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A novel paclitaxel-loaded poly(ε-caprolactone)/Poloxamer 188 blend nanoparticle overcoming multidrug resistance for cancer treatment

Yangqing Zhang [a,b,1], Lina Tang [c,1], Leilei Sun [d,1], Junbo Bao [c], Cunxian Song [c], Laiqiang Huang [a,b], Kexin Liu [d], Yan Tian [d], Ge Tian [d], Zhen Li [d], Hongfan Sun [c,*], Lin Mei [a,b,d,*]

[a] Department of Biological Sciences and Biotechnology, Tsinghua University, Beijing 100084, People's Republic of China
[b] The Shenzhen Key Laboratory of Gene and Antibody Therapy, Center for Biotech and Bio-Medicine and Division of Life Sciences, Graduate School at Shenzhen, Tsinghua University, Shenzhen, Guangdong 518055, People's Republic of China
[c] Institute of Biomedical Engineering, Peking Union Medical College and Chinese Academy of Medical Sciences, The Tianjin Key Laboratory of Biomaterial Research, Tianjin 300192, People's Republic of China
[d] College of Pharmacy, Dalian Medical University, Dalian Liaoning 116027, People's Republic of China

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ABSTRACT

Multidrug resistance (MDR) of tumor cells is a major obstacle to the success of cancer chemotherapy. Poloxamers have been used in cancer therapy to overcome MDR. The objective of this research is to test the feasibility of paclitaxel-loaded poly(ε-caprolactone)/Poloxamer 188 (PCL/Poloxamer 188) nanoparticles to overcome MDR in a paclitaxel-resistant human breast cancer cell line. Paclitaxel-loaded nanoparticles were prepared by a water–acetone solvent displacement method using commercial PCL and self-synthesized PCL/Poloxamer 188 compound, respectively. PCL/Poloxamer 188 nanoparticles were found to be of spherical shape and tended to have a rough and porous surface. The nanoparticles had an average size of around 220 nm, with a narrow size distribution. The in vitro drug release profile of both nanoparticle formulations showed a clear biphasic release pattern. There was an increased level of uptake of PCL/Poloxamer 188 nanoparticles (PPNP) in the paclitaxel-resistant human breast cancer cell line MCF-7/TAX, in comparison with PCL nanoparticles. The cytotoxicity of PCL nanoparticles was higher than commercial Taxol® in the MCF-7/TAX cell culture, but the differences were not significant. However, the PCL/Poloxamer 188 nanoparticles achieved a significantly higher level of cytotoxicity than both of PCL nanoparticle formulation and Taxol®, indicating that paclitaxel-loaded PCL/Poloxamer 188 nanoparticles could overcome MDR in human breast cancer cells and therefore could have considerable therapeutic potential for breast cancer.

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1. Introduction

The global incidence and mortality rates of breast cancer still remain high, although there has been great progress in understanding the molecular mechanisms underlying multistage carcinogenesis, tumor promotion and the establishment of molecular targeted therapies [1]. Multidrug resistance (MDR) to anti-cancer agents remains a major hurdle to successful cancer chemotherapy. The development of effective therapies overcoming MDR against invasive breast cancer and particularly highly metastatic disease still remains a high priority. Nanoparticles could reduce the MDR that characterizes many anti-cancer drugs, including paclitaxel, by a mechanism of internalization of the drug [2], reducing its efflux from cells mediated by the P-glycoprotein (P-gp) [3–6]. The use of nanoparticles in drug delivery systems is a far more effective cancer treatment method than conventional chemotherapy, which is typically limited by the toxicity of drugs to normal tissues, their short circulation half-life in plasma, their limited aqueous solubility and their non-selectivity [7,8].

Paclitaxel is a mitotic inhibitor used in cancer chemotherapy. It is effective for various cancers, especially breast and ovarian cancer. Its commercial formulation, Taxol®, is formulated in high concentration in Cremophor EL, which has been associated with severe side effects, including hypersensitivity reactions, nephrotoxicity and neurotoxicity. In order to eliminate the Cremophor EL-based adjuvant and in an attempt to increase the drug solubility, alternative formulations have been attempted, such as emulsification, micellization, liposome, non-liposomal lipid carriers (microspheres, nanoparticles, etc.), cyclodextrins and local drug delivery devices (drug-eluting stents etc.) [9]. Of these alternatives, the

* Corresponding author. Address: Department of Biological Sciences and Biotechnology, Tsinghua University, Beijing 100084, People's Republic of China. Tel.: +86 22 87892052; fax: +86 22 87892052.
E-mail addresses: sunhf@bme.org.cn (H. Sun), mei.lin@sz.tsinghua.edu.cn (L. Mei).
[1] These authors contributed equally to this work.

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nanoparticle formulation holds the greatest promise for this purpose in cancer treatment. The submicron size of nanoparticles offers numerous advantages, such as being more stable during storage [10]. Such a colloidal system is able to extravasate solid tumors into the inflamed or infected site, where the capillary endothelium is defective [3].

