Paclitaxel Nano-Delivery Systems: A Comprehensive Review

Ping Ma¹ and Russell J. Mumper¹,²*

¹Center for Nanotechnology in Drug Delivery, Division of Molecular Pharmaceutics, UNC Eshelman School of Pharmacy; University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA
²UNC Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, NC 27599, USA

Abstract

Paclitaxel is one of the most effective chemotherapeutic drugs ever developed and is active against a broad range of cancers, such as lung, ovarian, and breast cancers. Due to its low water solubility, paclitaxel is formulated in a mixture of Cremophor EL and dehydrated ethanol (50:50, v/v) a combination known as Taxol. However, Taxol has some severe side effects related to Cremophor EL and ethanol. Therefore, there is an urgent need for the development of alternative Taxol formulations. The encapsulation of paclitaxel in biodegradable and non-toxic nano-delivery systems can protect the drug from degradation during circulation and in-turn protect the body from toxic side effects of the drug thereby lowering its toxicity, increasing its circulation half-life, exhibiting improved pharmacokinetic profiles, and demonstrating better patient compliance. Also, nanoparticle-based delivery systems can take advantage of the enhanced permeability and retention (EPR) effect for passive tumor targeting, therefore, they are promising carriers to improve the therapeutic index and decrease the side effects of paclitaxel. To date, paclitaxel albumin-bound nanoparticles (Abraxane®) have been approved by the FDA for the treatment of metastatic breast cancer and non-small cell lung cancer (NSCLC). In addition, there are a number of novel paclitaxel nanoparticle formulations in clinical trials. In this comprehensive review, several types of developed paclitaxel nano-delivery systems will be covered and discussed, such as polymeric nanoparticles, lipid-based formulations, polymer conjugates, inorganic nanoparticles, carbon nanotubes, nanocrystals, and cyclodextrin nanoparticles.

Keywords: Nanoparticles; Poly(lactic-co-glycolic acid); Nanocapsules; Drug-polymer conjugates; Multi-drug resistance; Solid lipid nanoparticles

Abbreviations: Ab: Antibody; Au NPs: Gold Nanoparticles; AUC: Area Under the Curve; BBB: Blood-Brain Barrier; BrC16: 2’-2-Bro-Mo-hexadecanoyl; Brij 78: Polyoxyyl 20-Stearyl Ether; BSA: Bovine Serum Albumin; C22-PX: 2’-Behenoyl-Paclitaxel Conjugate; CD: Cyclodextrin; CHO: Cholesterol; CMC: Critical Micelle Concentration; CNT: Carbon Nanotubes; DHA: Docosahexaenoic Acid; DLPC: 1,2-Dilauroylphosphatidylcholine; DMAB: Didodecyl(dimethyammonium) Bromide; DNA: Deoxyribonucleic Acid; DOPC: 1,2-Dioleoyl-Sn-Glycero-3-Phosphocholine; DOTAP: N-[1-[2,3-Dioleoxoy]Propyl]-N,N,N-Trimethyl-Ammonium Methysulfate; DSPC: Dipalmitoyl-Phosphatidylcholine; DSCPC: 1,2-Distearoyl-Sn-Glycero-3-Phosphocholine; EE: Entrapment Efficiency; EPC: Egg Phosphatidylcholine; EPR: Enhanced Permeability and Retention; FA: Fatty Acid; FITC: Fluorescein Isothiocyanate; h: Hour; HA: Hyaluronic Acid; HER2: Human Epidermal Growth Factor Receptor 2; HO: Hydrotropic Oligomer-Glycol Chitosan; HPG: Hyperbranched Polyglycerol; HPMA: N-[2-Hydroxypropyl] Methacrylamide; HSA: Human Serum Albumin; HSPC: Hydrogenated Soybean Phosphatidylcholine; IC₅₀: Half Maximal Inhibitory Concentration; i.p: Intraperitoneal; l.v: Intravenous; kg: Kilogram; LRPL: Low-Density Lipoprotein Receptor-Related Protein 1; mAb: Monoclonal Antibody; MDR: Multiple Drug Resistance; mg: Milligram; min: Minute; mL: Milliliter; MNT: Montmorillonite; MNP: Magnetic Nanoparticle; mPEG: Methoxy Poly[Ethylene Glycol]; MTD: Maximum Tolerated Dose; NC: Nanocapsule; NSCLC: Non-Small Cell Lung Cancer; ng: Nanogram; NMR: Nuclear Magnetic Resonance; NP: Nanoparticle; OSA: Octyl-Modified Bovine Serum Albumin; PAGA: Poly[Alkyl Cyanoacrylate]; PAMAM: Poly[Amidoamine]; PBAE: Poly[ß-Amino Ester]; PCBAs: Poly[Butyl Cyanoacrylate]; PCL: Poly [ε-Caprolactone]; PE: Phosphatidyl Ethanolamine; PEEP: Poly[Ethyl Ethylene Phosphate]; PEG: Poly[Ethylene Glycol]; PEG-DSPE: Polyethylen Glycol-Distearylphosphatidylethanolamine; PEI: Polyethylenimine; PEO-b-PCL: Poly[Ethylene Oxide]-block-Poly[ε-Caprolactone]; PEO-PbAE: Poly[Ethylene Oxide]-Modified Poly[ß-Amino Ester]; PEO-PPO-PEO: Poly[Ethylene Oxide]-Poly[Propylene Oxide]-Poly[Ethylene Oxide]; PG: Poly[2-Ethyl-2-Oxazoline]; PG: Poly[L-Glutamic Acid]; PGG: Poly[L-γ-Glutamyl-Glutamine]; P-gp: P-glycoprotein; PLA: Poly[L-Lactide]; PLGA: Poly[Lactic-Co-Glycolic Acid]; Pluronic P85: Poly[Oxyethylene-b-Oxypropylene-b-Oxyethylene]; PEEA: Poly[2-Aminoethyl Ethylene Glycol]; PEG: Poly[Ethylene Glycol]; MTD: Maximum Tolerated Dose; NC: Nano-Montmorillonite; MNP: Magnetic Nanoparticle; mPEG: Methoxy Polyethylene Glycol 1000 Succinate; µg: Microgram; µL: Microliter; VIP: Vasoactive Intestinal Peptide; vs: Versus

Paclitaxel and its Limitations

Paclitaxel (PX), isolated from the bark of Pacific Yew (Taxus brevifolia), which was first discovered by Mrs. Monroe E. Wall and Mansukh C. Wani, is a white crystalline powder with the melting point

*Corresponding author: Russell J. Mumper, Vice Dean and John A. McNeill Distinguished Professor, Center for Nanotechnology in Drug Delivery, Division of Molecular Pharmaceutics, UNC Eshelman School of Pharmacy CB# 7355, 100G Beard Hall, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-7355, USA, Tel: +1-919-966-1271; Fax: +1-919-966-6919; E-mail: mumper@email.unc.edu

Received January 17, 2013; Accepted February 15, 2013; Published February 18, 2013

Citation: Ma P, Mumper RJ (2013) Paclitaxel Nano-Delivery Systems: A Comprehensive Review. J Nanomed Nanotechol 4: 164. doi:10.4172/2157-7439.1000164

Copyright: © 2013 Ma P, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
of ~210°C (Figure 1). It is one of the most effective chemotherapeutic drugs and is mainly used to treat lung, ovarian, and breast cancer, etc [1]. The mechanism of action of PX is to promote and stabilize microtubules and inhibit late G2 or M phases of cell cycle, thereby causing the cell death. The major limitation of PX is its low water solubility (~0.4 µg/mL); thus, it is formulated in organic solvents of polyoxyethylated castor oil (Cremophor EL) and dehydrated ethanol (50/50, v/v) under the trademark “Taxol”. However, Cremophor EL is known to cause serious side effects, such as hypersensitivity reactions [2]. As a result, prolonged infusion time and pretreatments are required. Moreover, the presence of Cremophor EL alters the pharmacokinetic profile of PX in vivo which was described as unpredictable non-linear plasma pharmacokinetics when PX was formulated in Cremophor EL [3]. In addition, PX is a substrate of P-glycoprotein (P-gp), which actively pumps PX out of the cells and induces drug resistance [4]. To overcome this problem, several P-gp inhibitors, such as verapamil [5] and PSC 833 [6], were co-administered with Taxol but the results were disappointing due to their toxicity and/or alteration of PX pharmacokinetics and biodistribution. Nano-delivery systems are promising vehicles in drug delivery because they improve solubility of hydrophobic drugs, such as PX, and generally have low toxicity as well. Abraxane®, a PX albumin-bound NP formulation with the particle size of ~130 nm, was approved by the FDA in 2005 for the treatment of metastatic breast cancer. This formulation had demonstrated some advantages in terms of reduced toxicity compared to Taxol. In addition, the total dose can be administered within 30 min without pretreatment. However, whether reduced toxicity compared to Taxol. In addition, the total dose can be administered within 30 min without pretreatment. However, whether reduced toxicity compared to Taxol. In addition, the total dose can be administered within 30 min without pretreatment.

Advantages of Nanoparticle-Based Paclitaxel Delivery Systems

Nanoparticle delivery systems have attracted increasing attention in recent years, especially for cancer therapies. As an effective chemotherapeutic agent, PX has been formulated in various nano-delivery systems which have several advantages over the standard-of-care therapy. First, the aqueous solubility of PX can be greatly enhanced when it is conjugated with water-soluble polymers, or encapsulated into lipid-based NPs. Second, they are small in size (several to several hundred nanometers in diameter), which enables the preferential delivery of PX into the tumor site due to the enhanced permeability and retention (EPR) effect. Third, they can escape the recognition of reticuloendothelial system (RES) in healthy tissues and therefore reduce the side effects of the drug. As a consequence, higher maximum tolerated doses (MTD) of NPs are realized. It should be noted that, in general, the addition of polyethylene glycol (PEG) on the surface of NPs is required to avoid RES clearance [7]. Fourth, the pharmacokinetic profiles of the drug from NPs is improved, for example, increasing the half-life and tumor accumulation of PX. Last, but not the least, the surface of PX NP systems can be functionalized with active ligands for targeting purpose, which in-turn will further increase the tumor uptake and decrease the side effects of the drug. For more details about the advantages of NP-based drug delivery systems, please refer to the referenced review articles [8-12].

Polymeric Nanoparticles

A summary of PX-loaded polymeric NPs is shown in Table 1.

Poly (lactic-co-glycolic acid) (PLGA) Nanoparticles

PLGA is one of the most widely used biodegradable co-polymers for the development of nano-delivery systems because it undergoes hydrolysis in the body and produces non-toxic products of lactic acid and glycolic acid, and eventually carbon dioxide and water. Since the body effectively deals with both degradants, the systemic toxicity associated with PLGA is minimal.

PX-loaded PLGA NPs have been engineered by different methods, such as o/w emulsion-solvent evaporation [13,14], nanoprecipitation [15] and interfacial deposition methods [16]. In most cases, PX was released from PLGA NPs in a biphasic pattern with a fast initial release during the first 1-3 days followed by a slow and continuous release [13,14,16-18]. PX-encapsulated PLGA NPs demonstrated enhanced in vitro cytotoxicity as compared to free PX in various cancer cell lines, such as glioma C6 cells [17], NCI-H69 human small cell lung cancer cells [16], MCF-7 [18] and HeLa cells [15,18]. Furthermore, in vivo PX-loaded PLGA NPs showed significantly better tumor growth inhibition effect with transplantable liver tumors [15].

The surface of PLGA NPs was modified for improved drug delivery. Chitosan-coated PLGA NPs exhibited slower in vitro drug release compared to non-coated PLGA NPs and significantly changed the zeta potential from the negative charge of -30.1 mV for PLGA NPs alone to the positive charge of 26 mV, which facilitated drug cell uptake than uncoated NPs [19]. Chakravarthi et al. [20] showed a 4-10-fold increase in cellular accumulation of PX and enhanced cytotoxicity when applied chitosan-modified PLGA NPs. In addition to chitosan, didodecyldimethylammonium bromide (DMAB), a cationic surfactant, was also applied to absorb on the surface of PX-loaded NPs by electrostatic attraction. Upon the addition of DMAB, the negatively-charged NPs shifted to become positively-charged [21]. This DMAB modified PX-incorporated PLGA NPs completely inhibited inital proliferation in a rabbit vascular injury model [22].

