

Research progress of paclitaxel drug delivery systems

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Abstract. Paclitaxel (PTX), a tetracyclic diterpenoid compound, is a broad-spectrum and highly effective antitumor drug. However, since it exhibited its complex chemical structure and low solubility, conventional PTX therapies are inefficient and even its solvent is toxic to humans. These drawbacks limited its wide application in cancer treatment. In contrast, PTX nano-delivery system has the advantages of high targeting and stability, which could significantly improve the solubility of PTX in water. The drug loading capacity is greatly increased due to prominent compatibility. By reviewing the relevant literature, this paper introduces several research directions of PTX drug delivery systems and lists the design applications of different nanocarriers in recent years. It also highlights the research progress of prodrugs and provides an outlook on its future direction.

Keywords: Paclitaxel, Nanomedicine, Antitumor, Targeted therapy, Drug delivery.

1. Introduction

Cancer is a significant public health issue and the second largest cause of death after cardiovascular disease, claiming nearly nine million lives each year and accounting for nearly one in six deaths worldwide [1]. In recent decades, the basic cancer treatments are surgery, chemotherapy and radiotherapy. Although cancer cells are effectively killed by these treatments, it also causes damage to normal cells and tissues, leaving patients in constant pain [2]. In contrast, antitumor nano drug delivery systems could diminish the toxic side effects and promote the efficacy of tumor targeting by loading drug molecules through functionalized nanocarriers [3].

Paclitaxel was firstly extracted from the bark of the yew tree *Taxus brevifolia* Nutt [4], as shown in Fig. 1. The chemical structure of PTX was analyzed by X-ray, which verified that it is a highly effective, low-toxic, broad-spectrum natural anti-cancer medicine. PTX could cause the microtubulin dimer that makeup microtubules lose dynamic balance. It induces microtubulin polymerization, microtubule assembly and prevent depolymerization. As a result, mitosis of cancer cells is inhibited, which induces apoptosis and stops the proliferation of cancer cells, acting as an anti-cancer agent [5]. Since it exhibited the poor water-solubility of PTX (about 0.4 mg/mL), it is difficult to make an injection with water as the solvent for intravenous administration. Therefore, improving the solubility of PTX to make it work better is the key to the study. The commonly used PTX injection [trade name: Taxol] is dissolved in a solution of polyoxyethylene castor oil (Cremophor EL) mixed with anhydrous ethanol 1:1 (v/v) to improve the solubility of PTX. However, Taxol's short half-life, weak targeting, short drug circulation time and poor tumor suppression in vivo lead to unsatisfactory results [6]. Also, the addition of Cremophor EL could cause some adverse effects such as neurotoxicity and hypersensitivity reactions [7]. Therefore, reducing the toxicity and therapeutic efficiency of PTX agents so that they could target cancer cells is the focus of current research.

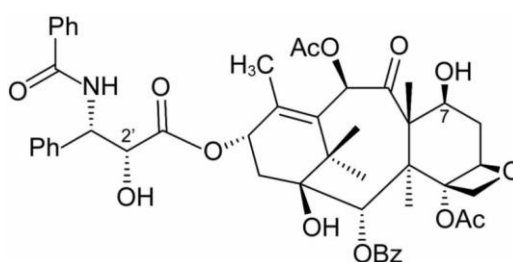


Figure 1. The chemical structure of paclitaxel [8]

With the rapid progress of nanotechnology, the nano-formulation of PTX attracted attention from researchers. It could not only decrease the side effects of PTX clinical application, but also heighten anticancer activity, which has great advantages compared with traditional PTX drugs. Based on the existing research results, the research progress of PTX nano-delivery systems at home and abroad are reviewed.

2. Drug delivery of PTX

As mentioned previously, the physical and chemical properties of PTX complicate its formulation. To address these issues, several PTX delivery systems including micelles, liposomes, nanoparticles, prodrugs, emulsions, implants and nanocrystals were developed to improve its solubility and pharmacological property. (Fig. 2)

