	N/A	N/A

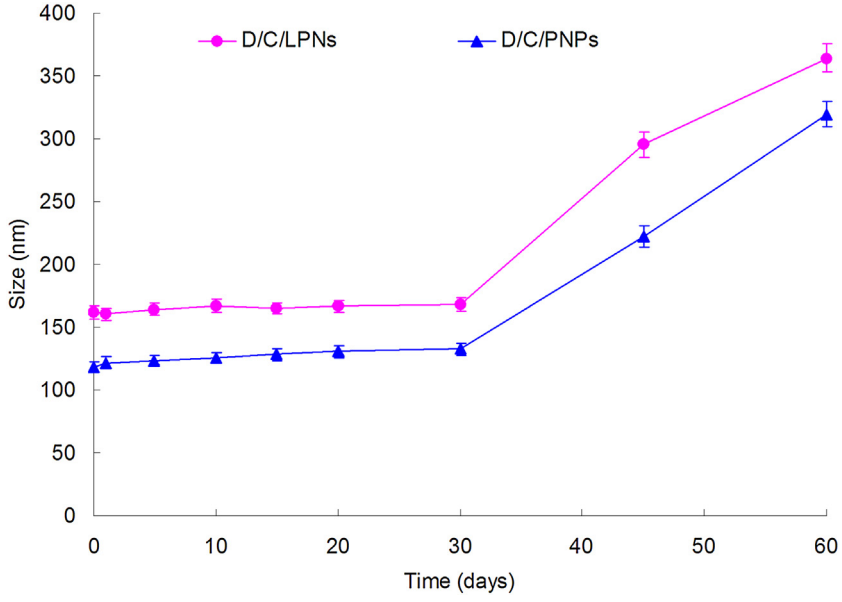

Fig. 1. The average diameter of D/C/LPNs and D/C/PNPs during 60 days.