PLGA NPs were also optimized using different emulsifiers. It is known that the employed emulsifiers/stabilizers could have strong influence on the properties of produced NPs, such as morphology, particle size, drug entrapment efficiency, in vitro release behavior, cellular uptake, in vitro cytotoxicity, pharmacokinetics and biodistribution, and as a consequence therapeutic efficacy [23]. Poly (vinyl alcohol) (PVA) is the most commonly used emulsifier. Other emulsifiers were also applied in PLGA NPs. For example, when α-tocopheryl polyethylene glycol 1000 succinate (TPGS) was utilized in PX-loaded PLGA NPs as the surfactant emulsifier, the PLGA/TPGS NPs could achieve drug encapsulation efficiency of 100% [24], better controlled drug release kinetics [25], and enhanced cellular uptake and cytotoxicity [26] compared to that of PVA-emulsified PLGA NPs. The TPGS-emulsified
PLGA NPs achieved 10-fold greater bioavailability than Taxol after oral administration [27]. Phospholipids were also used as natural emulsifiers in PLGA NPs, such as 1,2-dilauroylphosphatidylcholine (DLPC) [28] and dipalmitoyl-phosphatidylcholine (DPPC) [29]. Both of the emulsifiers demonstrated greater benefits compared to PVA. Montmorillonite (MMT) was also incorporated into PX-loaded PLGA NPs as both a matrix component and co-emulsifier. The addition of MMT did not change particle size, drug entrapment efficiency, or the in vitro drug release from PLGA NPs. Importantly, the PX-loaded PLGA/MMT NPs enhanced drug cellular uptake over that of pure PLGA NPs by 57-177% and 11-55% in Caco-2 and HT-29 cells, respectively [30]. The PX-loaded PLGA/MMT NPs were further decorated with human epidermal growth factor receptor 2 (HER2) antibodies for targeting purpose, and these targeted NPs exhibited a 12.7-fold enhanced cytotoxicity compared to non-targeted NPs in SK-BR-3 cells [31]. Other targeting ligands, such as RGD [32] and transferrin [33-35], have also been conjugated to PX-encapsulated PLGA NPs for better antitumor efficacy. For example, PX-incorporated PLGA NPs with

| Polymer | Modification | NP Preparation Method | % EE* | Status | References |
|---------|--------------|-----------------------|-------|--------|------------|
| PLGA    | —            | emulsion-solvent evaporation | 85    | in-vitro | [14]       |
|         | PLGA, PLGA-PEG, PCL-PEG | nanoprecipitation | 70    | in-vivo  | [15]       |
|         | Poloxamer 188 | interfacial deposition | >90   | in-vitro | [16]       |
|         | TPGS (emulsifier) | emulsion-solvent evaporation | 100   | in-vitro | [24]       |
|         | DLPC (emulsifier) | emulsion-solvent evaporation | 15-56 | in-vitro | [28]       |
|         | DPPC (emulsifier) | emulsion-solvent evaporation | 34-45 | in-vitro | [29]       |
|         | chitosan     | emulsion-solvent evaporation | 75-79 | in-vitro | [19]       |
|         | DMAB         | emulsion-solvent evaporation | 47    | in-vivo  | [21]       |
|         | MMT          | emulsion-solvent evaporation | ~50   | in-vitro | [30]       |
|         | MMT, HER2 (targeting) | emulsion-solvent evaporation | ~50   | in-vitro | [31]       |
|         | RGD (targeting) | emulsion-solvent evaporation | 60-65 | in-vivo  | [32]       |
| Pluronic P85, transferrin (targeting) | nanoprecipitation | 70-76 | in-vivo  | [33]       |
| PE-PCL  | —            | solvent displacement | >95   | in-vivo  | [63,64]    |
|         | PCL-pluronic F68 | emulsion-solvent evaporation | 84    | in-vivo  | [72]       |
|         | PCL-pluronic F68, DMAB | modified solvent displacement | 76-88 | in-vivo  | [193]      |
| mPEG-PCL, Angiopep (targeting) | emulsion and evaporation | 90    | in-vitro | [67,68]    |
| mPEG-PCL | —            | solid dispersion | 98    | in-vivo  | [69]       |
| PVP-PCL  | —            | modified nanoprecipitation | 85    | in-vitro | [73]       |
| PEG-PCL  | —            | co-solvent extraction | —     | in-vitro  | [66]       |
| PG-PCL, folic acid (targeting) | dialysis | —     | in-vitro  | [70]       |
| PCL-g-PVA | —            | dialysis | —     | in-vitro  | [74]       |
| PEI-Ox-PCL | —            | dialysis | 5-76  | in-vitro  | [75]       |
| PCL-PEEP, galactosamine, (targeting) | dialysis | —     | in-vitro  | [76]       |
| mPEG-PCL-PPEEA | emulsion-solvent evaporation | >90 | in-vivo  | [77]       |
| PLA-PEG | —            | thin film | 65    | in-vivo  | [49]       |
| PLA-PEG (star-branch) | solvent evaporation | 6-56 | in-vitro  | [48]       |
| PVA-PEG | —            | solvent evaporation | 20-62 | in-vitro | [50]       |
| Poly(γ-glutamic acid), galactosamine (targeting) | solvent evaporation | 50-54 | in-vitro  | [51]       |
| PLA-PEG-PLA, PEG-PLA-PEG | solvent evaporation | 14-31 | in-vitro  | [52,53]    |
| cholic acid | —            | dialysis | 92    | in-vitro  | [78,194]  |
| glycercy monooleate | emulsion-solvent evaporation | 98-100 | in-vitro  | [80]       |
| niPEG, cholesterol | —            | dialysis | 70    | in-vivo  | [81]       |
| N-acetyl histidine | —     | in-vitro  | [82]       |
| stearic acid, glutaraldehyde | ultrasonication | 94-99 | in-vitro  | [83]       |
| Gelatin | —            | desolvation | > 80  | in-vivo  | [109-112]  |
| HA      | —            | desolvation | 90    | in-vivo  | [95]       |
| PBCA    | —            | dialysis | —     | in-vitro  | [96]       |
| surfactants (dextran 70, cholesterol, PVA, and lecithin) | polymerization | 60-80 | in-vitro  | [100]      |
| Albumin | —            | high-pressure homogenization | —     | approved | [88]       |
| CREKA and LyP-1, peptides (targeting) | —     | in-vitro  | [91]       |
| folic acid (targeting) | desolvation | 95    | in-vitro  | [92]       |
| octaldehyde | —     | in-vitro  | [93]       |
| HPG     | PE-PG        | solvent evaporation | —     | in-vivo  | [102]      |

Table 1: Summary of PX-loaded Polymeric NPs. (*EE=Entrapment Efficiency).
transferrin ligand showed 5-fold enhanced cytotoxicity over that of non-targeted NPs or Taxol. The mice treated with targeted NPs demonstrated complete tumor inhibition and significantly prolonged survival compared to all controls after intratumoral injection in a PC3 prostate cancer mouse model [34].

Poly(lactide) (PLA) Nanoparticles

PLA is another widely used matrix material for polymeric NP preparation because of its biodegradable and safe properties. Methoxy poly(ethylene glycol)-poly(lactide) co-polymer (mPEG-PLA) was synthesized and incorporated into the NPs to provide long circulating properties. The in vitro cytotoxicity of these NPs increased by 33.3-fold over that of Taxol after 24 h in MCF-7 cells. In vivo pharmacokinetic studies demonstrated the AUC and half-life of PX mPEG-PLA NPs in rat plasma were 3.1- and 2.8-fold greater than that of Taxol, respectively [36,37]. PX-loaded NPs with PLA and mPEG-PLA at various ratios of 100/0, 75/25, 50/50, 25/75, and 0/100 were evaluated. It was found that as the mPEG-PLA component in the blend increased, the particle size of NPs and the glass transition temperature of PLA decreased, while the zeta potential of NPs and in vitro drug release increased [38]. Copolymers of PLA/Tween 80 were synthesized and PX-loaded PLA/Tween 80 NPs were shown to be about 3-fold more toxic than PX-loaded PLGA NPs in glioma C6 cells [39]. TPGS was also utilized as an emulsifier in PLA NPs. The Feng group [40] synthesized PLA-TPGS co-polymers using a ring-opening polymerization method. Compared to PX-loaded NPs, the PLA/TPGS NPs showed 1.8- and 1.4-fold enhanced cellular uptake of PX in HT-29 and Caco-2 cells, respectively. The IC50 value of PLA/TPGS NPs was also found to be 40% lower than that of Taxol in HT-29 cells [41].

In vivo this PX-loaded PLA/TPGS NP formulation achieved a 27.4- and 1.6-fold greater half-life and AUC, respectively, in a xenograft tumor model when compared to Taxol [42]. PX-loaded PLA/TPGS NPs with various ratios of PLA and TPGS were evaluated, and the results demonstrated that the PLA/TPGS ratio had little effect on particle size. However, PLA/TPGS NPs with PLA/TPGS ratio of 89/11 were the optimized formulation in terms of drug entrapment efficiency, cellular uptake, and in vitro cytotoxicity [43]. Folate-decorated PX-loaded PLA-TPGS NPs were further formulated to achieve even better therapeutic effect [44,45]. Other targeted PX-loaded PLA NPs, such as HER2 [46], bixin and folic acid [47], were also reported to greatly improve efficacy both in vitro and in vivo.

PLA co-polymer micelles have also been reported for PX delivery [48-53]. For example, PX-loaded PEG-b-PLA micelles were prepared and the mechanism of action was investigated. It was found that the micelles first interacted with cell membranes and then the loaded PX was released. After that, PX was internalized into the cells by lipid/raft/caveolae-mediated endocytosis pathway. In this way, PEG-b-PLA micelles were able to overcome multiple drug resistance (MDR) which was confirmed by the increased cellular uptake of PX in resistant A2780/T cells. The results also suggested PEG-b-PLA micelles could inhibit P-gp efflux [49]. Pauxceed® is a polymeric micelle formulation where PX is encapsulated in PLA-b-mPEG diblock co-polymers. The micellar formulation was found to be more efficacious than Taxol at the maximum tolerated dose (MTD) upon intraperitoneal injection in an MV-522 lung tumor bearing mouse model [54]. Currently, Pauxceed® is in phase II clinical trials [55]. Genexol-PM remains the most successful PX micellar formulation to date, which is composed of PLA-b-PEG diblock co-polymers [56]. A preclinical in vivo study with Genexol-PM was found to have 3-fold increased MTD and 2-3-fold higher drug concentration in various tissues and more importantly in tumors, compared to Taxol in nude mice. The in vivo antitumor efficacy of Genexol-PM was also significantly improved [57]. In phase I clinical studies, the MTD dose was determined to be 180 mg/m2. The plasma AUC and Cmax increased by 3- and 4-fold, respectively, when the dose increased from 80 to 200 mg/m2 [58], which suggested the pharmacokinetics of Genexol-PM were dose-proportional. In phase II clinical studies, Genexol-PM was found to be safe and effective in patients with metastatic breast or advanced pancreatic cancer [59,60]. Phase III clinical studies are currently in process.

Trilek co-polymers of PLA-PEG-PLA and PEG-PLA-PEG were synthesized as carriers for PX. The results demonstrated that the drug release from PEG-PLA-PEG micelles was slower than from PLA-PEG-PLA micelles, and PEG contents in micelles influenced the Stealth properties of the micelles. Both of micelles showed 4-fold decreased monocyte cell uptake compared to PLA micelles [52,53]. In another study, a four-armed (star-branched) co-polymer of PLA and PEO was synthesized. Compared to di- and tri-block co-polymers, the star-branched micelles exhibited better controlled and more complete release manner over 2 weeks. Furthermore, the star-shaped micelles had smaller particle size which had the potential to take more advantages of the EPR effect in cancer therapy [48].

In addition to PEG-modified PLGA micelles, PX-incorporated PVP-b-PLA micelles were prepared by Gaucher et al. [50] by an o/w emulsion solvent evaporation method. The cryoprotectant property of PVP allowed the same particle size upon reconstitution after lyophilization, while PEG-modified PEG-b-PLA micelles did not. For targeting purpose, a galactosamine targeted PX-loaded micelle formulation composed of poly(ε-glutamic acid) and PLA was developed. The targeted NP formulation showed the most significant antitumor efficacy compared to other controls and importantly more drug accumulation in tumors was observed in hepatoma tumor-bearing nude mice [51].

Poly(ε-caprolactone) (PCL) Nanoparticles

Deshpande et al. [61] developed poly(ethylene oxide)-modified poly(ε-caprolactone) (PEO-PCL) NPs for co-delivery of PX and C2- ceramide (an apoptotic signaling molecule) to overcome MDR. The prepared PEO-PCL NPs had high drug entrapment efficiency of >95% with PX and C2-ceramide drug loading of 10% (w/w). The particle size of the NPs was ~270 nm in diameter. In resistant human ovarian cancer SKOV3TR cells, PX and C2-ceramide loaded PEO-PCL NPs showed 100-fold enhanced cytotoxicity compared to free PX [62]. In vivo PEO-PCL NPs demonstrated remarkable tumor growth inhibition in both wild-type SKOV3 and resistant SKOV3TR xenograft mouse models compared to all the controls. The results indicated the combination of PX and C2-ceramide incorporated into PEO-PCL NPs overcame MDR in ovarian cancer [63]. The combination of PX and tamoxifen loaded PEO-PCL NPs was also evaluated both in vitro and in vivo. In vitro this formulation lowered the IC50 by 10- and 3-fold in SKOV3 and resistant SKOV3TR cells, respectively, when compared to free PX. The in vivo PEO-PCL NPs significantly enhanced antitumor efficacy and no acute toxicity was observed [64]. Later, polymeric NP systems for the co-delivery of both PX and P-gp silencing siRNA were developed. In order to do that, poly(ethylene oxide)-modified poly(β-amino ester) (PEO-PbAE) and PEO-PCL NPs were formulated to encapsulate P-gp silencing siRNA and PX, respectively. The co-administration of P-gp silencing siRNA-loaded PEO-PbAE NPs and PX-loaded PEO-PCL NPs completely reversed the MDR based on the fact that the similar cytotoxicity activity of NPs in both sensitive SKOV3 and resistant SKOV3TR cells [65].