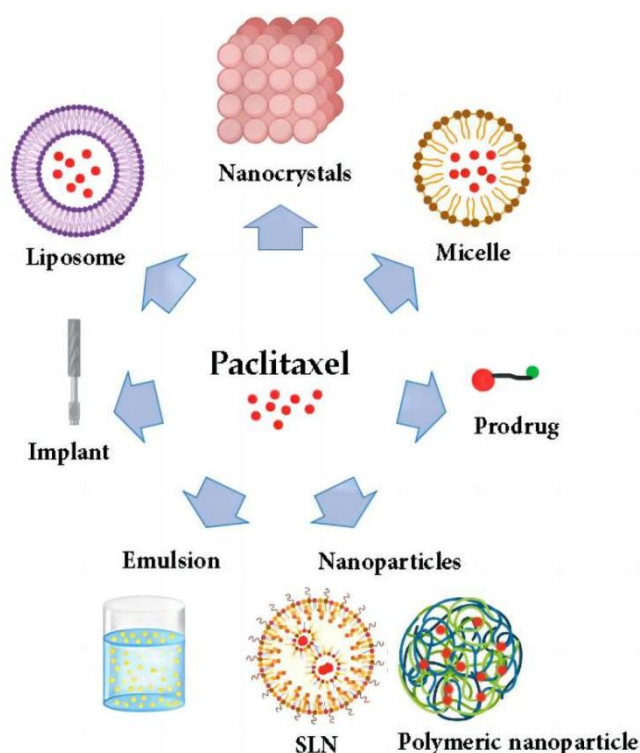


Figure 2. Main research directions of paclitaxel delivery system [9]

2.1. Polymeric micelles

The micelles are amphiphilic block copolymers formed by the self-assembly of hydrophilic and hydrophobic areas in water. The hydrophobic segments of the copolymers automatically aggregate into a hydrophobic core under the action of water molecules, and the hydrophilic segments of the copolymers form a stable hydrophilic outer [10]. The hydrophilic shell prevents aggregation and precipitation of micelles, which dissolves insoluble small molecules of drugs, protecting the hydrophobic core [5]. Polymer micelles could be passively targeted through tumor tissue retention effects and high permeability. The polymer surface could also be modified for active targeting [11]. Shuai et al. [12] combined functionalized polyethylene glycol-polylactic acid (PEG-PLA) with a self-assembling transcriptional activator (TAT) for loading PTX. PEG-PLA and TAT formed nano micelles (TAT-NP-PTX) with a particle size of 20 nm, which accumulated in human breast cancer cells, resulting in a significant increase in cytotoxicity. This study illustrates the ability of polymeric micelles in enhancing the bioavailability of PTX.

2.2. Prodrugs

A prodrug is usually an inactive form of a parent medicine that is modified to give it specific physicochemical properties during drug delivery [13]. When it reaches a specific organ, tissue, or cell stimulated by certain conditions, it is converted into an active parent drug, which exerts pharmacological effects. The correct setting of the prodrug could effectively overcome the problems of low solubility, poor specificity and toxicity that are easily caused by the parent drug in the drug delivery process. It was found that the design site of PTX prodrugs is usually at the 2'-OH or 7-OH position. The free hydroxyl group in the C-2' fraction is considered to be required for cytotoxicity, the ester in the C-2' fraction is unstable and could be selectively synthesized without protecting the C-7 hydroxyl group [14]. The modified prodrug at the C-2' position regains activity in the specific environment in vivo, releasing PTX and specifically improving the anti-tumor effect. The following is a brief overview of the PTX prodrugs in recent years.

2.2.1. Hypoxia-responsive PTX prodrugs

One of the characteristics of the tumor microenvironment is hypoxia, where the balance between oxygen supply and consumption is disrupted in tumor tissues due to rapid tumor cell proliferation and abnormal blood supply in the tumor [15]. The hypoxic microenvironment has a significant impact on tumor proliferation and drug therapy. A typical example is photodynamic therapy (PDT), which mainly relies on the reaction of photosensitizers (PS) to light generates reactive oxygen species (ROS), thus photodynamic therapy is closely related to oxygen. Therefore, tumor hypoxia has a hindering effect on the therapeutic effect of PDT.

Under hypoxic conditions, prebiotics with hypoxia-sensitive fractions could be restored to the active condition by cellular enzymes and then exert precise tumor targeting [16]. Zhou et al. [17] synthesized a hypoxia-activated PTX prodrug (PTX2-Azo). It was found that combining this PTX prodrug with a peptide copolymer modified with the photosensitizer dihydroporphyrin e6 (Ce6) allowed the preparation of light-promoted PTX nanoparticles (Ce6/PTX2-Azo NP). As shown in Fig. 3. Under hypoxia, light further accelerated the hypoxia of the tumor microenvironment, which promoted the targeted release of prodrug in turn and exerted just the right anti-tumor effect.

