Nano Research
https://doi.org/10.1007/s12274-018-2171-0
Review Article
ISSN 1998-0124
CN 11-5974/O4

Current taxane formulations and emerging cabazitaxel delivery systems

Boyang Sun[1,2], Robert M. Straubinger[3], and Jonathan F. Lovell[1,2] (✉)

[1] *Department of Biomedical Engineering, University at Buffalo, State University of New York. Buffalo, NY 14260, USA*
[2] *Department of Chemical and Biological Engineering, University at Buffalo, State University of New York. Buffalo, NY 14260, USA*
[3] *Department of Pharmaceutical Sciences, University at Buffalo, State University of New York. Buffalo, NY 14214, USA*

Received: 23 May 2018
Revised: 9 August 2018
Accepted: 10 August 2018

KEYWORDS
cabazitaxel,
Jevtana®,
taxanes,
drug delivery systems,
nanocarriers

ABSTRACT

Cabazitaxel is a second-generation taxane with promising anti-tumor activity and is approved for treating hormone-refractory metastatic prostate cancer previously treated with docetaxel. Although first-generation taxanes (i.e. paclitaxel and docetaxel) have sparked broad interest in a variety of drug delivery vehicles, fewer have yet been developed for cabazitaxel. This review summarizes several clinical-stage approaches for taxane formulation and recent efforts to develop novel cabazitaxel delivery systems.

1 Introduction

1.1 Background

The taxane family of microtubule-interacting molecules is well-established for treating a broad range of common solid tumors including lung, breast, and ovarian cancers [1]. Paclitaxel and docetaxel (Fig. 1) are first-generation taxanes and have been developed into numerous commercialized formulations in various stages of clinical use, development, or marketing [2]. Notably, paclitaxel formulated with Kolliphor EL (Taxol®), docetaxel formulated in Tween 80 (Taxotere®), and albumin-bound paclitaxel (Abraxane®), have achieved substantial clinical penetration. At the preclinical stage of research, a wide range of unique nanoscale delivery systems have been and continue to be developed for docetaxel and paclitaxel [3, 4].

Cabazitaxel (Fig. 1) is a novel second-generation taxane [5]. Formulated with Tween 80 as Jevtana®, it has activity both in docetaxel-sensitive and docetaxel-resistant tumors owing to lower P-glycoprotein (P-gp)

Address correspondence to jflovell@buffalo.edu

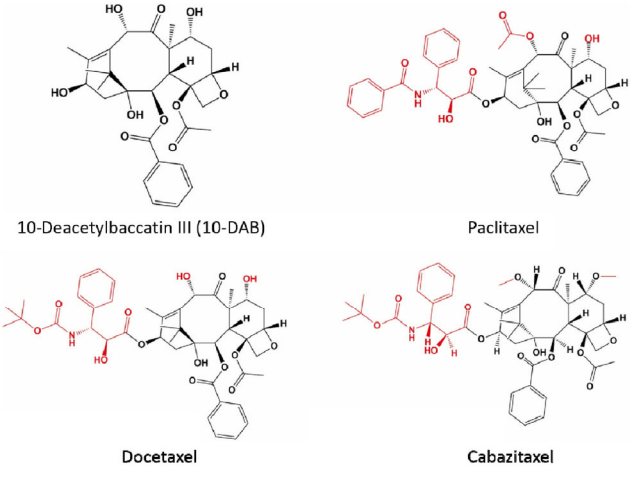

Figure 1 Chemical structures of 10-DAB, paclitaxel, docetaxel, and cabazitaxel.

affinity relative to that of paclitaxel and docetaxel [6, 7]. In a Phase III clinical trial, cabazitaxel treatment induced longer overall survival compared to mitoxantrone treatment in metastatic, castrate-resistant prostate cancer patients previously treated with docetaxel (15 months vs. 12 months), leading to the United States Food and Drug Administration (FDA) approval of Jevtana® for this indication in 2010 [8]. Because cabazitaxel is a newer taxane, fewer delivery systems have been developed for it. On one hand, less precedence for its use might potentially diminish the demand for new cabazitaxel formulations. On the other hand, the creation of intellectual property protection for new and effective cabazitaxel formulations could provide a pathway towards continued cabazitaxel use beyond patent expirations related to Jevtana®. This review summarizes several taxane delivery systems that have undergone substantial clinical development, as insight from these formulations may be relevant for guiding new formulations specific for cabazitaxel. We later summarize recent efforts in developing novel cabazitaxel formulations.