Similarly, PEG-PCL polymeric micelles were prepared by a co-
solvent extraction technique. A series of PX prodrugs were synthesized and encapsulated into micelles and it turned out that 7'-hexonoate PX loaded PEG-PCL NPs demonstrated improved pharmacokinetic profile compared to Taxol [66]. Xin et al. [67] prepared mPEG-PCL NPs to encapsulate PX by an emulsion-solvent evaporation method. In vitro PX-loaded mPEG-PCL NPs showed higher cytotoxicity than Taxol and PCL NPs. Importantly, mPEG-PCL NPs increased the mean survival time to 28 days versus 20 and 23 days for Taxol and PCL NPs, respectively, in a C6 tumor-bearing mouse model. Angiopep, a peptide, was further conjugated on mPEG-PCL NPs to target the low-density lipoprotein receptor-related proteins over-expressed on blood-brain barrier (BBB) and facilitate chemotherapeutic agent of PX across BBB [68]. Similarly, Wang and co-workers [69] developed PX-loaded mPEG-PCL NPs by solid dispersion method without the use of organic solvents. The NPs achieved drug loading of 25.6% (w/w) and an entrapment efficiency of 98%. The MTD of NPs was 2.6-fold greater than Taxol in BALB/c mice after bolus intravenous injection. The tissue distribution of PX in NPs was different from that of Taxol and significantly greater tumor accumulation was observed. Chen et al. [70] prepared more complicated PEG-PCL NPs where a PEG-PCL di-block co-polymer was hyperbranched aliphatic polyester Boltorn H40, and then folic acid was further coated on the surface of the NPs. The PX-loaded NPs demonstrated increased cytotoxicity in vitro.

In addition to PEG-modified PCL NPs, a PX-loaded PCL/pluronic F68 NP (PCL/F68) formulation was prepared using a solvent evaporation method. The incorporation of pluronic F68 into PCL NPs formed pores and thus expedited drug release from NPs. The PX-loaded PCL/F68 NPs had increased cellular uptake and enhanced toxicity as compared to PCL NPs and Taxol in resistant MCF-7/TAX cells [71]. In vivo the PCL/F68 NPs demonstrated the improved tumor inhibitory activity after a single intratumoral injection compared to multiple intraperitoneal injections of Taxol in a murine breast cancer model [72]. DMAB was further adsorbed on PCL/F68 NPs via charge-charge interaction to enhance NPs internalized into the arterial wall in animal angioplasty models [22].

Other PX-loaded PCL-based NPs have also been reported. For example, PVP-b-PCL NPs demonstrated significantly superior antitumor efficacy to Taxol in hepatic H22 tumor-bearing mice [73]. PCL-grafted PVA (PCL-g-PVA) NPs were engineered and PX-loaded PCL-g-PVA NPs were characterized and exhibited reduced drug release rate profiles [74]. PX-loaded poly(2-ethyl-2-oxazoline) (PEtOz)-PCL NPs [75], galactosamine targeted poly(ethyl ethylene phosphate) (PEEP)-PCL NPs [76], and mPEG-PCL-poly(2-aminoethyl ethylene phosphate) (mPEG-PCL-PPEEA) NPs [77] were reported to have better antitumor activity than Taxol in vitro and/or in vivo.

**Chitosan Nanoparticles**

Kim et al. [78] synthesized PX-loaded cholic acid-modified chitosan NPs using a simple dialysis method with drug loading of 10% (w/w). This NP formulation showed faster cellular uptake and better therapeutic efficacy in SCC7 tumor-bearing mice compared to Taxol. Hydrotrropic oligomer-glucyol chitosan (HO-GC) was synthesized to enhance the aqueous solubility of PX in NPs, and achieved a higher drug loading up to 20% and maximum entrapment efficiency of 97%. The PX-encapsulated HO-GC NPs demonstrated a sustained in vitro release profile, and importantly PX predominantly accumulated in tumor site in vivo [79]. Glycerol monooleate-modified chitosan NPs loaded with PX was reported to increase by 4- and 1,000-fold the cellular uptake and cytotoxicity, respectively, in MDA-MB-231 cells as compared to free PX [80]. A more complex chitosan derivative modified with mPEG and cholesterol (CHO) was synthesized for PX delivery. The mPEG-CHO-chitosan NPs showed similar cytotoxicity as free PX in vitro, but significantly slower tumor growth rate and improved life span compared to free PX at the dose of 10 mg/kg in a tumor-bearing mouse model [81]. A pH-sensitive self-assembled modified chitosan NP formulation was developed based on the fact that hydrophobic acetyl histidine modified chitosan could self-assemble at neutral pH but disassemble at slightly acidic environment due to the protonation of its imidazole group. The PX-loaded modified NPs were then confirmed to endocytose into cells and release drug in acidic endosomes [82]. In another study, the hydrophobic fatty acid of stearic acid was grafted to chitosan oligosaccharide and the micelles were self-assembled. Glutaraldehyde was then crosslinked to the shells of NPs to further increase the stability of the micelles. The PX-loaded glutaraldehyde-crosslinked chitosan oligosaccharide micelles were found to enhance PX solubility, and had less burst release and slower drug release compared to non-crosslinked NPs [83].

**Albumin Nanoparticles**

Albumin is a versatile natural protein carrier for targeted drug delivery. Human serum albumin (HSA) is the most abundant plasma protein in the human blood with a half-life of 19 days. It can reversibly bind hydrophobic drug substances, transport them in the body and release drugs at cell surface [84]. In addition, albumin is actively transported into tumors via a selective over-expression of a 60 kDa glycoprotein (gp60) receptor (albondin) [85]. Albumin-bound PX NPs (Abraxane®) was approved by US FDA in 2005 for the treatment of metastatic breast cancer in patients who fail other chemotherapy or relapse. In October 2012, the FDA approved Abraxane® to treat non-small cell lung cancer (NSCLC), the most common form of lung cancer [86]. The albumin-bound PX NPs have an average particle size of about 130 nm. Since this NP formulation completely eliminates Cremophor EL and ethanol in Taxol, it is administered in a shorter period of 30 min with no need for premedication. For more details about Abraxane® product, please refer to the review articles [87-90]. Interestingly, targeted Abraxane formulations with two peptides of CREAKA and LyP-1 (CGKNKRTRGC), respectively, were developed and LyP-1-Abraxane demonstrated significantly improved antitumor efficacy compared to untargeted Abraxane in an MDA-MB-435 xenograft mouse model [91]. In addition to human albumin, Zhao et al. [92] prepared PX-loaded bovine serum albumin (BSA) NPs using a desolvation method, and subsequently coated NPs by folic acid for targeting. The folate-decorated NPs exhibited high stability and desired surface properties which specifically targeted to human prostate cancer PC3 cells. In another study, a novel octyl-modified bovine serum albumin (OSA) was synthesized to improve the lipophilicity of albumin and facilitate to form PX-loaded core-shell nanomicelles. The OSA NPs had smaller particle size, higher drug entrapment efficiency, and greater stability compared to unmodified NPs [93].

**Hyaluronic Acid (HA) Nanoparticles**

HA is a natural non-toxic and biodegradable polysaccharide. Recently, it has been widely used as a targeting agent since most malignant solid tumors over-express HA receptors, such as CD44 and hyaluronan-mediated motility receptor (RHAMM) [94]. PX-loaded HA NPs were reported by Al-Ghananeem et al. [95]. Although the in vitro cytotoxicity of NPs was comparable to free PX in both MDA-MB-231 and ZR-75-1 breast cancer cells, PX NPs showed superior antitumor efficacy to free PX when intratumorally injected into 7,12-dimethylbenz[a]anthracene-induced breast cancer tumor-bearing rats. A modified HA was synthesized with an amine-terminated...
hydrotropic oligomer, which enhanced PX solubility and achieved the drug loading up to 20.7%. The NPs were found to selectively target SCC-7 cells which over-expressed CD44, and exhibited enhanced cytotoxicity in this cell line than normal fibroblast CV-1 cells [96].

**Poly(butyl cyanoacrylate) (PBCA) Nanoparticles**

Biodegradable poly-(alkyl cyanoacrylate) (PACA) NPs have been widely used for the delivery of various active pharmaceutical ingredients during recent 10 years. Among all different kinds of PACA NPs, poly-(butyl cyanoacrylate) (PBCA) is the most widely used as a carrier because it interacts with a variety of drugs [97]. Huang et al. [98] developed PX-loaded PBCA NPs with the addition of pluronic F127 as the surfactant using a mini-emulsion method. It was found that the drug loading and entrapment efficiency of pluronic F127 modified NPs were significantly increased. The PBCA NPs prepared from the mini-emulsions showed a gradual drug release up to 80% within 96 h. Hyaluronic acid (HA)-coated PBCA NPs encapsulated with PX were reported to reduce the initial burst release of the drug and decrease the cytotoxicity of placebo HA-PBCA NPs compared to non-HA coated PBCA NPs. Importantly, PX-loaded HA-PBCA NPs enhanced by 9.5-fold the cellular uptake in Sarcoma-180 cells and showed more potent antitumor inhibition activity versus non-HA coated PX PBCA NPs when injected i.v. into Sarcoma-180 tumor-bearing mice [99]. Mitra and Lin [100] studied the effect of various surfactants on PX-encapsulated PBCA NPs. The surfactants of dextran 70, cholesterol, PVA, and lecithin were utilized and the results demonstrated that the NPs incorporated with surfactants were better than without surfactants in terms of particle size and stability. Among the four surfactants, the natural lipids of cholesterol and lecithin were superior to the other two in terms of producing NPs with smaller particle size, higher zeta potential and drug entrapment efficiency, and better controlled drug release profiles.

**Hyperbranched Polyglycerol (HPG) Nanoparticles**

HPG is a water-soluble polymer with minimal toxicity. It is one of a few hyperbranched polymers that can be synthesized in a controlled manner [101]. Mugabe et al. [102] loaded PX into two types of modified HPG NPs (HPG-C10-PEG and PEI-C18-HPG) using a solvent evaporation method. The particle size of both NPs was less than 20 nm. The PX was released up to 80% from HPG-C10-PEG while only 40% from PEI-C18-HPG. PX-loaded HPG-C10-PEG NP formulation was better tolerated and exhibited significantly improved antitumor efficacy in vivo as compared to Taxol, although the in vitro cytotoxicity was slightly decreased compared to Taxol.

**Poly (Ethylene Glycol)-Phosphatidyl Ethanolamine (PEG-PE) Nanoparticles**

The Torchilin group [103,104] developed polymeric micelles composed of PEG and diacyllipids, such as phosphatidyl ethanolamine (PE) for PX delivery. The presence of two hydrocarbon chains of PE increased hydrophobic interactions and therefore provided better stability of the micelles. The PX-loaded micelles had similar size to the placebo micelles. An immunomicelle formulation was prepared by attaching monoclonal antibody (mAb) 2C5 on the surface of the micelles, and it showed better antitumor activity both in vitro and in vivo compared to Taxol or non-targeted micelles in a Lewis lung carcinoma mouse model. Later, PX-loaded mixed micelles were developed by the mixture of PEG-PE and egg phosphatidylcholine, or the mixture of PEG-PE, solid triglycerides, and cationic Lipofectin lipids. The mixed polymeric micelles further improved antitumor efficacy [105,106]. The Rubinstein laboratory prepared sterically stabilized mixed micelles (SSMM) consisting of polyethylene glycol-distearylophosphatidylethanolamine (PEG-DSPE) and egg phosphatidylcholine. PX loading in SSMM was 1.5-fold higher than that of PEG-DSPE micelles at the same lipid concentration. PX-loaded SSMM, PEG-DSPE micelles, and free PX had comparable cytotoxicity in MCF-7 cells [107]. Actively targeted vasoactive intestinal peptide (VIP)-grafted SSMM (SSMM-VIP) was further engineered for the targeting purpose. The PX-loaded SSMM-VIP was significantly more potent than PX-loaded SSMM and free PX in drug resistant BC19/3 cells [108].