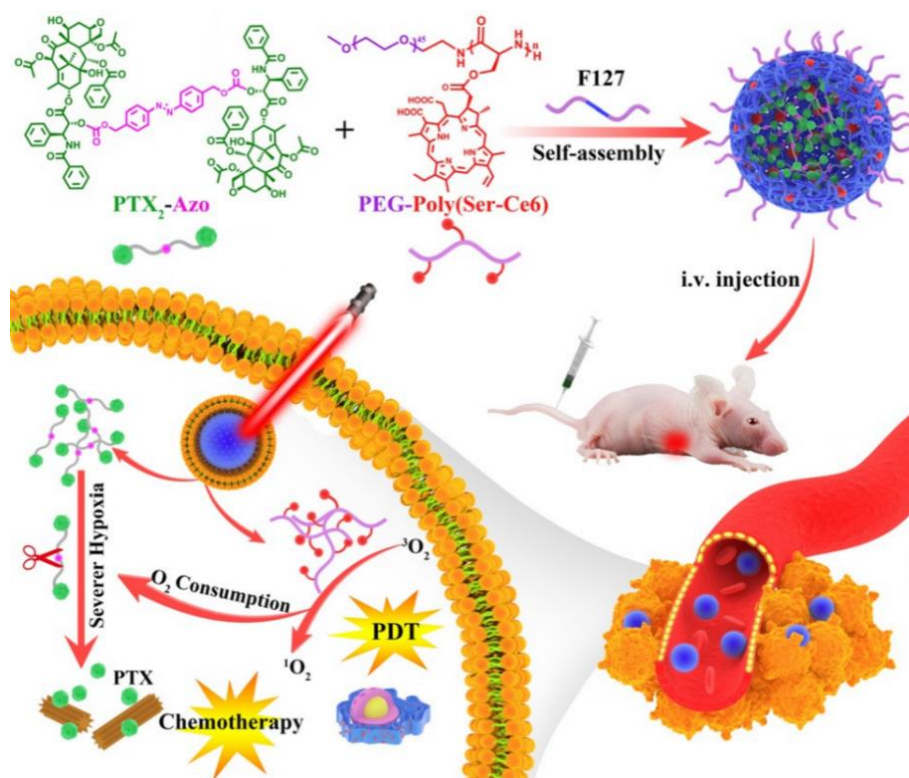


Figure 3. Components of Ce6/PTX2-Azo NP and their mechanism of action [17]

2.2.2. Redox-responsive dimeric PTX prodrugs

For the special redox microenvironment of tumor cells, various redox-responsive drug delivery systems could be established on this basis to effectively treat tumors [18]. Redox-responsive carriers were gaining widespread attention because of their advantages of long circulation, high response, and targeted drug release [19]. Redox-sensitive chemical bridges are commonly utilized to set up nano-drug delivery systems. Common chemical bridges mainly include: thioether bonds, single sulfur bond, disulfide bonds, thioketone bond, and diselenium bonds [20].

The high redox microenvironment in the tumor triggers the targeted release of drugs, increasing the killing of tumor cells while reducing the damage to the organism. Lu et al. [19] synthesized dimeric PTX precursors using different bridging agents and found that PTX precursors containing diselenium bonds could release drugs on demand in response to redox heterogeneous intracellular microenvironment, followed by combining PTX dimers with clinically used carrier materials and screening the best carrier materials by comprehensive evaluation of different indicators. Among the anchored dimeric PTX nanoformulations such as F127, iron-tannic acid complex, human serum albumin and DSPE-PEG, F127 showed the best antitumor effect. It provides a reference for the development of precursor nanoparticle drugs with enhanced chemotherapeutic effects.

2.2.3. pH-responsive PTX nanoparticle prodrugs

The alteration of the tumor microenvironment is not only related to redox substances but also may be closely related to the interstitial fluid pressure, oxygen content, pH, value, and various enzymes inside and outside the tumor cells [21]. When PTX was embedded in pH-responsive polymer micelles, the structure of the polymer micelle at a pH of 7.4 loaded with the drug is intact in normal tissue and did not release the drug. However, when encountering tumor tissue with low pH, the encapsulated drug could be released rapidly, which greatly enhances the targeting of the medicine to the tumor.