1.2 Paclitaxel and docetaxel

The first-generation taxanes, paclitaxel and docetaxel, have played a key role in frontline chemotherapy of solid tumors for several decades. The discovery of paclitaxel traces back to 1962, when the United States Department of Agriculture and the National Cancer Institute initiated a screening program to identify new anti-cancer drugs from natural sources [9]. Over 110,000 plant extracts were screened from 1960 to 1981. In 1971, Wall and Wani from the Research Triangle Institute extracted paclitaxel from the Pacific Yew tree, *Taxus brevifolia*, and demonstrated its cytotoxic activity [10]. The low yield of paclitaxel from slow-growing Pacific yew trees initially hampered development. Subsequently, it was determined that paclitaxel and other taxanes could be produced semi-synthetically, using 10-deacetylbaccatin III (10-DAB; Fig. 1), a naturally-derived precursor of higher abundance that can be isolated from the European yew tree. Paclitaxel has broad spectrum anti-cancer activity against breast, lung, ovarian, bladder, prostate, head and neck, Kaposi's sarcoma, esophageal, cervical, and endometrial cancers [11, 12].

In 1979, Horwitz identified tubulin as the cellular target of paclitaxel, opening the door for structure-activity optimization of new taxanes [13]. In 1981, a collaboration between Rhône-Poulenc and Institute de Chimie des Substances Naturelles in France resulted in the discovery of docetaxel [14, 15]. Docetaxel replaces an acetate ester group of paclitaxel with a hydroxyl group and a paclitaxel benzyl amide group with a tert-butyl carbamate group. Relative to paclitaxel, docetaxel has 1.9-fold higher tubulin binding affinity and induces the assembly of tubulin at 2.1-fold lower protein concentrations [16]. Improved taxane molecules are desirable because paclitaxel resistance is a major problem associated with its use [17]. Docetaxel has activity in solid metastatic tumors that are resistant to paclitaxel [18–22]; however, docetaxel resistance is also observed [23–26]. Thus, the development of new taxanes is of ongoing interest.

1.3 Cabazitaxel

Chemotherapy resistance can occur when cancer cells overexpress P-gp, which is also known as the multi-drug resistance protein (MDR1) or ATP-binding cassette sub-family B member 1 (ABCB1). P-gp actively pumps out drugs from cells, decreasing their intracellular concentration and cytotoxicity [27]. P-gp activity is thought to be a major cause of resistance to taxanes, although resistance may also arise from mutations that alter tubulin structure, or alterations in intracellular

signaling [28, 29]. To overcome P-gp-mediated taxane resistance, docetaxel derivative libraries were screened using docetaxel resistance models [30]. This screening yielded cabazitaxel. The antitumor efficacy of 450 candidate molecules was evaluated from three perspectives: microtubule de-polymerization activity *in vitro*, killing of resistant cell lines *in vitro*, and antitumor efficacy in a docetaxel-resistant melanoma tumor model (B16/TXT) *in vivo* [7]. The murine B16/TXT tumor model was developed by repeatedly passaging the tumor in docetaxel-treated mice, thus mimicking the process of clinical docetaxel resistance development [7]. Figure 2 shows the structure-activity relationships of cabazitaxel functional groups. Researchers initially replaced the C2′-Boc with other groups and found that *in vitro* cytotoxicity decreased. The modification of the cabazitaxel 3′-phenyl, C2-benzoate, and C4-acetate groups improved *in vitro* activity to some extent, but there was no gain in potency against docetaxel-resistant cell lines. Cabazitaxel replaces docetaxel hydroxyl groups (C7 and C10) with methoxy groups, resulting in higher cytotoxicity in docetaxel-resistant cell lines [31]. Like paclitaxel and docetaxel, cabazitaxel is produced semi-synthetically from 10-DAB. *In vivo*, cabazitaxel shows potent antitumor efficacy both in docetaxel-sensitive and docetaxel-resistant tumor models [32]. In microtubule assays, cabazitaxel has equivalent potency to other taxanes with respect to microtubule stabilization [7]. Cabazitaxel has been reported to cross the blood-brain barrier more efficiently than other taxanes, providing the potential for treating central nervous system tumors [32].

Clinical activity: Prostate cancer is a common malignancy in males. In the United States, there were approximately 190,000 cases diagnosed and 26,000 deaths in 2016 [33]. Androgen deprivation therapy is the standard treatment. However, many men develop resistance and progress to metastatic castration-resistant prostate cancer (mCRPC) [34]. Over 50% of mCRPC patients will develop bone metastases [35]. The standard therapy for mCRPC following androgen deprivation therapy is docetaxel, but eventual tumor resistance is a problem. In Phase III clinical trials, 755 mCRPC patients who were previously treated with docetaxel were randomized and treated intravenously with cabazitaxel (Jevtana®) or mitoxantrone (both