**Gelatin Nanoparticles**

Lu et al. [109-112] developed PX-loaded gelatin NPs using a desolvation method. The IC50 value of NPs was nearly identical to that of free PX in RT4 bladder transitional carcinoma cells. The pharmacokinetic and biodistribution studies indicated that the NP formulation altered drug plasma concentration, clearance and tissue distribution in mice. The PX-loaded gelatin NPs showed significantly improved antitumor activity compared to free PX in intravesical bladder cancer therapy in dogs.

**PEG-Polyaspartate Micellar Nanoparticles (NK 105)**

PEG-polyaspartate micellar NPs (NK 105) are constructed by copolymers of PEG and polyaspartate followed by the incorporation of PX into the core of the micelles via hydrophobic interaction [113]. The drug loading was up to 23% (w/w) with the particle size of 85 nm. In preclinical studies, NK 105 exhibited 90- and 25-fold greater plasma and tumor AUCs compared to free PX, respectively, and significantly better antitumor efficacy than free PX in a human colorectal cancer HT-29 xenograft mouse model. In addition, the neurotoxicity of NK 105 was dramatically lower than that of free PX [114]. In phase I clinical studies, the MTD of NK 105 was determined to be 180 mg/m² and the plasma AUC was 15-fold higher than Taxol at the dose of 150 mg/m² [115]. Currently, NK 105 is in phase III clinical studies.

**Lipid-Based Nanoparticles**

A summary of PX-loaded lipid-based NPs is shown in Table 2.

**Liposomes**

Liposomes are a mature and versatile drug delivery platform for both lipophilic and hydrophilic compounds. Zhang et al. [116] developed a novel lyophilized liposome-based PX formulation using phosphatidylcholine, cholesterol, and cardiolipin. The particle size did not change upon reconstitution after lyophilization. In addition, the formulation was physically and chemically stable at either 2-8°C or 25°C for at least 12 months. The in vitro drug release from liposome formulations was slow with less than 6% of PX released after 120 h. Yoshizawa and co-workers [117] formulated PX into liposomes composed of hydrogenated soybean phosphatidylcholine (HSPC), cholesterol, and PEG-DSPE2000. The plasma AUC of PEGylated liposomes was 3.6-fold higher than non-PEGylated liposome formulation in normal rats. In colon-26 solid tumor-bearing mice, the PX-PEGylated liposome had significantly better antitumor efficacy and greater tumor uptake of PX compared to non-PEGylated liposomes. PX-loaded multilamellar liposomes were developed by Fettery and Straubinger [118] which were composed of phosphatidylglycerol and phosphatidylcholine. Pharmacokinetic and biodistribution studies of PX liposomes were performed. The results showed that the AUC values in blood were comparable to Taxol, but tissue biodistribution was different. In general, the AUCs were significantly higher for Taxol
in bone marrow, skin, kidney, brain, adipose, and muscles, indicating the reduced toxicity of lipid-based formulations.

EndoTAG-1, PX-loaded cationic lipid formulations developed by MediGene, had the potential to treat cancer. EndoTAG-1 consisted of N-((1-(2,3-dioleoyloxy)propyl)-N,N,N-trimethylammonium methylsulfate (DOTAP) and 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), which bound to negatively charged endothelial cells in tumor blood vessels. In a prostate cancer mouse model, the mice treated with EndoTAG-1 had significantly smaller tumor volumes compared to the other controls [119]. In a different orthotopic pancreatic cancer model, the combination of EndoTAG-1 and gemcitabine inhibited the pancreatic metastasis [120]. Currently, EndoTAG-1 is in phase II clinical trials.

### Solid Lipid Nanoparticles (SLNs)

Serpe et al. [121] developed PX-loaded SLNs composed of tripalmitin as the oil phase, Epikuron 20 as the surfactant, and Na-taurocholate, butanol, and cholesteryl hemisuccinate as the co-surfactants. Although the in vitro cytotoxicity of SLNs was comparable to that of Taxol in HT-29 colorectal cancer cells, the combination of PX and doxorubicin (DOX) loaded SLNs exerted a synergistic effect which was more potent than the mixture of Taxol and free DOX. Chen et al. [122] prepared two types of SLNs using Brij 78, or pluronic F68 and PEG-DSPE as the surfactants. Both of PX-incorporated SLNs as the oil phase, Epikuron 20, butanol, Na-taurocholate, cholesteryl hemisuccinate were more potent than the mixture of Taxol and free DOX. Chen et al. [122] prepared two types of SLNs using Brij 78, or pluronic F68 and PEG-DSPE as the surfactants. Although the drug entrapment efficiency was low for glycerol tristearate SLNs, the NPs were performed in A549 cells, resulting in uptake in the order of glycerol tristearate>monostearin>stearic acid>ATO 888. Since the drug entrapment efficiency was low for glycerol tristearate SLNs, the monostearin SLNs were the optimized formulations for PX delivery. The Mumper laboratory [130,131] developed PX-encapsulated SLNs with phospholipids and sucrose fatty acid esters using either solvent or ultrasound emulsification method.

The Mumper laboratory [130,131] developed PX-encapsulated SLNs using emulsifying wax as the oil phase, and Brij 78 as the surfactant. The drug loading achieved 150 µg/mL final PX concentration with entrapment efficiency about 50%. The NPs showed significantly enhanced toxicity in P-gp resistant HCT-15 cells, and also increased brain uptake using an in-situ rat brain perfusion model. The in vivo antitumor efficacy of PX-loaded NPs was conducted in a

---

### Table 2: Summary of PX-loaded Lipid-based NPs. (*EE=Entrapment Efficiency).

| Platform          | Composition                                                                 | % EE* | Particle Size (nm) | Status       | Ref.   |
|-------------------|-----------------------------------------------------------------------------|-------|--------------------|--------------|--------|
| **Liposomes**     | phosphatidylycerine, cholesterol, cardiolipin                              | >90   | ~150               | in-vitro     | [116]  |
|                   | HSPC, cholesterol, PEG-DSPE                                               | —     | ~100               | in-vivo      | [117]  |
|                   | phosphatidylglycerol, phosphatidylcholine                                  | —     | 200, 900           | in-vivo      | [118]  |
|                   | tripalmitin, Epikuron 20, butanol, Na-taurocholate, cholesteryl hemisuccinate | —     | 160                | in-vitro     | [121]  |
|                   | stearic acid, lecithin, Brij 78 (or pluronic F68 and DSPE-PEG)             | 58-75 | 100-220            | in-vivo      | [122]  |
|                   | trimyristin, EPC, PEG<sub>2000</sub>, PE                                 | 72-89 | 200-250            | in-vivo      | [123, 124] |
|                   | glyceryl palmitylolesteinate (or glyceryl monostearate), poloxamer 407     | 55-90 | ~200               | in-vitro     | [127, 128] |
| **Solid Lipid Nanoparticles** | Lipid S 100, sucrose fatty acid esters                                    | 89-92 | 150-190            | in-vitro     | [129]  |
|                   | stearylamine, soya lecithin, poloxamer 188                                | 75    | 70-130             | in-vivo      | [125]  |
|                   | monostearin, stearyl acid, glycerol tristearate, ATO 888                  | 36-76 | 160-260            | in-vivo      | [126]  |
|                   | emulsifying wax, Brij 78                                                  | ~50   | <100               | in-vivo      | [130, 131] |
|                   | glyceryl tridecanoate, Brij 78                                            | ~85   | 170                | in-vivo      | [132, 133] |
| **Lipid Nanocapsules** | Labrafac<sup>®</sup>, Lipoid<sup>®</sup> S75-3, Solutol<sup>®</sup> HS15 | —     | ~50                | in-vivo      | [134-136] |
|                   | Captex<sup>®</sup> 8000, Lipoid<sup>®</sup> S75-3, Solutol<sup>®</sup> HS15 | 93    | ~50                | in-vivo      | [137-140] |
|                   | Miglyol 812, Brij 78, TPGS                                                | 85-97 | ~200               | in-vivo      | [132, 133] |
|                   | PLGA, lecithin, DSPE-PEG<sub>2000</sub>, DSPC, RGD (targeting)            | 82    | 68                 | in-vivo      | [142, 143] |
|                   | Lipidol, PEG-PPO-PEO, functionalized PEG, folic acid (targeting)           | 46    | 110                | in-vivo      | [144]  |
|                   | lecithin, Dynasan 118, Miglyol 812, folate-PEG-PE, Span 60 (or PEG-PE)     | 98    | 207                | in-vivo      | [145]  |
| **Micro- and Nano-Emulsions** | vitamin E, TPGS, poloxamer 407                                           | —     | 100                | phase III / discontinued | [154] |
|                   | oil blend, EPC, Tween 80, glycerol                                        | >95   | 150                | in-vivo      | [156]  |
|                   | lecithin, butanol, myvacet (or capmul, myvacet)                            | —     | ~110               | in-vivo      | [157, 158] |
|                   | pine nut oil, egg lecithin, stearylamine, deoxycholic acid                | —     | 90-120             | in-vivo      | [159]  |
|                   | egg lecithin, flavseed oil, DSPE-PEG<sub>2000</sub>                        | 97-100| 130-150            | in-vitro     | [160]  |
resistant HCT-15 xenograft mouse model and NPs demonstrated slower tumor growth rate compared to Taxol. Taken together, this PX-loaded NP formulation had the potential to overcome P-gp-mediated MDR both in vitro and in vivo. Later, novel PX SLNs were developed using glyceryl tridodecanoate as the core lipid. Compared to previous emulsifying wax-based SLNs, the novel PX-loaded NPs had higher drug entrapment efficiency of 85%, superior physical stability, slower and sustained release profile and even elimination of initial drug burst release [132,133].

Lipid Nanocapsules

Benoit and colleagues [134-136] has developed PX-loaded lipid nanocapsules, which were composed of Labrafac® (triglycerides), Lipoid® ST-3 (soybean lecithin), and Solutol® HS15 (Polyethylene glycol 660 12-hydroxystearate), sodium chloride, and water. The NP formulations demonstrated longer circulation time in blood, and slower distribution and elimination in Wistar rats. Furthermore, the PX-loaded NPs could significantly increase the life span as compared to all controls. Captex® 8000 (glyceryl tricaprylate) was utilized instead of Labrafac® to engineer another version of lipid nanocapsule formulation, which also showed benefits over that of Taxol in vivo and potentially overcame P-gp-mediated drug resistance [137-140].

The Mumper laboratory [132,133] developed PX-loaded nanocapsules using a warm microemulsion precursor method, which consisted of Miglyol 812 as the oil phase, and Brij 78 and TPGS as the surfactants [141]. This lipid-based nanocapsule system overcame P-gp-mediated drug resistance both in vitro and in vivo, and the mechanisms were investigated which included 1) increase drug cell uptake and retention; 2) inhibit P-gp; and 3) deplete ATP. Ho et al. [142,143] prepared a complex self-assembled immuno-nanocapsule formulation. First, the PLGA polymeric core was formed to encapsulate PX with the aid of lecithin and DSPE-PEG$_{2000}$. Another lipid layer with DSPC and DSPE-PEG$_{2000}$ was further coated on the PLGA core to load a second drug of combretastatin A4 (a vascular disrupting agent). Moreover, RGD peptide targeting ligand was conjugated on the surface of the lipid layer. This dual-drug loaded nanocapsule delivery system was shown to be promising in cancer therapy. Bae et al. [144] designed PX-loaded PEG-PPG-PEO/PEG nanocapsules with a targeting ligand of folic acid and a lipid of Lipiodol (an iodized ethyl ester of fatty acid). In order to do so, Lipiodol, PEO-PEO co-polymer, and amine functionalized six-arm-branched PEG were used to first form Lipiodol-encapsulated PEO-PEO-PEG nanocapsules using emulsion-solvent evaporation method. PX was then loaded into the nanocapsules and the targeting ligand of folic acid was conjugated on the surface of NPs. PX loading capacity in the NPs was about 5-fold higher than without the targeting ligand as compared to the oil phase of Lipiodol. This polymeric nanocapsule formulation with an oil core was served as a novel platform for water-insoluble drug delivery. Another novel folate-mediated solid-liquid lipid NP formulation was designed and developed to deliver PX. The idea was from that the combination of solid lipids and liquid oils could increase drug loading and entrapment efficiency [145]. The NPs demonstrated prolonged and sustained in vitro release and exhibited better antitumor efficacy compared to Taxol in S-180 tumor-bearing mice [145].

PX Fatty Acid-Prodrug Lipid-Based Nanoparticles

Although PX is a poorly water-soluble compound, its solubility in many lipids is also limited. Therefore, PX has the tendency to aggregate or crystallize from lipid-based NPs. To overcome the problem, modification of PX to a prodrug is a potential approach. Fatty acids could be used to conjugate to PX, improve the lipophilicity of PX and facilitate its retention in the core of lipid-based NPs.