The pH in tumor tissues is lower compared to normal tissues. Therefore, this feature could be exploited to construct PTX nano prodrugs. Huang et al. [22] designed an amphiphilic polymer, which consists of a poly(ethylene glycol)-acetal-PTX (PEG-acetalPTX, PAP) coupling, wrapped around free PTX. Particles enter tumor cells through a strong permeation and retention effect (EPR) and tumor cells internalize the particles through endocytosis. Acetal bonds fracture in the acidic conditions of the endosome/lysosome compartment and cause breakage of the nanoparticles, resulting in the fast liberation of the packaged PTX. The formerly concealed acetal bond was exposed to an acidic environment, eventually releasing the incorporated PTX entirely. The observed programmed drug release behavior showed a difference in the mechanism and rate of drug release between encapsulated PTX and bound PTX, which may lead to higher intracellular drug concentrations and prolonged effects.

2.3. Nanoemulsions

Nanoemulsions (NEs) consist of transparent or semi-transparent, low-viscosity and thermostable oil-water mixtures formed spontaneously from the aqueous phase, oil phase and surfactants in appropriate proportions [23]. NEs include oil-in-water (O/W), water-in-oil (W/O) and bicontinuous types in terms of structure [24]. NEs have higher solubility and adsorption capacity than simple micellar dispersions. Its unique properties and smaller size give it greater kinetic stability and drug solubility. The drug in the NEs diffuses from the oil into the surfactant layer and then diffuses into the aqueous phase to achieve sustained release [5]. Ding et al. [25] combined a phospholipid-drug complex (PLDC) prepared by PTX with a self-nanoemulsifying drug delivery system (SNEDDS) to form the PLDC-SNEDDS system. After dispersion in aquatic media, PLDC-SNEDDS formed NEs with the average diameter of about 30 nm. In vivo, PTX-PLDC-SNEDDS could significantly enhance the bioavailability and oral absorption efficiency of PTX. Although NEs have many advantages, they are still relatively little used in clinical applications. The preparation of NEs requires large amounts of surfactants and co-surfactants, which may produce adverse effects such as gastrointestinal irritation [24].

2.4. Liposomes

Liposomes are amphiphilic molecules with hydrophobic tails aggregated with each other and hydrophilic heads revealed in the water phase, forming sealed capsule with a bilayer structure [10]. Liposomes could enhance drug solubility and reduce adverse drug reactions. Due to the bilayer protection of liposomes, drugs have higher stability in complex biological environments. The hydrophilic core could encapsulate hydrophilic drugs and nucleic acid drugs, and the hydrophobic region between the bilayers could encapsulate hydrophobic drugs. This design increases the solubility of the drug, thus improving the therapeutic effect [26]. Liposomes have greater development value because of the wide source of prepared materials, easy preparation in large quantities, ability to be metabolized normally in vivo, good biocompatibility, and low toxicity [27]. Currently, liposomes are developing well, and liposomes such as common passively targeted liposomes, actively targeted liposomes, environmentally responsive liposomes, dual drug-loaded liposomes, and elastomeric liposomes emerged [23]. Li et al. [28] constructed PTX-loaded liposomes with dual modification of the cell-penetrating peptide dNP2 and the tumor microenvironment-cleavable folate (FA) for targeted delivery in gliomas. Modification of dNP2 obviously increased migration crossing the blood-brain barrier, and FA cleavage further maximized the cellular penetration of dNP2, displaying augmented tumor targeting.

2.5. Nanoparticles

Nanoparticles (NPs) are biocompatible and could stay in the human body for a longer period of time, which could significantly improve the solubility and bioavailability of PTX. NPs could enhance and modify drug properties such as solubility, half-life and release characteristics to enhance pharmacodynamic and pharmacokinetic parameters [29]. Polymer NPs made from amphiphilic block copolymers could significantly enhance the solubility of PTX. Coralie et al. [30] synthesized several polyinosinic-b-polyglutamic acid γ -benzyl esters (PSar-b-PGluOBn) block copolymers by ring-opening polymerization (ROP) of N-carboxylic anhydrides (NCAs). PTX was added to this copolymer to prepare PSar-b-PGluOBn NPs. The NPs exhibited superior loading rates and copolymer recovery. The polymer significantly improved the apparent water solubility of PTX by a factor of up to 660-6600 $\mu\text{g/mL}$, and this PTX-loaded PSar-b-PGluOBn nanoparticle has superior potential for cancer therapy.