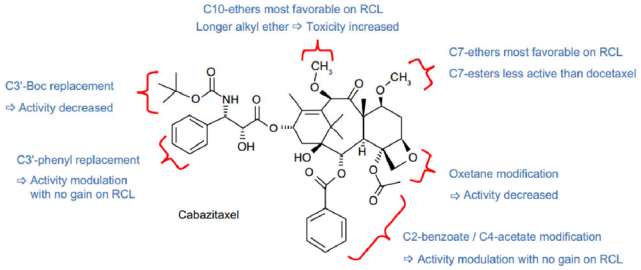

Figure 2 Structure-activity relationships for cabazitaxel. RCL: resistant cell line. Reproduced with permission from Ref. [31], © Wiley-VCH 2012.

were combined with prednisone) [8]. Patients in the Jevtana® treatment group exhibited a longer overall survival (15.1 months) compared to patients in the mitoxantrone treatment group (12.7 months). The median progression-free survival of 2.8 months was twice as long for the Jevtana® group than for the mitoxantrone group. Serious adverse effects (≥ grade 3) in the Jevtana® group included neutropenia (82% of patients) and leukopenia (68% of patients). The FDA approved cabazitaxel for mCRPC in 2010, a milestone in the continuing improvement and advancement of taxanes [8, 36, 37]

1.4 Taxane mechanism of action

As shown in Fig. 3, the cytotoxic mechanism of action of taxanes is interference with microtubule function, which leads to apoptosis [39]. Microtubules are composed of polymerized tubulin protein dimers composed of α-tubulin and β-tubulin monomers. Assembled microtubules exist in a highly dynamic equilibrium with tubulin dimers, in a continuous process of microtubule assembly and disassembly [40]. Taxanes bind β-tubulin, stabilizing microtubules and inhibiting their disassembly (Fig. 4) [41, 42]. Microtubules are an essential component of the eukaryotic cell cytoskeleton, and are involved in mitotic spindle formation, cell shape maintenance, intracellular transport, and cell signaling [39]. By interfering with microtubule dynamics, cells fail to carry out mitosis properly and ultimately die. Taxanes readily bind and dissociate from microtubules and alter tubulin dynamics [43]. In docetaxel-resistant cancer cells *in vitro*, cabazitaxel has a 10-fold lower concentration mediating half-maximal inhibition of cell proliferation (IC_{50}) than docetaxel [7].

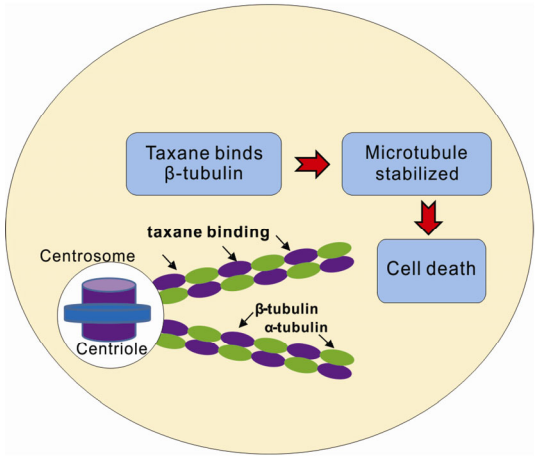

Figure 3 Schematic illustration of taxane mechanism of action. Reproduced with permission from Ref. [38], © Bentham Science Publishers 2015.

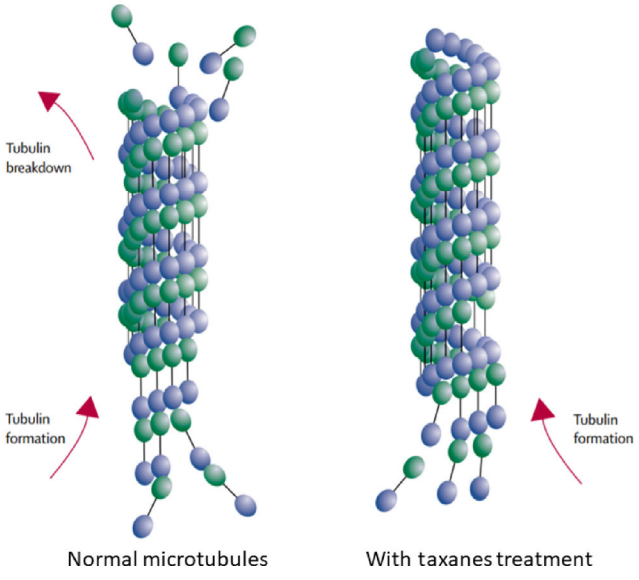

Figure 4 Tubulin and microtubules. Reproduced with permission from Ref. [44], © Elsevier B.V. 2005.