Ansell et al. [146] synthesized series of PX prodrugs formulated in lipophilic NPs. Succinic acid and diglycolic acid were used as linkers. The diglycolic linkage offered a higher hydrolysis rate compared to succinate analogues. In in vitro cytotoxicity studies, succinate-linked prodrugs were 3-10-fold and 30-90-fold less potent than diglycolic linked prodrugs and free PX, respectively, in A2780 and MCF-7 cells. This was consistent with the fact that diglycolic linkage was more susceptible to hydrolysis. To evaluate the partition behavior of the prodrug NP formulations in vivo, NP plasma elimination studies were performed. The results showed that prodrugs in the NPs released first and then esterases cleaved the ester bond to form active PX form in their lipid NP formulations. Furthermore, the partitioning half-lives of diglycolate prodrugs from particles were increased as the aliphatic chain length increased, which indicated that the release rate of the prodrug from NPs could be adjusted by the length of aliphatic chains. Interestingly, succinate prodrug-containing NPs showed ineffective in vivo in an HT29 human colon carcinoma xenograft mouse model, which was probably due to the low hydrolysis rate and the slowly released PX was not sufficient to achieve needed efficacy. In contrast, diglycolate prodrug-loaded NPs showed tumor growth inhibition and the antitumor activity was correlated with the partitioning half-lives of these prodrugs, where longer aliphatic chain length with longer partitioning half-life led to improved efficacy.

Lundberg et al. [147] synthesized a PX-oleate conjugate and incorporated it into a lipid emulsion formulation with the mean particle size of 50 nm. The formulated PX-oleate was much more lipophilic than PX and had water solubility of 34 nM and $K_{o/w}$ of 8,074 versus PX water solubility of 12.8 µM and $K_{o/w}$ of 311 at 20°C. This highly lipophilic PX-oleate conjugate in the NP formulation showed significantly greater AUC, higher $C_{max}$, lower systemic clearance compared to PX formulated in Cremophor EL/ethanol in rabbits. Perkins et al. [148] attached a 16-carbon acyl chain to PX and this 2'-2-bromo-hexadecanoyl PX (BrC16-PX) conjugate was further incorporated into lipid-coated particles termed ‘lipocores’. The particle size of BrC16-PX-containing lipocores was 50-100 nm. In an in vivo study, the lipocores demonstrated antitumor activity in an ovarian carcinoma SCID mice model after intraperitoneal or intravenous administration, and were far less toxic than Taxol. Stevens et al. [149] synthesized a PX-2'-carbonyl-cholesterol (PX-Chol) conjugate to increase lipophilicity of PX and formulated it into a lipid NP formulation. The % entrapment of PX-Chol was greater than 90% at a drug/lipid ratio of 1:20, which significantly improved drug loading efficiency compared to the previous PX-loaded lipid NPs with the loading efficiency of 70%. In addition, the PX-Chol-incorporated NPs exhibited excellent colloidal stability. Ma et al. [150] synthesized a novel lipophilic palmitaxel derivative, 2'-behenoyl-palmitaxel (C22-PX), and then incorporated this conjugate into a lipid-based NP formulation for the treatment of metastatic breast cancer. The results of in vitro and in vivo experiments demonstrated that C22-PX NPs were much better tolerated, had significantly greater plasma and tumor AUCs, and superior anti-tumor efficacy compared to Taxol at MTD in a subcutaneous 4T1 mouse model.

The most successful PX-fatty acid prodrug is docosahexaenoic acid-PX (DHA-PX) conjugate, which currently is in phase III clinical trials [151]. DHA (22 carbon chain) is found in human milk and is known to be essential nutrition for brain development. DHA was linked to PX through an ester bond on its C-2’ position. The DHA-PX conjugate did not have microtubule assembly activity and was non-toxic. It converted to active PX form when metabolized by esterases in the body. Therefore,
the conjugate prolonged the exposure of PX and reduced the peak concentration, which allowed the administration of 4.4-fold higher doses of DHA-PX conjugate over that of PX alone in mice. In an M109 mouse tumor model, the tumor AUCs of PX from DHA-PX conjugate were 1.71- and 5.79-fold higher than those of PX when intravenously injected into mice at equimolar and equitoxic doses, respectively [152, 153]. It should be noted that DHA-PX is still formulated in Cremophor EL and ethanol, and this DHA-PX conjugate is beyond the scope of this review which is focused on PX nano-medicine delivery systems.

Micro- and Nano-Emulsions

TOCOSOL™ is an emulsion formulation consisting of vitamin E, TPGS, and poloxamer 407. In this formulation, PX was formulated in an o/w microemulsion with the particle size of 100 nm and high drug loading of 10 mg/mL. TOCOSOL™ completely eliminated Cremophor EL and ethanol in Taxol formulation, and without any modification of PX molecular structure. In preclinical studies, TOCOSOL™ showed much better tolerance and significantly improved antitumor efficacy compared to Taxol in both B16 and HCT-15 tumor-bearing mouse models. After intravenous injection of TOCOSOL™ at the dose of 10 mg/kg to mice implanted with B16 cells, tumor AUC was 2.2-fold higher than that of Taxol, although plasma AUC was comparable. The phase I clinical studies confirmed that TOCOSOL™ was well tolerated and less toxic than Taxol [154,155]. However, all the phase III clinical trials of TOCOSOL™ were closed due to its comparable objective response rate to Taxol in women with metastatic breast cancer.

Kan et al. [156] optimized PX in an o/w emulsion with an oil blend (tributyrin, tricaprin, and tricaprylin), egg phosphatidylcholine (EPC), Tween 80, and glycerol. The particle size of the NPs was ~150 nm at the concentration, which allowed the administration of 4.4-fold higher doses of DHA-PX conjugate over that of PX alone in mice. In an M109 mouse tumor model, the tumor AUCs of PX from DHA-PX conjugate were 1.71- and 5.79-fold higher than those of PX when intravenously injected into mice at equimolar and equitoxic doses, respectively [152, 153]. It should be noted that DHA-PX is still formulated in Cremophor EL and ethanol, and this DHA-PX conjugate is beyond the scope of this review which is focused on PX nano-medicine delivery systems.

Drug-Polymer Conjugates

A summary of PX-Polymer conjugates is shown in Table 3. Poly(amideamine) (PAMAM) dendrimer-based PX conjugates were designed and synthesized. Khandare et al. [161] prepared PAMAM dendrimer-succinyl acid-PX conjugate and showed that the cytotoxicity of the conjugate was 10-fold higher than that of free unconjugated drug in A2780 human ovarian carcinoma cells. Multifunctional PAMAM dendrimer was also engineered. The functional molecules of fluorescein isothiocyanate (FITC, an imaging agent), folic acid, and PX were conjugated to PAMAM dendrimer. This conjugate was evaluated and confirmed to have both targeted chemotherapeutic and imaging functions to cancer cells in vitro [162].

Wang et al. [163] synthesized a series heparin-PX conjugates with various single amino acid spacers, namely, valine, leucine, and phenylalanine. All the three conjugates exhibited greater cytotoxicity than that of free PX in MCF-7 cells. The hydrolysis properties of the conjugates in physiological and plasma conditions were different and the fastest hydrolysis was observed using leucine as the spacer. This heparin-PX conjugate with leucine spacer had similar antitumor efficacy compared to Taxol at a dose of 30 mg PX/kg in an SKOV 3 mouse model. Similarly, hyaluronic acid was utilized as the carrier to conjugate with PX. Different amino acids as the spacers were applied, such as valine, leucine, and phenylalanine. The conjugates exhibited increased cytotoxicity compared to free PX in MCF-7 cells [164]. A ternary conjugate of heparin-folic acid-PX was synthesized for further targeting purpose. This conjugate proved to selectively recognize folate receptor positive KB-3-1 cells and remarkably enhanced tumor inhibitory activity in a subcutaneous KB-3-1 xenograft model [165]. The Yu group [166-168] developed a novel poly(L-glutamyglutamine)-PX (PGG-PX) conjugate. Interestingly, this conjugate self-assembled into NPs with the particle size of 12-15 nm. The formulation had low toxicity in mice and its in vivo antitumor activity was superior to Abraxane® in multiple tumor models. Later, a more complex targeted PGG-PX-PEG-RGD conjugate was synthesized to further improve the therapeutic index [169].

An HPMA-co-polymer-PX conjugate (PNU 166945) was developed by covalent bonding of PX at its 2'-OH position with an enzymatic degradable tetrapeptide linker of Gly-Phe-Leu-Gly. The polymer/PX ratio was about 19/1(w/w). It was the first polymer-PX conjugate that entered phase I clinical trials. In the phase I studies, PNU 166945 was administered by 1 h infusion every 3 weeks to a small patient cohort of 12 patients. One patient had a partial response with advanced breast cancer. However, PNU 166945 demonstrated neurotoxicity and because of that the clinical studies were discontinued [170].

The most promising polymer-PX conjugate to date is undoubtedly the poly (L-glutamic acid)-PX conjugate (PG-PX, CT-2103), where PG is conjugated to 2'-OH position of PX via an ester linkage. The conjugate showed significantly better antitumor efficacy compared to Taxol in several tumor-bearing mouse models, and in some cases it completely eliminated tumors. In addition, the MTD and tumor uptake of CT-2103 were about 2- and 5-fold higher than Taxol, respectively, and prolonged circulation time was also observed in mouse tumor models. Currently, CT-2103 is in phase III clinical trials [171,172].

| Polymer | Linker / Spacer | Status | Ref. |
|---------|----------------|-------|-----|
| PAMAM   | Ester / succinic acid | in-vitro | [161] |
| PAMAM   | Ester / FITC-folic acid | in-vitro | [162] |
| Heparin | Ester / valine, leucine, phenylalanine | in-vivo | [163] |
| Heparin | Ester / folic acid | in-vivo | [165] |
| PGG     | ester | in-vivo | [166-168] |
| PGG     | Ester / PEG-RGD | in-vitro | [169] |
| HA      | Ester / valine, leucine, phenylalanine | in-vitro | [164] |
| HPMA    | Ester / Gly-Phe-Leu-Gly | phase II / discontinued | [170] |
| PG      | ester | phase III | [171, 172] |

Table 3: Summary of PX-polymer Conjugates.
Inorganic Nanoparticles
Gold Nanoparticles
Gibson et al. [173] covalently attached PX with a hexaethylene glycol linker to phenol-terminated gold NPs. Thermogravimetric analysis indicated there was about 70 PX molecules per 1 gold NP. The NPs were characterized by various traditional analytical techniques, such as NMR, TEM, SEC, etc., and concluded that the PX-coated gold NPs were able to be engineered in a controlled manner and this offered an alternative platform for PX delivery. Oh et al. [174] described a novel PX-loaded gold/chitosan/pluronic NP system. To prepare the modified gold NPs, PX was first dissolved in TWEEN 80 and this PX/TWEEN 80 was then dispersed into placebo gold NPs. Next, chitosan was introduced to the mixture to form PX-loaded gold/chitosan NPs via ionic interaction. The gold/chitosan NPs were then freeze-dried with pluronic F127 to obtain powders. The results showed that PX was released up to 90% from NPs over a 12-day period with a minimum initial burst release. Therefore, PX-loaded gold NPs may serve as an effective nanomedicine for better cancer therapy. Heo and co-workers [175] described a complex PX-functionalized gold NP system with PEG, biotin, and rhodamine B-linked β-CD. In the system, PEG served as an anti-fouling shell, biotin as a targeting ligand, rhodamine B as a fluorescent marker, β-CD as the carrier for both PX and rhodamine B. The PX-loaded gold NP demonstrated more potent cytotoxicity in cancer cell lines of HeLa, A549, and MG63 than the normal NIH3T3 cells, which indicated its potential use in cancer treatment.

Magnetic Nanoparticles (MNPs)

Hua et al. [176] designed poly(aniline-co-sodium N-(1-one-butyric acid) aniline) (SPAnNa) coated Fe3O4 MNPs. PX was immobilized onto the surface of MNPs to form SPAnNa/MNPs-bound-PX (bound-PX). The drug loading achieved up to 302.75 µg per mg of SPAnNa/MNPs. The bound-PX demonstrated higher stability than free PX at 37°C (half-life of 37 vs 19 h). Importantly, this bound-PX exhibited more potent toxicity compared to free PX in both PC3 and CWR22R prostate cancer cells. Moreover, the cell inhibition activity was even enhanced when a magnetic field was applied. All together, these results indicated that this magnetic delivery system had the potential to treat prostate cancer. Hwu and co-workers [177] developed PX-containing Fe-MNPs. The aqueous solubility of PX in PX-Fe-MNPs increased 780-fold (312 vs 0.4 µg/mL). The beauty of the design was that phosphodiester moiety was incorporated as the linker of PX. Since dephosphorylation took place easier in tumor cells, PX was able to be released from NPs once the NPs reached the tumor site. This was confirmed by the fact that 91% free PX was hydrolyzed and released from NPs after 10 days. In vitro cytotoxicity studies were conducted in both human cancer OECM1 cells and human normal HUVEC cells. It was found that PX-Fe-MNPs were 14,050-fold more toxic in cancer cells than normal human cells (IC50 of 5.03×10-7 vs 3.58×10-3 µg/mL).