3. Conclusion and Outlook

Cancer is one of the most hazardous and incurable illnesses threatening the health of human beings today. PTX, an effective microtubule-targeted antitumor drug, is a hot spot in the field of antitumor drug research. With the in-depth research on the structure of PTX in recent years, the pathway of its biosynthesis was established and improved, and the production cost of PTX was reduced, making the widespread clinical application of PTX possible. Although the anti-tumor mechanism of PTX was initially clarified, its molecular mechanism of action is still unclear. With the continuous innovation of experimental technology, the mechanism of action at the molecular level would be gradually clarified, which would contribute to the development of PTX drug delivery system. This paper reviews several approaches of PTX antitumor mechanism and drug delivery systems. On this basis, the clinical research progress and generation mechanisms of each drug delivery system are summarized.

Although nano-delivery systems could boost the biological availability of PTX and diminish adverse effects, there are many problems to overcome. For example, the instability and the efficacy of drug delivery system. With the cross-collaboration of the disciplines of materials science, pharmacology and biology, the development of a more stable, effective and safe PTX delivery system is just around the corner.

References

- [1] Ezrahi S, Aserin A, Garti N. Basic principles of drug delivery systems-the case of paclitaxel [J]. *Advances in Colloid and Interface Science*, 2019, 263: 95 - 130.
- [2] Sharifi-rad J, Quispe C, Patra J K, et al. Paclitaxel: Application in Modern Oncology and Nanomedicine-Based Cancer Therapy [J]. *Oxidative Medicine and Cellular Longevity*, 2021, 2021: 3687700.
- [3] Zhou Zhuxian, Shen Youqing, Zhao Yuliang. Research and Frontiers in Nano-Drug Delivery Systems for Cancer Therapy [J]. *China Basic Science*, 2022, 24 (01): 25 - 36.
- [4] Yang Yanhua, Mao Jiawang, Tan Xiaoli. Research progress on the source, production, and anti-cancer mechanisms of paclitaxel [J]. *Chinese Journal of Natural Medicines*, 2020, 18 (12): 890 - 7.
- [5] Zhai Ruidong, Liu Zhepeng, Zhao Shoujin. Research progress in oral drug preparation of paclitaxel [J]. *Practical Pharmacy and Clinical Remedies*, 2022, 25 (01): 92 - 6.
- [6] Zhou Wei, Zhou Caicun, Meng Shuyan, et al. The anti-tumor effects of lung cancer-targeting long-circulating paclitaxel-containing liposomes [J]. *Tumor*, 2011, 31 (03): 203 - 9.
- [7] Weiss R B, Donehower R C, Wiernik P H, et al. Hypersensitivity reactions from taxol [J]. *Journal of Clinical Oncology*, 1990, 8 (7): 1263 - 8.
- [8] Ma Jingjing, Yang Zheng, Guo Hui, et al. Research progress in improving water solubility and targeting of paclitaxel by prodrugs [J]. *Chinese Journal of New Drug*, 2021, 30 (16): 1489 - 97.
- [9] Haddad R, Alrabadi N, Altaani B, et al. Paclitaxel Drug Delivery Systems: Focus on Nanocrystals’ Surface Modifications [J/OL] 2022, 14 (4).
- [10] Yang Xu, Zou Linghui, Ding Wenya, et al. Research progress on liposome and nanomicelle targeted drug delivery system across blood-brain barrier [J]. *China Journal of Chinese Materia Medica*, 2022, 47 (22): 5965 - 77.
- [11] Zhao Lijuan, Chen Xiang, Yang Min. Research Progress on Paclitaxel Oral Administration System [J]. *Pharmaceutical Biotechnology*, 2020, 27(02): 169-72.
- [12] Shuai Qi, Cai Yue, Zhao Guangkuo, et al. Cell-Penetrating Peptide Modified PEG-PLA Micelles for Efficient PTX Delivery [J]. *International Journal of Molecular Sciences*, 2020, 21(5): 1856.
- [13] Wang Jian, Pei Qing, Xie Zhigang. Research progress of paclitaxel dimer nanoprodugs [J]. *Chemical Research*, 2021, 32 (04): 283 - 9+377.
- [14] Skwarczynski M, Hayashi Y, Kiso Y. Paclitaxel Prodrugs: Toward Smarter Delivery of Anticancer Agents [J]. *Journal of Medicinal Chemistry*, 2006, 49 (25): 7253 - 69.
- [15] Höckel M, Vaupel P. Tumor Hypoxia: Definitions and Current Clinical, Biologic, and Molecular Aspects [J]. *JNCI: Journal of the National Cancer Institute*, 2001, 93 (4): 266 - 76.
- [16] Guo Dongbo, Xu Shuting, Yasen Wumaier, et al. Tirapazamine-embedded polyplatinum (iv) complex: a prodrug combo for hypoxia-activated synergistic chemotherapy [J]. *Biomaterials science*, 2020, 8 (2): 694 - 701.
- [17] Zhou Shiyu, Hu Xiuli, Xia Rui, et al. A Paclitaxel Prodrug Activatable by Irradiation in a Hypoxic Microenvironment [J]. *Angewandte Chemie International Edition*, 2020, 59 (51): 23198 - 205.
- [18] Guo Xiaoshuang, Cheng Yuan, Zhao Xiaotian, et al. Advances in redox-responsive drug delivery systems of tumor microenvironment [J]. *Journal of Nanobiotechnology*, 2018, 16 (1): 74.
- [19] Lu Shaojin, Xia Rui, Wang Jian, et al. Engineering Paclitaxel Prodrug Nanoparticles via Redox-Activatable Linkage and Effective Carriers for Enhanced Chemotherapy [J]. *ACS Applied Materials & Interfaces*, 2021, 13 (39): 46291 - 302.
- [20] Zhu Dingcheng, Yan Huijie, Liu Xin, et al. Intracellularly Disintegrable Polysulfoniums for Efficient Gene Delivery [J]. *Advanced Functional Materials*, 2017, 27 (16): 1606826.
- [21] Chen Meihua, Xiang Rong, Wen Yuan, et al. A whole-cell tumor vaccine modified to express fibroblast activation protein induces antitumor immunity against both tumor cells and cancer-associated fibroblasts [J]. *Scientific Reports*, 2015, 5 (1): 14421.
- [22] Huang Da, Zhuang Yaping, Shen Hong, et al. Acetal-linked PEGylated paclitaxel prodrugs forming free-paclitaxel-loaded pH-responsive micelles with high drug loading capacity and improved drug delivery [J]. *Materials Science and Engineering: C*, 2018, 82: 60 - 8.