2 Clinically-approved taxane formulations

A desirable taxane formulation should minimize adverse side effects and optimize drug deposition and release at tumor sites. Colloidal stability is also a notable prerequisite, because taxanes tend to undergo molecular aggregation and precipitate out of most delivery vehicles [45–51]. None of the most highly successful taxane formulations (e.g. Taxol®, Taxotere®, Jevtana®, and Abraxane®), are provided in aqueous solution, and they are only stable for a limited period of time following preparation and dilution of the drug formulation for infusion. Taxol®, Taxotere®, and Jevtana® are formulated in liquid surfactants (Tween 80 or Kolliphor EL) to dissolve the drug. However, surfactant administration increases the risk of adverse hypersensitivity reactions [52–55]. Other successful taxane delivery systems include polymeric materials, human albumin, lipid micelles, and polymer or covalently-linked protein conjugates. Overall, there is strong competition amongst numerous nanoscale taxane delivery systems [56]. Insights gained from the development of these formulations could help guide the development of new cabazitaxel formulations. The following descriptions of taxane formulation are selected from those that have undergone some degree of clinical testing.

2.1 Surfactant-based taxane formulations

Paclitaxel was initially commercialized as the Taxol® formulation, which was approved by the FDA in 1992. Taxol® is approved for a broad range of cancers including breast cancer, metastatic breast cancer, non-small lung cancer, ovarian cancer, bladder cancer, and AIDS-related Kaposi's sarcoma [57]. It is used off-label to treat other indications. Each milliliter of Taxol contains 6 mg paclitaxel, 527 mg Kolliphor EL (formerly known as Cremophor EL), and dehydrated alcohol (50% v/v) [55]. It is typically administered intravenously as a 3-hour infusion, with a dose of up to 175 mg/m^2 every three weeks. Each intravenous infusion administers 22–29 g of Kolliphor EL and 21–27 mL of alcohol to the patient. The major serious adverse effects associated with Taxol® include neutropenia, neuropathy, hypotension, and hypersensitivity reactions [58, 59].

Kolliphor EL is a non-ionic liquid surfactant with an approximate molecular weight of 3 kDa. Kolliphor EL has a variable composition and is formed from polyoxyethylene glycerol 35 ricinoleate (Fig. 5). Kolliphor EL is widely used to solubilize hydrophobic drugs, including immunosuppressive agents, anesthetics, photosensitizers, and anticancer drugs. Notably, Kolliphor EL leaches phthalate-type plasticizers from plastic products, which can cause hepatic toxicity [60, 61]. Therefore, standard polyvinylchloride infusion bags and polyethylene tubing must be avoided for Taxol® administration. Kolliphor EL has a relative slow

in vivo clearance and is limited to the central plasma compartment; following a 3-hour infusion, Kolliphor EL has an ~ 84 h elimination half-life (Fig. 5) [62, 63]. The elimination rate of the Kolliphor EL carrier was diminished in patients with severe hepatic dysfunction [64], but not in a patient with impaired renal function [65], even though taxane pharmacokinetics were altered. It has been hypothesized that Kolliphor EL may be degraded by serum carboxylesterases [62]. The slow elimination of Kolliphor EL and its extended residence time in blood can result in undesirable side effects.

Kolliphor EL can activate the complement cascade and trigger acute hypersensitivity reactions [66–69]. It has been suggested that anti-cholesterol antibodies can bind the hydroxyl-surface of Kolliphor EL, and this process underlies the complement activation and hypersensitivity reactions [66]. The minimum Kolliphor EL concentration required for complement activation is 2 μL/mL, which is exceeded when patients receive a conventional dose of Taxol® [70, 71]. To reduce Kolliphor EL-induced hypersensitivity reactions, patients are pre-medicated with immunosuppressive agents such as corticosteroids, diphenhydramine, and H2 antagonists. Furthermore, slow infusion rates are used to minimize the severity of hypersensitive reactions.

The high volumes of Kolliphor EL administered with Taxol® impact paclitaxel pharmacokinetics and pharmacodynamics. Taxol® pharmacokinetics are non-linear with respect to dose: A 30% increase in drug dose can result in a 68% increase in the maximum serum concentration (C_{max}) and an 89% increase in the area under the plasma concentration-time curve (AUC) [55]. Kolliphor EL can alter the interaction between paclitaxel and plasma components, which complicates Taxol® pharmacokinetics. Paclitaxel has higher affinity for Kolliphor EL than for plasma proteins [72], and because of the high concentration of Kolliphor EL in blood, circulating surfactant micelles form, which trap paclitaxel, resulting in Kolliphor-dependent pharmacokinetics profiles. Kolliphor EL also alters the electrophoretic and density gradient of plasma lipoproteins (high density lipoprotein (HDL) and low density lipoprotein (LDL)), further impacting paclitaxel behavior [73]. Some studies have shown that Kolliphor