Nanocrystals

The Huang group [181] developed a PX nanocrystal formulation using TPGS as the sole excipient. The utilization of TPGS in the formulation was to stabilize PX nanocrystals as well as reverse MDR. The average particle size of nanocrystals was 40×150 nm. The nanocrystals exhibited slower and sustained release than Taxol, and enhanced in vitro cytotoxicity and in vivo antitumor efficacy in resistant NCI/ADR-RES tumor models. PX/Pluronic F127 nanocrystals were also engineered and reported. The drug loading and entrapment efficiency were high and this formulation demonstrated significantly tumor growth inhibition activity in both human lung cancer and murine breast cancer mouse models [182]. Interestingly, it was found that the micellization of Pluronic F127 enhanced at elevated temperature, which was because the critical micelle concentration (CMC) of Pluronic F127 decreased at higher temperature. Therefore, the increased temperature during preparation procedure may provide better stability of nanocrystals [183].

Cyclodextrin (CD) Nanoparticles

Zhang et al. [184] synthesized a CD-functionalized hyperbranched polyglycerol (HPG) as the carrier for PX delivery. The HPG-g-CD self-assembled micelles in water with the particle size of 200-300 nm. PX-loaded HPG-g-CD had high drug loading (~8%, w/w) and entrapment efficiency (82-88%), and slow and sustained release profile. A β-CD derivative, heptakis (6-O-hexanoyl) cyclomaltoheptaose-β-CD (6-O-CAPRO-β-CD) was synthesized to stabilize PX NPs with high drug loading and reduce the burst release. Since the carrier of 6-O-CAPRO-β-CD demonstrated low hemolysis and cytotoxicity, it may serve as an alternative formulation for current Taxol [185-187].

Nanogel

Lee et al. [188] developed PX-loaded injectable in situ-forming gel with mPEG-PCL diblock co-polymer. The formulation was in a liquid state at room temperature but rapidly formed gel at body temperature. PX in the gel was released in a sustained manner for more than 2 weeks in vitro. PX-loaded gel depot had significantly improved antitumor efficacy compared to Taxol, saline (control), and placebo gel in a B16F10 tumor-bearing mouse model upon intratumoral injection. OncoGel is a PX injectable depot developed by MacroMed Inc (Sandy, Utah) for local tumor treatment. The gel was composed of the thermosensitive triblock co-polymer of PLGA-PGA-PLGA, which transformed to a water-insoluble hydrogel at body temperature. It had sustained release properties for up to 6 weeks upon injection. OncoGel was proven to be safe and reduced systemic exposure of PX because PX concentration in plasma was negligible after single injection into solid tumor site. Currently, it is in phase II clinical trials [189,190].

ANG 1005

ANG 1005 is a PX-peptide conjugate, which consists of three PX
molecules coupled to one molecule of a novel peptide, Angiopep-2. Angiopep-2 is a 19-aa amino-acid peptide which targets low-density lipoprotein receptor-related protein 1 (LRP1) receptor to facilitate PX across BBB for the treatment of brain disease. In preclinical studies, ANG 1005 demonstrated better tumour efficacy and increased survival time in several tumour-bearing mouse models. Currently, it is in phase II clinical trials [191,192].

Conclusions and Future Perspective

PX is one of the most effective anticancer drugs ever developed. It is active against a broad range of cancers. However, the current Taxol formulations have issues related to the use of Cremophor EL and ethanol. Since nano-delivery systems could have the potential to be free of Cremophor EL and ethanol, enhance PX solubility, and ethanol. Since nano-delivery systems could have the potential to be free of Cremophor EL and ethanol, enhance PX solubility, improve PX pharmacokinetic profiles in vivo, decrease its side effects, passively or actively target to tumor sites due to the EPR effect and the use of targeting ligands, respectively, nanotechnology is a very active research area in both academic and industrial settings. Therefore, various types of PX nano-delivery systems have been developed as discussed in this review, such as polymeric nanoparticles, lipid-based formulations, polymer conjugates, inorganic nanoparticles, carbon nanotubes, nanocrystals, and cyclodextrin nanoparticles. To date, the PX albumin-bound NPs (Abraxane®) have been approved by the FDA for the treatment of metastatic breast cancer and NSCLC, and there are a number of novel PX NP formulations in clinical trials (Table 4). Some of them have demonstrated certain advantages in terms of toxicity, such as lower incidence of hypersensitivity reactions, myelosuppression, etc. However, whether these novel formulations may improve survival is largely unknown.

Although it has been established that nano-delivery systems are feasible and promising in cancer therapy, there are a lot challenges as well to hinder the application of these systems. First, it is difficult to fully characterize the physicochemical properties of NP systems and it seems that every NP delivery system is unique; and related to this, the lack understanding of NP stability and drug release mechanisms from NP formulations in-vivo, or in general, the fate of the drug as well as the vehicles in human body. Third, the theory of EPR effect is debatable and now it is generally considered that tumor leakage is cancer-type dependent, and nano-delivery systems with particle sizes below 40 nm are desirable to have a better chance to passively target tumors. Fourth, it is important to search for new tumor targeting ligands which can be precisely characterized and exclusively expressed in the targeted organs. Fifth, the long-term toxicity of these nano-materials in the human body must be investigated. In regard to this mandate, biodegradable and non-toxic polymers or lipids are less toxic and likely have a better opportunity. In addition, the price of NP delivery systems is expected to be high. Nevertheless, the future of NP delivery systems remains promising and is sure to have a role in improving cancer therapy.

Acknowledgements

The authors are supported, in part, by Award Number U54 CA151652 from the National Cancer Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health.

| Name          | Delivery Strategy         | Company                    | Clinical Stage | Disease Condition Used / Treated                      |
|---------------|---------------------------|----------------------------|----------------|------------------------------------------------------|
| Abraxane      | protein-bound particle    | Abraxis Bioscience (now Celgene) | approved      | metastatic breast cancer / NSCLC                     |
| NK-105        | polymeric micelle         | NanoCarrier                | phase III     | metastatic breast cancer / stomach cancer            |
| CT-2103       | polymeric conjugate       | Cell Therapeutics          | phase III     | ovarian cancer                                       |
| Genexol-PM    | polymeric micelle         | Samyang                    | phase III     | metastatic breast cancer                            |
| Tocosol       | emulsion                  | Sonus Pharmaceuticals       | phase III / discontinued | metastatic breast cancer                            |
| ANG 1005      | peptide-bound conjugate   | Angiochem                  | phase II      | glioma                                               |
| EndoTag       | cationic liposome         | Medigen                    | phase II      | metastatic breast cancer / pancreatic cancer         |
| Paxceed       | polymeric micelle         | Angiotech Pharmaceuticals   | phase II      | psoriasis                                            |
| LEP-ETU       | liposome                  | NeoPharm                   | phase II      | metastatic breast cancer                            |
| OncoGel       | gel                       | Protherics                 | phase II / discontinued | esophageal cancer / primary brain cancer             |
| PNU166945     | polymeric conjugate       | Pfizer                     | phase II / discontinued | —                                                   |

Table 4: Summary of PX-loaded NPs in Clinical Development.

References

1. Jordan MA, Wilson L (2004) Microtubules as a target for anticancer drugs. Nat Rev Cancer 4: 283-285.
2. Gelderblom H, Verweij J, Nooter K, Sparreboom A (2001) Cremophor EL: the drawbacks and advantages of vehicle selection for drug formulation. Eur J Cancer 37: 1590-1596.
3. Sparreboom A, van Tellingen O, Nuijten WJ, Beijnen JH (1996) Nonlinear pharmacokinetics of paclitaxel in mice results from the pharmaceutical vehicle Cremophor EL. Cancer Res 56: 2112-2115.
4. Gallo JM, Li S, Guo P, Reed K, Ma J. (2003) The effect of P-glycoprotein on paclitaxel brain and brain tumor distribution in mice. Cancer Res. 63: 5114-5117.
5. Berg SL, Tolcher A, O’Shaughnessy JA, Denicoff AM, Noone M, et al. (1995) Effect of R-verapamil on the pharmacokinetics of paclitaxel in women with breast cancer. Clin Oncol 13: 2039-2042.
6. Fracasso PM, Westervelt P, Fears CL, Rosen DM, Zuhowski EG, et al. (2000) Phase I study of paclitaxel in combination with a multidrug resistance modulator, PSC 833 (Valspodar), in refractory malignancies. J Clin Oncol 18: 1124-1134.
7. Storm G, Belliot SO, Daemen T, Lasic DD (1995) Surface modification of nanoparticles to oppose uptake by the mononuclear phagocyte system. Advanced Drug Delivery Reviews 17: 31-48.
8. Alexis F, Pridgen EM, Langer R, Farokhzad OC (2010) Nanoparticle technologies for cancer therapy. Handb Exp Pharmacol : 55-86.
9. Wang J, Sui M, Fan W (2010) Nanoparticles for tumor targeted therapies and their pharmacokinematics. Curr Drug Metab 11: 129-141.
10. Hallek B, Frenkel E (2008) Nanoparticles for drug delivery in cancer treatment. Urol Oncol 26: 57-64.
11. Suri SS, Fenniri H, Singh B. (2007) Nanotechnology-based drug delivery systems. J Occup Med Toxicol 2: 16.
12. Jain RK, Stylianopoulos T (2010) Delivering nanomedicine to solid tumors. Nat Rev Clin Oncol 7: 653-664.
13. Jin C, Wu H, Liu J, Bai L, Guo G (2007) The effect of paclitaxel-loaded nanoparticles with radiation on hypoxic MCF-7 cells. J Clin Pharm Ther 32: 41-47.
14. Jin C, Bai L, Wu H, Liu J, Guo G, et al. (2008) Paclitaxel-loaded poly(D,L-lactide-co-glycolide) nanoparticles for radiotherapy in hypoxic human tumor cells in vitro. Cancer Biol Ther 7: 911-916.
15. Danhier F, Lecouturier N, Vroman B, Jérôme C, Marchand-Brynaert J, et al.

Citation: Ma P, Mumper RJ (2013) Paclitaxel Nano-Delivery Systems: A Comprehensive Review. J Nanomed Nanotechol 4: 164. doi:10.4172/2157-7439.JNMNT.4.164
(2009) Paclitaxel-loaded PEGylated PLGA-based nanoparticles: in vitro and in vivo evaluation. J Control Release 133: 11-17.

16. Fonseca C, Simões S, Gaspar R (2002) Paclitaxel-loaded PLGA nanoparticles: preparation, physicochemical characterization and in vitro anti-tumoral activity. J Control Release 83: 273-286.

17. Dong Y, Feng SS (2007) Poly(D,L-lactide-co-glycolide) (PLGA) nanoparticles prepared by high pressure homogenization for paclitaxel chemotherapy. Int J Pharm 342: 208-214.

18. Jin C, Bai L, Wu H, Song W, Guo G, et al. (2009) Cytotoxicity of paclitaxel incorporated in PLGA nanoparticles on hypoxic human tumor cells. Pharm Res 26: 1776-1784.

19. Kim BS, Kim CS, Lee KM (2008) The intracellular uptake ability of chitosan-coated poly(D,L-lactide-co-glycolide) nanoparticles. Arch Pharm Res 31: 1050-1054.

20. Chakravarthi SS, Robinson DH (2011) Enhanced cellular association of paclitaxel delivered in chitosan-PLGA particles. Int J Pharm 409: 111-120.

21. Bhadwaj V, Ankola D, Gupta S, Schneider M, Lehr CM, et al. (2009) PLGA nanoparticles stabilized with cationic surfactant: safety studies and application in oral delivery of paclitaxel to treat chemical-induced breast cancer in rat. Pharm Res 26: 2495-2503.

22. Mei L, Sun H, Jin X, Zhu D, Sun R, et al. (2007) Modified paclitaxel-loaded nanoparticles for inhibition of hyperplasia in a rabbit arterial balloon injury model. Pharm Res 24: 955-962.

23. Vandervoort J, Ludwig A (2002) Biocompatible stabilizers in the preparation of PLGA nanoparticles: a factorial design study. Int J Pharm 238: 77-92.

24. Mu L, Feng SS (2003) A novel controlled release formulation for the anticancer drug paclitaxel (Taxol): PLGA nanoparticles containing vitamin E TPGS. J Control Release 86: 33-48.