- [23] Gui Gang, Xu Qin. Research progress of paclitaxel nanometer drug delivery systems [J]. *Acta Medicinæ Sinica*, 2020, 33 (02): 175 - 9.
- [24] Fei Zerong, Li Fengyun, Gong Jia-ning, et al. Research progress on nano-drug delivery systems for antitumor active components of traditional Chinese medicine [J]. *Chinese Traditional and Herbal Drugs*, 2021, 52(24): 7658-67.
- [25] Ding Dawei, Sun Bingjun, Cui Weiping, et al. Integration of phospholipid-drug complex into self-nanoemulsifying drug delivery system to facilitate oral delivery of paclitaxel [J]. *Asian Journal of Pharmaceutical Sciences*, 2019, 14 (5): 552 - 8.
- [26] Bruch G E, Fernandes L F, Bassi B L T, et al. Liposomes for drug delivery in stroke [J]. *Brain Research Bulletin*, 2019, 152: 246 - 56.
- [27] Yang Mei, Gao Yutong, Zhang Xinyu, et al. Nano delivery system of modified carbohydrate [J]. *Chemistry of Life*, 2021, 41(03): 452 - 61.
- [28] Li Man, Shi Kairong, Tang Xian, et al. pH-sensitive folic acid and dNP2 peptide dual-modified liposome for enhanced targeted chemotherapy of glioma [J]. *European Journal of Pharmaceutical Sciences*, 2018, 124: 240 - 8.
- [29] George A, Shah P A, Shrivastav P S. Natural biodegradable polymers-based nano-formulations for drug delivery: A review [J]. *International Journal of Pharmaceutics*, 2019, 561: 244 - 64.
- [30] Lebleu C, Plet L, Moussy F, et al. Improving aqueous solubility of paclitaxel with polysarcosine-b-poly (γ -benzyl glutamate) nanoparticles [J]. *International Journal of Pharmaceutics*, 2023, 631: 122501.