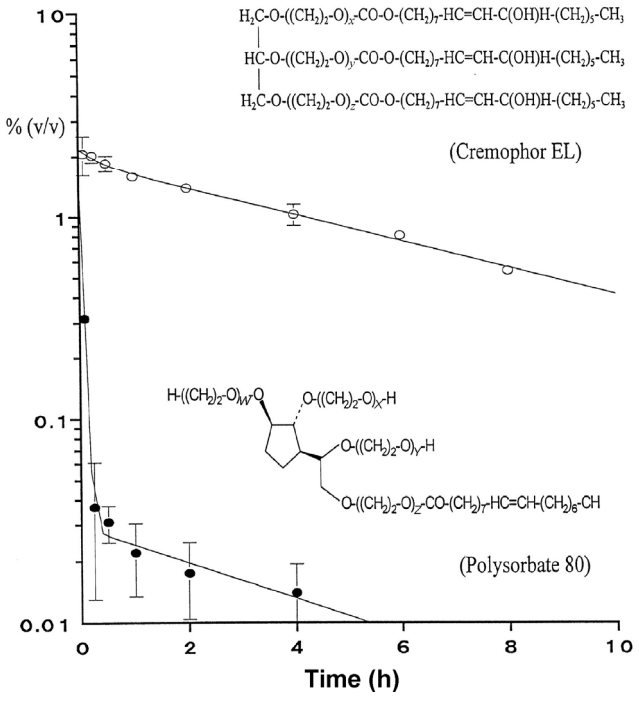

Figure 5 Molecular structures and plasma concentration–time curves of Tween 80 (Polysorbate 80) and Kolliphor EL (formerly known as Cremophor EL) in mice receiving 0.83 mL/kg of each of these surfactants by intravenous bolus injection. Reproduced with permission from Ref. [62], © American Association for Cancer Research 1998.

EL also has affinity for lipoprotein components, thereby decreasing the amount of paclitaxel that can bind to lipoproteins [74].

Taxotere® is a docetaxel formulation containing Tween 80 surfactant and ethanol. In a 20-mL vial of Taxotere®, each milliliter contains 20 mg docetaxel in 1 mL of a 1:1 volume ratio of Tween 80:ethanol. To safely treat ethanol-sensitive patients, Teikoku Pharma developed an alcohol-free formulation, which received FDA approval in 2014. This formulation contains docetaxel, Tween 80, soybean oil, citric acid, and polyethylene glycol 300. Taxotere® is approved by the FDA for treating head and neck, non-small cell lung, breast, and prostate cancers [53, 75]. A typical dose is 75 mg/m^2 administered every three weeks as a 1–2 h intravenous infusion. In Phase III trials, Taxotere®–carboplatin combination treatment demonstrated similar activity as Taxol®–carboplatin in ovarian cancer, and superior overall survival in metastatic breast cancer compared to paclitaxel [18, 76, 77]. Although neutropenia was observed with the treatment, the

recovery period was shorter than for paclitaxel [76].

Jevtana® is a Tween 80-based formulation comprised of 40 mg of cabazitaxel dissolved in 1 mL of Tween 80. A 13% ethanol diluent is required for dilution immediately prior to infusion. In 2010, Jevtana® was approved by the FDA for mCRPC [54]. Dosing is 25 mg/m^2 every three weeks, combined with 10 mg orally administrated prednisone daily. Thus, the cabazitaxel dose is substantially lower than that typically used for Taxol® (175 mg/m^2) or Taxotere® (75 mg/m^2).

Tween 80 has a molecular weight of 1.3 kDa and the structure is shown in Fig. 5. The hydrocarbon chains are hydrophobic and the ethylene oxide units are hydrophilic. Unlike formulations containing Kolliphor EL, Tween 80-based Taxotere® and Jevtana® have pharmacokinetics (AUC or C_{max}) that are linear with increasing dose. Figure 5 shows the more rapid elimination of Tween 80 compared with Kolliphor EL after intravenous injection, which may result from degradation of Tween 80 in blood [62]. Hydrolysis of Tween 80 by carboxylesterases occurs in serum, resulting in oleic acid side chain cleavage [62]. From a hypersensitivity perspective, oleic acid, which is a major building block of Tween 80, causes histamine release and may result in acute hypersensitivity reactions with Taxotere® [78]. Premedication with corticosteroids and antihistamines is used to alleviate hypersensitive reactions [79]. Jevtana® does not induce severe hypersensitive reactions; the reason may lie in the lower amount of Tween 80 administered compared with that in Taxotere®, or the use of oral prednisone.