25. Feng SS, Mu L, Win KY, Huang G (2004) Nanoparticles of biodegradable polymers for clinical administration of paclitaxel. Curr Med Chem 11: 413-424.

26. Feng SS, Zeng W, Teng Lim Y, Zhao L, Yin Win K, et al. (2007) Vitamin E TPGS-emulsified poly(lactic-co-glycolic acid) nanoparticles for cardiovascular restenosis treatment. Nanomedicine (Lond) 2: 333-344.

27. Zhao L, Feng SS (2010) Enhanced oral bioavailability of paclitaxel formulated in vitamin E TPGS emulsified nanoparticles of biodegradable polymers: in vitro and in vivo studies. J Pharm Sci 99: 3552-3560.

28. Liu Y, Pan J, Feng SS (2010) Nanoparticles of lipid monolayer shell and biodegradable polymer core for controlled release of paclitaxel: effects of surfactants on particles size, characteristics and in vitro performance. Int J Pharm 395: 243-250.

29. Feng SS, Huang G (2001) Effects of emulsifiers on the controlled release of paclitaxel (Taxol) from nanospheres of biodegradable polymers. J Control Release 71: 53-69.

30. Dong Y, Feng SS (2005) Poly(D,L-lactide-co-glycolide)/montmorillonite nanoparticles for oral delivery of anticancer drugs. Biomaterials 26: 6068-6076.

31. Sun B, Ranganathan B, Feng SS (2008) Multifunctional poly(D,L-lactide-co-glycolide)/montmorillonite (PLGA/MMT) nanoparticles decorated by Trasizumab for targeted chemotherapy of breast cancer. Biomaterials 29: 475-486.

32. Wang Z, Chui WK, Ho PC (2011) Nanoparticulate delivery system targeted to tumor neovascularization for combined anticancer and antiangiogenesis therapy. Pharm Res 28: 585-596.

33. Shah N, Chaudhari K, Daniluiri P, Murthy RS, Das S (2009) Paclitaxel-loaded PLGA nanoparticles surface modified with transferrin and Pluronic® P85, an in vitro cell line and in vivo biodistribution studies on rat model. J Drug Target 17: 533-542.

34. Sahoo SK, Ma W, Labhasetwar V (2004) Efficacy of transferrin-conjugated paclitaxel-loaded nanoparticles in a murine model of prostate cancer. Int J Cancer 112: 335-340.

35. Sahoo SK, Labhasetwar VA (2005) Enhanced antiproliferative activity of transferrin-conjugated, paclitaxel-loaded nanoparticles mediated via sustained intracellular drug retention. Mol Pharm 2: 373-383.

36. Dong Y, Feng SS (2004) Methoxy poly(ethylene glycol)-poly(lactide) (MPEG-PLA) nanoparticles for controlled delivery of anticancer drugs. Biomaterials 25: 2843-2849.

37. Dong Y, Feng SS (2007) In vitro and in vivo evaluation of methoxy polyethylene glycol-poly(lactide) (MPEG-PLA) nanoparticles for small-molecule drug chemotherapy. Biomaterials 28: 4154-4160.

38. Dong Y, Feng SS (2006) Nanoparticles of poly(D,L-lactide)/methoxy polyethylene glycol-poly(D,L-lactide) blends for controlled release of paclitaxel. J Biomed Mater Res A 78: 12-19.

39. Zhang Z, Feng SS (2006) In vitro investigation on poly(lactide) Tween 80 copolymer nanoparticles fabricated by dialysis method for chemotherapy. Biomacromolecules 7: 1139-1146.

40. Zhang Z, Feng SS (2006) Nanoparticles of poly(lactide)/vitamin E TPGS copolymer for cancer chemotherapy: synthesis, formulation, characterization and in vitro drug release. Biomaterials 27: 282-290.

41. Zhang Z, Feng SS (2006) Self-assembled nanoparticles of poly(lactide)—vitamin E TPGS copolymers for oral chemotherapy. Int J Pharm 324: 191-198.

42. Zhang Z, Lee SH, Gan CW, Feng SS (2008) In vitro and in vivo investigation on PLA-TPGS nanoparticles for controlled and sustained small molecule chemotherapy. Pharm Res 25: 1925-1935.

43. Zhang Z, Feng SS (2006) The drug encapsulation efficiency, in vitro drug release, cellular uptake and cytotoxicity of paclitaxel-loaded poly(lactide)-tocopherol polyethylene glycol succinate nanoparticles. Biomaterials 27: 4025-4033.

44. Pan J, Feng SS (2008) Targeted delivery of paclitaxel using folate-decorated poly(lactide)-vitamin E TPGS nanoparticles. Biomaterials 29: 2663-2672.

45. Zhang L, Hu CH, Cheng SX, Zhuo RX (2010) Hyperbranched amphiphilic polymer fowl with folate mediated targeting property. Colloids and Surfaces B: Biointerfaces 79: 427-433.

46. Cirstoiu-Hapca A, Buchegger F, Bossy L, Kosinski M, Gurny R, et al. (2009) Nanomedicines for active targeting: physico-chemical characterization of paclitaxel-loaded anti-HER2 immunonanoparticles and in vitro functional studies on target cells. Eur J Pharm Sci 38: 230-237.

47. Patil YB, Toti US, Khodair A, Ma L, Panyam J (2009) Single-step surface functionalization of polymeric nanoparticles for targeted drug delivery. Biomaterials 30: 859-866.

48. Jie P, Venkatraman SS, Min F, Freddy BY, Huat GL (2005) Micelle-like nanoparticles of star-branched PEO-PLA copolymers as chemotherapeutic carrier. J Control Release 110: 20-33.

49. Xiao L, Xiong X, Sun X, Zhu Y, Yang H, et al. (2011) Role of cellular uptake in the reversal of multidrug resistance by PEG-b-PLA polymeric micelles. Biomaterials 32: 5148-5157.

50. Gaucher G, Loreux M, Ehrlich A, Perrier E, Figg WD, et al. (2005) Poly(Vinylpyrrolidone)-block-poly(D,L-lactide) as polymeric emulsifier for the preparation of biodegradable nanoparticles. J Pharm Sci 94: 1763-1775.

51. Venkatraman SS, Jie P, Min F, Freddy BY, Leong-Huat G (2005) Micelle-like nanoparticles of PLA-PEG-PLA triblock copolymers as targeted drug delivery system for the treatment of liver cancer. Biomaterials 27: 2051-2059.

52. He G, Ma LL, Pan J, Venkatraman S (2007) ABA and BAB type triblock copolymers of PEG and PLA: a comparative study of drug release properties and “stealth” particle characteristics. Int J Pharm 334: 48-55.

53. Venkatraman SS, Jie P, Min F, Freddy BY, Leong-Huat G (2005) Micelle-like nanoparticles of PLA-PEG-PLA triblock copolymer as chemotherapeutic carrier. Int J Pharm 298: 219-232.

54. Zhang X, Jackson JK, Burt HM (1996) Development of amphiphilic diblock copolymers as micellar carriers of Taxol. Int J Pharm 132: 195-206.

55. Ehrlich A, Booser S, Becerra Y, Boris DL, Figg WD, et al. (2004) Micellar paclitaxel improves severe psoriasis in a prospective phase II pilot study. J Am Acad Dermatol 50: 533-540.

56. Kim SC, Kim DW, Shim YH, Bang JS, Oh HS, et al. (2001) In vivo evaluation of polymeric micellar paclitaxel formulation: toxicity and efficacy. J Control Release 72: 191-202.
68. Xin H, Jiang X, Gu J, Sha X, Chen L, et al. (2011) Angiopep-conjugated poly(ethylene glycol)-b-poly(ε-caprolactone) nanoparticles: preparation and evaluation. Int J Pharm 414: 251-259.

69. Chen S, Zhang XZ, Cheng SX, Zhuo RX, Gu ZW (2008) Functionalized amphiphilic hyperbranched polymers for targeted drug delivery. Biomacromolecules 9: 2578-2585.

70. Zhang Y, Tang L, Sun L, Bao J, Song C, et al. (2010) A novel paclitaxel-loaded poly(ε-caprolactone)-poloxamer 188 blend nanoparticle overcoming multidrug resistance for cancer treatment. Acta Biomater 6: 2045-2053.

71. Ma GL, Yang J, Zhang LH, Song CX. (2010) Effective antitumor activity of poly(ethylene glycol)-co-poly(ε-caprolactone) nanoparticles as dual-targeting drug delivery system for brain glioma. Biomaterials 32: 4293-4305.

72. Wang C, Wang Y, Wang Y, Fan M, Luo F, et al. (2011) Characterization, pharmacokinetics and disposition of novel nanoscale preparations of paclitaxel. Int J Pharm 414: 251-259.

73. Chen S, Zhang XZ, Cheng SX, Zhuo RX, Gu ZW (2008) Functionalized amphiphilic hyperbranched polymers for targeted drug delivery. Biomacromolecules 9: 2578-2585.

74. Zhang Y, Tang L, Sun L, Bao J, Song C, et al. (2010) A novel paclitaxel-loaded poly(ε-caprolactone)-poloxamer 188 blend nanoparticle overcoming multidrug resistance for cancer treatment. Acta Biomater 6: 2045-2053.

75. Ma GL, Yang J, Zhang LH, Song CX. (2010) Effective antitumor activity of poly(ethylene glycol)-co-poly(ε-caprolactone) nanoparticles as dual-targeting drug delivery system for brain glioma. Biomaterials 32: 4293-4305.