Nanoparticles serving in an anti-cancer drug delivery system may be comprised, in whole or in part, of various lipids and natural and synthetic polymers. The synthetic polymers most commonly used in nanoparticle-based drug delivery systems are biodegradable. Among the FDA-approved biodegradable polymers, poly(lactide) (PLA), poly(L,L-lactide-co-glycolide) (PLGA) and poly(caprolactone) (PCL) have been used most often according to the drug delivery system literature. PCL occupies a unique position: it is at the same time both biodegradable and miscible with a variety of polymers, and it crystallizes very readily [11]. In addition, it lacks toxicity and has great permeability [11]. Poloxamer 188 is a member of the poloxamer family (trade name Pluronics®) that is widely used as surfactants in many applications. It is soluble in both water and organic solvent. Poloxamers and poloxamine non-ionic surfactants have diverse applications in various biomedical fields, ranging from drug delivery to medical imaging [12]. In this research, Poloxamer 188 was incorporated into PCL as a pore-forming agent and enhancer of drug release. Previous studies by our group have demonstrated that the amount of Poloxamer 188 blended into PCL could affect the microspheres' morphology and control paclitaxel release [13]. Recently, it was also demonstrated that poloxamers interact with MDR tumors, resulting in drastic sensitization of these tumors with respect to various anti-cancer agents [12,14]. The key attribute for the biological activity of poloxamers is their ability to incorporate into membranes followed by subsequent translocation into cells, thereby affecting various cellular functions, such as mitochondrial respiration, ATP synthesis, activity of drug efflux transporters, apoptotic signal transduction and gene expression. As a result, poloxamers cause drastic sensitization of MDR tumors to various anticancer agents, including paclitaxel, enhance drug transport across the blood–brain and intestinal barriers, and cause transcriptional activation of gene expression both in vitro and in vivo [14–15]. Recent studies have further demonstrated that Poloxamer 188 is a potent in vitro inhibitor of both P-gp and CYP3A4 [4,16]. Thus, in this research we investigate the hypothesis that a novel paclitaxel-loaded PCL/Poloxamer 188 blend nanoparticles, overcoming MDR, will achieve better therapeutic effects in a paclitaxel-resistant human breast adenocarcinoma MCF-7 cell line.

2. Materials and methods

2.1. Materials

Briefly, paclitaxel of 99.9% purity was purchased from Beijing Union Pharmaceutical Factory (Beijing, China). Polycaprolactone (M_n ~42,500) and polyvinyl alcohol (PVA) (M_w 30,000–70,000) were obtained from Sigma–Aldrich (St. Louis, MO, USA). Cell Counting Kit-8 (CCK-8) was from Dojindo Molecular Technologies Inc. (Kumamoto, Japan). ε-Caprolactone monomer (ε-CL) of 99.9% purity was also purchased from Sigma–Aldrich (St. Louis, MO, USA). The monomer was further purified by vacuum distillation over CaH_2. Poloxamer 188 (Pluronic F68), with M_w around 8300 and containing approximately 80% poly(ethyl oxide) (PEO) and 20% poly(propyl oxide) (PPO), was from BASF, Germany. The Poloxamer 188 was incorporated into the PCL matrix to a 10% weight ratio as a molecular distribution, which would leach out into aqueous medium to leave a porous structure in the PCL matrix [17]. Acetonitrile and methanol, used as the mobile phase in high-performance liquid chromatography (HPLC), were purchased from EM Science (ChromAR, HPLC grade, Mallinckrodt Baker, USA). All other chemicals were HPLC grade and were used without further purification. Ultrapure water, produced by Boon Environmental Tech. Industry Co., Ltd. (Tianjin, China), was used throughout all experiments.

2.2. Synthesis of PCL/Poloxamer 188 compound

Fig. 1 shows the end-capping reaction of Poloxamer 188 and a schematic description of the synthesis mechanism of poly(ε-caprolactone) [17]. Briefly, the terminal free hydroxyl groups of Poloxamer 188 molecules were capped with acetyl groups to make

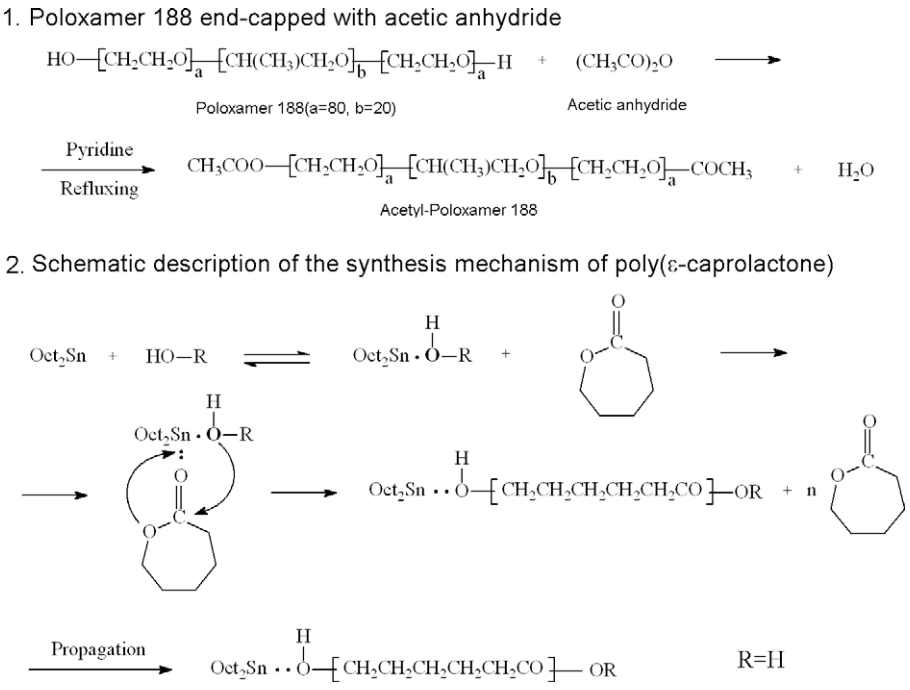

Fig. 1. The end-capping reaction of Poloxamer 188 and a schematic description of the synthesis mechanism of poly(ε-caprolactone).

ID	Title	Pages
1406	A novel paclitaxel-loaded poly(ε-caprolactone)/Poloxamer 188 blend nanoparticle overcoming multidrug resistance for cancer treatment	8

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