2.2 Nanoparticle albumin-bound paclitaxel

Abraxane® is also known as protein-bound paclitaxel, ABI-007, or nanoparticle albumin-bound paclitaxel (Nab-Paclitaxel). In 2005, Abraxane was first approved by the FDA for metastatic breast cancer that failed to respond to combination chemotherapy. Abraxane was approved for first-line treatment of advanced non-small cell lung cancer in 2012 and late-stage pancreatic cancer in 2013 [80]. Abraxane® is prepared as a human serum albumin (HSA) colloidal suspension, with an emulsion-solvent evaporation method using high-pressure homogenization. In the synthesis, new albumin disulfide bonds are produced, and 130–150 nm nanoparticles are formed that encapsulate paclitaxel at ~ 10 wt.% [81]. Abraxane® has several advantages over Taxol®. First, the maximum tolerated dose (MTD) of Abraxane® is nearly 50% higher. Second, because of the lack of surfactants, Abraxane® can be infused in just 30 min (without hypersensitivity premedication), as opposed to the 1–3 h infusion with immunosuppression medication required for surfactant-based formulations. Abraxane® exhibited promising anticancer efficacy in Phase III trials in patients with breast cancer [58]. Patients who received 260 mg/m^2 Abraxane® without premedication had a significantly higher response rate than those who received 175 mg/m^2 of Taxol® (33% vs. 19%). In patients treated with Abraxane®, the neutropenia incidence was lower but the neuropathy incidence was higher. Abraxane® also showed superior antitumor efficacy over Taxotere®, with significantly prolonged progression-free survival (12.9 months vs. 7.5 months) [82]. Although high-grade neutropenia was observed with Abraxane® treatment, the frequency was less than that with Taxotere®.

The improved clinical performance of Abraxane® is based on the use of HSA as the nanocarrier. HSA is an abundant plasma protein in blood with a 19-day half-life. It can trap hydrophobic drugs and transport them throughout the body [83]. Creating a colloidal HSA suspension imparts additional beneficial properties. Although the nanoparticulate carrier's circulating lifetime is shorter than that of HSA, the rate of paclitaxel release from the nanoparticle is probably slower than the drug exchange rate of drug from native HSA. As a result, it is likely that the drug leaches from the circulating particles more slowly than it does from other formulations, and plasma concentrations of free (released) drug fall more quickly below an empirically-determined concentration threshold (CT) of 0.05 μM that is associated with toxicity [84]. As a nanoparticle, Abraxane® may accumulate at the tumor site via the enhanced permeability and retention (EPR) phenomenon [85]. Its deposition has also been speculated to be augmented by transcytosis of HSA binding to albumin receptors overexpressed by tumors, such as Secreted Protein Acid and Rich in Cysteine (SPARC) and P-glycoproteins (albondin, 60 kDa) [81, 86–88]. However, this has been called into question due to the anticipated competition from innate albumin in blood, and a lack of data correlating SPARC expression

with Abraxane® deposition in tumor model systems [89, 90].

2.3 Next-generation taxane formulations

Despite the success of surfactant-based and albumin-based taxane formulations, the desire to produce new formulations with improved drug delivery properties and reduced side effects with respect to hypersensitivity, neutropenia, and peripheral neuropathy, has driven innovation and continuing development. Several such formulations are being developed and commercialized, and following the commercial success of Abraxane®, there is currently an intense and ongoing "battle of nano-paclitaxel" [56].

Genexol-PM®, also known as Cynviloq®, is a polymeric micelle paclitaxel formulation. Genexol-PM® employs poly(ethylene glycol)-block-poly(lactic acid) (PEG-b-PLA), a biodegradable amphiphilic block copolymer consisting of 50 wt.%–60 wt.% hydrophilic PEG block, and has a size of ~ 25 nm. Genexol-PM® is prepared via a solvent evaporation method: Paclitaxel and PLA-b-PEG block copolymer are dissolved in acetonitrile and stirred until solvent evaporation. The clear micelle solution is then sterile filtered and lyophilized [19]. Genexol-PM® has exhibited promising results in clinical trials and has a high MTD of up to 390 mg/m^2, which is higher than that of the Abraxane® paclitaxel formulation [91]. The plasma AUC and C_{max} exhibit pharmacokinetic profiles that are generally linear with dose [91]. The effects of Genexol-PM® have been assessed in metastatic breast cancer, non-small cell lung cancer, and pancreatic cancer in Phase II trials and have shown promising antitumor activity [19, 92]. The major side effect is neutropenia. In the Republic of Korea, Genexol-PM® is approved for breast cancer and lung cancer [93].