76. Wang C, Wang Y, Wang Y, Fan M, Luo F, et al. (2011) Characterization, pharmacokinetics and disposition of novel nanoscale preparations of paclitaxel. Int J Pharm 414: 251-259.
117. Yoshizawa Y, Kono Y, Ogawara K, Kimura T, Higaki K (2011) PEG
116. Zhang JA, Anyarambhatla G, Ma L, Ugwu S, Xuan T, et al. (2005) Development
115. Hamaguchi T, Kato K, Yasui H, Morizane C, Ikeda M, et al. (2007) A phase
114. Hamaguchi T, Matsumura Y, Suzuki M, Shimizu K, Goda R, et al. (2005)
113. Kataoka K, Kwon GS, Yokoyama M, Okano T, Sakurai Y (1993) Block
112. Tsai M, Lu Z, Wang J, Yeh TK, Wientjes MG, et al. (2007) Effects of carrier
110. Lu Z, Yeh TK, Tsai M, Au JL, Wientjes MG (2004) Paclitaxel-loaded gelatin
109. Lu Z, Yeh TK, Wang J, Chen L, Lyness G, et al. (2011) Paclitaxel gelatin
120. Eichhorn ME, Ischenko I, Luedemann S, Strieth S, Papyan A, et al. (2010)
119. Bode C, Trojan L, Weiss C, Kraenzlin B, Michaelis U, et al. (2009) Paclitaxel
118. Fetterly GJ, Straubinger RM (2003) Pharmacokinetics of paclitaxel-containing
107. Krishnadas A, Rubinstein I, Onyüksel H (2003) Sterically stabilized
105. Kainthan RK, Muliawan EB, Hatzikiriakos SG, Brooks DE (2006) Synthesis,
101. Kainthan RK, Muliawan EB, Hatzikiriakos SG, Brooks DE (2006) Synthesis,
103. Gao Z, Lukyanov AN, Gao Z, Papahadjopoulos-Sternberg B (2003)
111. 90. Sheth K, Saha S, Wagenknecht A, Mudgett LF, Lipshultz S, et al. (2005) The
cytotoxicity of patupilisicariludeladipgypncleotide nanoparticles overcome
110. Mitra A, Lin S (2003) Effect of surfactant on fabrication and characterization of
109. Lu Z, Yeh TK, Wang J, Chen L, Lyness G, et al. (2011) Paclitaxel gelatin
108. Lu Z, Yeh TK, Tsai M, Au JL, Wientjes MG (2004) Paclitaxel-loaded gelatin
107. Krishnadas A, Rubinstein I, Onyüksel H (2003) Sterically stabilized
106. Shenoy VS, Gude RP, Murthy RSR (2009) Paclitaxel-loaded glyceryl
105. Wang J, Mongayt D, Torchilin VP (2005) Polymeric micelles for delivery of
poorly soluble drugs: preparation and antitumor activity in vitro of paclitaxel
incorporated into mixed micelles based on poly(ethylene glycol)-lipid conjugate
and positively charged lipids. J Drug Target 13: 73-80.
104. Gao Z, Lukyanov AN, Chaklam AR, Torchilin VP (2003) PEG-PE/
phosphatidylcholine mixed immunomicelles specifically deliver encapsulated
taxol to tumor cells of different origin and promote their efficient killing. J Drug
111. Target 11: 87-92.
103. Gao Z, Lukyanov AN, Chaklam AR, Torchilin VP (2003) PEG-PE/
phosphatidylcholine mixed immunomicelles specifically deliver encapsulated
taxol to tumor cells of different origin and promote their efficient killing. J Drug
111. Target 11: 87-92.
112. Tsai M, Lu Z, Wang J, Yeh TK, Wientjes MG, et al. (2007) Effects of carrier
on disposition and antitumor activity of intraperitoneal paclitaxel. Pharm Res
24: 1691-1701.
113. Kataoka K, Kwon GS, Yokoyama M, Okano T, Sakurai Y (1993) Block
copolymer micelles as vehicles for drug delivery. J Control Release 274: 327-
330.
109. Lu Z, Yeh TK, Wang J, Chen L, Lyness G, et al. (2011) Paclitaxel gelatin
nanoparticles for intravesical bladder cancer therapy. J Urol 185: 1478-1483.
110. Lu Z, Yeh TK, Tsai M, Au JL, Wientjes MG (2004) Paclitaxel-loaded gelatin
nanoparticles for intravesical bladder cancer therapy. Clin Cancer Res 10:
7677-7684.
111. Yeh TK, Lu Z, Wientjes MG, Au JL (2005) Formulating paclitaxel in
nanoparticles alters its disposition. Pharm Res 22: 867-874.
112. Tsai M, Lu Z, Wang J, Yeh TK, Wientjes MG, et al. (2007) Effects of carrier
on disposition and antitumor activity of intraperitoneal paclitaxel. Pharm Res
24: 1691-1701.
113. Kataoka K, Kwon GS, Yokoyama M, Okano T, Sakurai Y (1993) Block
copolymer micelles as vehicles for drug delivery. J Control Release 274: 327-
330.
109. Lu Z, Yeh TK, Wang J, Chen L, Lyness G, et al. (2011) Paclitaxel gelatin
nanoparticles for intravesical bladder cancer therapy. J Urol 185: 1478-1483.
110. Lu Z, Yeh TK, Tsai M, Au JL, Wientjes MG (2004) Paclitaxel-loaded gelatin
nanoparticles for intravesical bladder cancer therapy. Clin Cancer Res 10:
7677-7684.
111. Yeh TK, Lu Z, Wientjes MG, Au JL (2005) Formulating paclitaxel in
nanoparticles alters its disposition. Pharm Res 22: 867-874.
112. Tsai M, Lu Z, Wang J, Yeh TK, Wientjes MG, et al. (2007) Effects of carrier
on disposition and antitumor activity of intraperitoneal paclitaxel. Pharm Res
24: 1691-1701.
113. Kataoka K, Kwon GS, Yokoyama M, Okano T, Sakurai Y (1993) Block
copolymer micelles as vehicles for drug delivery. J Control Release 274: 327-
330.
109. Lu Z, Yeh TK, Wang J, Chen L, Lyness G, et al. (2011) Paclitaxel gelatin
nanoparticles for intravesical bladder cancer therapy. J Urol 185: 1478-1483.
110. Lu Z, Yeh TK, Tsai M, Au JL, Wientjes MG (2004) Paclitaxel-loaded gelatin
nanoparticles for intravesical bladder cancer therapy. Clin Cancer Res 10:
7677-7684.
111. Yeh TK, Lu Z, Wientjes MG, Au JL (2005) Formulating paclitaxel in
nanoparticles alters its disposition. Pharm Res 22: 867-874.
112. Tsai M, Lu Z, Wang J, Yeh TK, Wientjes MG, et al. (2007) Effects of carrier
on disposition and antitumor activity of intraperitoneal paclitaxel. Pharm Res
24: 1691-1701.
113. Kataoka K, Kwon GS, Yokoyama M, Okano T, Sakurai Y (1993) Block
copolymer micelles as vehicles for drug delivery. J Control Release 274: 327-
330.
109. Lu Z, Yeh TK, Wang J, Chen L, Lyness G, et al. (2011) Paclitaxel gelatin
nanoparticles for intravesical bladder cancer therapy. J Urol 185: 1478-1483.
110. Lu Z, Yeh TK, Tsai M, Au JL, Wientjes MG (2004) Paclitaxel-loaded gelatin
nanoparticles for intravesical bladder cancer therapy. Clin Cancer Res 10:
7677-7684.
111. Yeh TK, Lu Z, Wientjes MG, Au JL (2005) Formulating paclitaxel in
nanoparticles alters its disposition. Pharm Res 22: 867-874.
112. Tsai M, Lu Z, Wang J, Yeh TK, Wientjes MG, et al. (2007) Effects of carrier
on disposition and antitumor activity of intraperitoneal paclitaxel. Pharm Res
24: 1691-1701.
113. Kataoka K, Kwon GS, Yokoyama M, Okano T, Sakurai Y (1993) Block
copolymer micelles as vehicles for drug delivery. J Control Release 274: 327-
330.
109. Lu Z, Yeh TK, Wang J, Chen L, Lyness G, et al. (2011) Paclitaxel gelatin
nanoparticles for intravesical bladder cancer therapy. J Urol 185: 1478-1483.
110. Lu Z, Yeh TK, Tsai M, Au JL, Wientjes MG (2004) Paclitaxel-loaded gelatin
nanoparticles for intravesical bladder cancer therapy. Clin Cancer Res 10:
7677-7684.
111. Yeh TK, Lu Z, Wientjes MG, Au JL (2005) Formulating paclitaxel in
nanoparticles alters its disposition. Pharm Res 22: 867-874.
112. Tsai M, Lu Z, Wang J, Yeh TK, Wientjes MG, et al. (2007) Effects of carrier
on disposition and antitumor activity of intraperitoneal paclitaxel. Pharm Res
24: 1691-1701.
143. Wang Z, Ho PC (2010) A nanocapsular combinatorial sequential drug delivery system for antitumor treatment and anticancer activities. Biomaterials 31: 7115-7123.

144. Bae KH, Lee Y, Park TG (2007) Oil-encapsulating PEO-PPO-PEO/PEG shell cross-linked nanocapsules for target-specific delivery of paclitaxel. Biomacromolecules 8: 650-656.

145. Jores K, Meinert W, Drechsler M, Bunjes H, Johann C, et al. (2004) Investigations on the structure of solid lipid nanoparticles (SLN) and oil-loaded solid lipid nanoparticles by photon correlation spectroscopy, field-flow fractionation and transmission electron microscopy. J Control Release 95: 217-227.

146. Ansell SM, Johnstone SA, Tardi PG, Lo L, Xie S, et al. (2008) Modulating the therapeutic activity of nanoparticle delivered paclitaxel by manipulating the hydrophobicity of prodrug conjugates. J Med Chem 51: 3288-3296.

147. Lundberg BB, Risovic V, Ramaswamy M, Wasan KM (2003) A lipophilic paclitaxel derivative incorporated in a lipid emulsion for parenteral administration. J Control Release 86: 93-100.

148. Perkins WR, Ahmad I, Hirsh DJ, Masters GR, et al. (2000) Novel therapeutic nano-particles (lipocores): trapping poorly water soluble compounds. Int J Pharm 200: 27-39.

149. Stevens PJ, Sekido M, Lee RJ (2004) A folate receptor-targeted lipid nanoparticle formulation for a lipophilic paclitaxel prodrug. Pharm Res 21: 2153-2157.

150. Ma P, Benhabbour RS, Feng L, Mumper RJ (2012) 2’-Behenoyl-paclitaxel derivative incorporated in a lipid emulsion for parenteral administration. J Control Release 159: 935-939.

151. Khandare JJ, Jayant S, Singh A, Chandna P, Wang Y, et al. (2006) Dendrimer nanoemulsion formulations to overcome multidrug resistance in tumor cells. Mol Pharm 3: 923-930.

152. Heo DN, Yang DH, Moon HJ, Lee JB, Bae MS, et al. (2012) Gold nanoparticles surface-functionalized with paclitaxel drug and biotin receptor as theranostic agents for cancer therapy. Biomaterials 33: 856-866.

153. Hua MY, Yang HW, Chuang CK, Tsai RY, Chen WJ, et al. (2010) Magnetic nanoparticle-modified paclitaxel for targeted therapy for prostate cancer. Biomaterials 31: 7355-7363.

154. Galic VL, Herzog TJ, Wright JD, Lewin SN (2011) Paclitaxel polyglumex for ovarian cancer. Expert Opin Investig Drugs 20: 813-821.

155. Bishop JW (2005) Paclitaxel polyglumex (XYOTAX, CT-2103): a macromolecular taxane. J Control Release 109: 120-126.

156. Vessal B, Liu HQ, Tan HR, Liu Y (2010) Delivery of paclitaxel by physically mixed polymeric nanoparticles. J Control Release 143: 297-305.

157. Oh KS, Kim RS, Lee J, Kim D, Cho SH, et al. (2008) Gold/chitosan/pluronic composite nanoparticles for drug delivery. J Appl Polym Sci 108(5):3239-3244.

158. Liu Y, Huang CH, Huang CK, Tsai SY, Chen CJ, et al. (2010) Magnetic nanoparticle-modified paclitaxel for targeted therapy for prostate cancer. Biomaterials 31: 7355-7363.

159. Hwu JR, Lin YS, Josephraj HN, Huo MH, Cheng FY, et al. (2009) Targeted paclitaxel by conjugation to iron oxide and gold nanoparticles. J Am Chem Soc 131: 66-68.

160. Liu Z, Chen K, Davis C, Sherlock S, Cao Q, et al. (2008) Drug delivery with carbon nanotubes for in vivo cancer treatment. Cancer Res 68: 6652-6660.

161. Lay CL, Liu HQ, Tan HR, Liu Y (2010) Delivery of paclitaxel by physically mixed polymeric nanoparticles for potent cancer therapeutics. Nanotechnology 21: 065101.

162. Fung L, Chang JT, Yang JH, Chen MC, et al. (2011) Novel nonpeptide RGD ligand density and PEG molecular weight on the conformation of poly(VLγ-glutamyl-glutamate)-paclitaxel conjugates. J Mol Model 17: 2973-87.

163. Liu Y, Huang L, Liu F (2010) Paclitaxel nanocrystals for overcoming multidrug resistance in cancer. Mol Pharm 7: 863-869.

164. Liu F, Park JY, Zhang Y, Conwell C, Liu Y, et al. (2010) Targeted cancer therapy with novel high drug-loading nanocrystals. J Pharm Sci 99: 3542-3551.

165. Deng J, Huang L, Liu F (2010) Understanding the structure and stability of paclitaxel nanocrystals. Int J Pharm 390: 242-249.

166. Zhang X, Zhang X, Wu Z, Gao X, Cheng C, et al. (2011) A hydrotropic β-cyclodextrin grafted hyperbranched polyglycerol co-polymer for hydrophobic drug delivery. Acta Biomater 7: 585-592.

167. Bilensky E, Gürkaynak O, Ertan M, Sen M, Hincal AA (2008) Development of nonsurfactant cyclodextrin nanoparticles loaded with anticancer drug paclitaxel. J Pharm Sci 97: 1519-1529.

168. Bilensky E, Gürkaynak O, Doğan AL, Hincal AA (2008) Safety and efficacy of amphiphilic beta-cyclodextrin nanoparticles for paclitaxel delivery. Int J Pharm 347: 163-170.
187. Memisoglu E, Bochot A, Sen M, Charon D, Duchêne D, et al. (2002) Amphiphilic beta-cyclodextrins modified on the primary face: synthesis, characterization, and evaluation of their potential as novel excipients in the preparation of nanocapsules. J Pharm Sci 91: 1214-1224.

188. Lee JY, Kim KS, Kang YM, Kim ES, Hwang SJ, et al. (2010) In vivo efficacy of paclitaxel-loaded injectable in situ-forming gel against subcutaneous tumor growth. Int J Pharm 392: 51-56.

189. Jeong B, Bae YH, Lee DS, Kim SW (1997) Biodegradable block copolymers as injectable drug-delivery systems. Nature 388: 860-862.

190. Zentner GM, Rathi R, Shih C, McRea JC, Seo MH, et al. (2001) Biodegradable block copolymers for delivery of proteins and water-insoluble drugs. J Control Release 72: 203-215.

191. Wen PY (2010) American Society of Clinical Oncology 2010: report of selected studies from the CNS tumors section. Expert Rev Anticancer Ther 10: 1367-1369.

192. Regina A, Demeule M, Che C, Lavallee I, Poirier J, et al. (2008) Antitumour activity of ANG1005, a conjugate between paclitaxel and the new brain delivery vector Angiopep-2. Br J Pharmacol 155: 185-197.

193. Mei L, Sun H, Song C (2009) Local delivery of modified paclitaxel-loaded poly(epsilon-caprolactone)/pluronic F68 nanoparticles for long-term inhibition of hyperplasia. J Pharm Sci 98: 2040-2050.

194. Kim JH, Kim YS, Kim S, Park JH, Kim K, et al. (2006) Hydrophobically modified glycol chitosan nanoparticles as carriers for paclitaxel. J Control Release 111: 228-234.