NK105 is another paclitaxel formulation based on polymeric micelles. Amphiphilic poly(ethylene glycol)-poly(aspartic acid) block copolymers are used and NK105 is formed via self-assembly in solution. The resulting nanoparticles are ~ 85 nm in diameter. NK105 has a prolonged circulating half-life and a dose-dependent C_{max} and AUC. At a dose of 150 mg/m^2, the AUC is approximately 15-fold higher than Taxol [94, 95]. NK105 has been assessed clinically in lung, ovarian, and gastric cancers. In Phase I clinical studies, patients suffered from low grade neuropathy and hypersensitivity. In Phase II trials, patients were administered 150 mg/m^2 by infusion every 3 weeks, and 65% of patients had grade 3 neutropenia, 17.5% of patients had leucopenia, and 8.8% of patients had lymphopenia [94]. However, phase III results of a breast cancer trial failed to show non-inferior progression-free survival compared to Taxol [96]. Because NK105 shows longer persistence in blood, it may have potential to be used as a platform for active targeting strategies to direct the particles to surface receptors found on tumor cells.

PICN® is an injectable paclitaxel formulation comprising polyvinyl-pyrrolidone, cholesteryl sulfate, and caprylic acid [97]. Much of PICN® development has been in India where it is approved to treat breast cancer [98]. PICN® can be infused over 30 min, and has a higher MTD than Abraxane® with equivalent efficiency [97]. The particle size is 100–110 nm and is uniform. PICN® is currently undergoing Phase III testing in the United States.

Liposomes offer numerous advantages as drug delivery vehicles [99]. There has been broad interest in liposomal taxane formulations [100], although liposomal cabazitaxel formulations have yet to be reported. Lipusu® is a paclitaxel formulation that was approved in China in 2006 [101]. Lipusu® has a mean diameter of 400 nm and 99% encapsulation efficacy [102]. This intravenous liposome formulation is prepared with lecithin and cholesterol at a mass ratio of 87:13 [102]. Compared to Taxol®, Lipusu® shows comparable activity against breast, gastric and non-small lung cancer, but with less severe side effects. In Phase I clinical trials, Lipusu® was administered at 175 mg/m^2, the same dose as Taxol®, with premedication with corticosteroids [103]. Side effects included diarrhea, anemia, neutropenia, thrombocytopenia, hepatotoxicity, and chest pain, but these were milder than those of patients treated with Taxol® [104]. Liposome Entrapped Paclitaxel Easy-To-Use (LEP-ETU®) is a liposomal paclitaxel formulation initially developed by Neopharm and then acquired by Insys Therapeutics. This formulation consists of dioleoylphosphatidylcholine (DOPC), cardiolipin, and cholesterol at a molar ratio of 9:0.5:0.5, respectively [105]. LEP-ETU® liposomes are 150 nm and have a

90% drug entrapment efficacy [106]. The formulation exhibited a high MTD of 325 mg/m^2 in a Phase I study [107]. Neutropenia, neuropathy, and dehydration were side effects. Bioequivalence studies showed that LEP-ETU is bioequivalent with Taxol® [108]. LEP-ETU, along with Endotag-1® (below), is liposomal taxane formulations that progressed to Phase II clinical trials [109].

A meta-analysis of clinical pharmacokinetic data for several paclitaxel formulations, including Abraxane®, LEP-ETU®, and Taxol® suggested that drug release rates and overall plasma pharmacokinetics of the nanoparticulate formulations were similar, and projected that neutropenia upon treatment with Abraxane® and LEP-ETU® should be similar if administered head-to-head [84]. Furthermore, the analysis suggested that Taxol® and another surfactant-based formulation have greater toxicity because they mediate sustained, elevated free drug concentrations in plasma, whereas the nanoparticulate formulations more rapidly reduce plasma concentrations below the threshold associated with neutropenia.

SB05, also known as Endotag-1®, is a cationic liposomal formulation of paclitaxel of ~ 200 nm in size [110]. SB05 consists of the cationic lipid 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP) and DOPC at a molar ratio of 53:47 [105, 110]. In a prostate cancer mouse model, EndoTAG-1® induced tumor inhibition and suppressed angiogenesis [111]. Because of the cationic character provided by DOTAP, EndoTAG-1® binds to the tumor vasculature [112, 113]. In Phase II trials in patients with advanced pancreatic cancer, EndoTAG-1® combined with gemcitabine produced a higher survival rate compared to standard therapy [114]. Currently, EndoTAG-1® is in Phase II clinical trials, and a planned Phase III clinical trial will treat triple negative breast cancer at a dose of 135 mg/m^2 paclitaxel every three weeks. The side effects include fatigue, hypersensitivity, fever, and neutropenia.

The oral route for taxane delivery is an emerging approach that provides advantages for patient quality of life and produces somewhat different pharmacokinetic profiles compared to the intravenous route. Pharmacokinetic profiles of oral paclitaxel have lower C_{max}, which is correlated with side effects. An oral approach could allow for more frequent dosing that would sustain paclitaxel serum concentrations for a longer duration over a minimal inhibitory concentration required for cancer cell killing. Patients have more flexibility, as they are not constricted to long infusions at treatment sites, do not have infusion-related pain or side effects, and do not require hypersensitivity pre-medication. Oral delivery opens new possibilities for patients to receive drugs in low-dose, metronomic therapy regimens.

DHP107 is an oral paclitaxel formulation developed by Daehwa Pharmaceutical. DHP107 contains paclitaxel, monoolein, tricaprylin, and Tween 80 at a mass ratio of 1:55:27.5:16.5 [115]. Upon oral administration, DHP 107 spontaneously forms 10-μm diameter micelles inside the gut, and is stable at low pH in the presence of bile acids [116]. DHP107 produces plasma AUCs higher than those of Taxol®. In Phase I clinical trials, DHP107 was safe in patients at doses up to 600 mg/m^2, without grade 4 toxicities [117]. In a Phase III trial, DHP107 showed non-inferior efficacy at 200 mg/m^2 twice daily oral dosing (day 0, 8 and 15, every month), compared with intravenous paclitaxel at 175 mg/m^2 dosing every 3 weeks [118].

Oraxol is an oral paclitaxel product being developed by Athenex that is based on a strategy of co-administration with a P-gp inhibitor. Paclitaxel exhibits low oral availability because of active excretion by P-gp in intestinal epithelial cells [119]. Oraxol was first developed in the Republic of Korea [120]. It is composed of a combination of paclitaxel and HM30181A, a P-gp inhibitor that assists in paclitaxel absorption across the GI tract mucosa. HM30181A is minimally absorbed itself, so is unlikely to reach plasma concentrations sufficient to inhibit systemic P-gp, which could cause side effects. In Phase I clinical trials, the MTD was not determined because no dose-limiting toxicity was observed [121]. High plasma exposure of paclitaxel was observed, demonstrating the proof-of-principle of the HM30181 concept. In Phase II clinical trials, patients with gastric cancer were treated with 150 mg/m^2 paclitaxel, resulting in a median progression-free survival and overall survival of 2.6 and 10.7 months, respectively [121]. The major side effects were neutropenia and diarrhea (≥ grade 3). Currently, Oraxol is in Phase 3 trials for treatment of cutaneous

angiosarcomas (NCT02594371), for which it has received orphan status. It is also being investigated in combination with Ramucirumab (NCT02970539).

A prodrug is a covalently modified form of an active compound that eventually degrades back into the original drug [122]. Compared with the parent drug, prodrugs can offer increased solubility, modulated pharmacokinetics and reduced tissue toxicity, a self-assembly capacity, or improved targeting [123]. PNU166945 is a novel water soluble paclitaxel prodrug reported from the Netherlands, in which paclitaxel was covalently linked onto a propyl-methacrylamide (HPMA) polymer [124]. In Phase I clinical studies, twelve patients were administered a starting dose of 80 mg/m^2. The maximum dose was determined to be 196 mg/m^2. PNU166945 exhibited linear pharmacokinetics with increasing dose and one case of grade 3 neurotoxicity was reported.

Paclitaxel has been covalently conjugated to docosahexaenoic acid (DHA) and developed as Taxoprexin®. The DHA conjugate is a prodrug synthesized from a natural fatty acid conjugated to the paclitaxel 2′-oxygen through an ester bond [125]. This prodrug formulation can self-assemble and accumulates passively at tumor sites. DHA is natural nutrient approved by the FDA that is found in infant milk formula and milk products as a vitamin supplement. Taxoprexin® contains 80% less Kolliphor EL than Taxol®. Because of the low amount of surfactant, patients in Phase I trials were administered Taxoprexin® intravenously over 2 h at doses that ranged from 200 to 1,100 mg/m^2 every 21 days. Grade 3–4 neutropenia was observed at 1,100 mg/m^2. No patients developed peripheral neuropathy or musculoskeletal toxicities [126, 127]. The development of Taxoprexin® demonstrates that despite added complexity, taxane prodrugs can be considered as viable options in taxane formulations.

3 New cabazitaxel delivery systems

Given the advantages of cabazitaxel, including its higher potency and diminished susceptibility to P-gp efflux, novel cabazitaxel formulation strategies are actively being investigated. As shown in Fig. 6, several diverse nanoplatforms have been investigated for cabazitaxel delivery, which will be discussed in this section. The overall goal is to provide compelling advantages over the current commercial cabazitaxel formulation, Jevtana®, as well as other established paclitaxel and docetaxel formulations. The most significant area for improvement is increased antitumor efficacy. Another potential advantage could be decreased toxicity. Traditionally, mitigating toxicity has been a key strategy for the clinical advancement of nanomedicines [128]. Finally, because Jevtana® requires two separate dilutions prior to administration, and is only stable for a limited period following preparation for infusion, new formulations could address technical issues in drug administration.

3.1 Polymeric nanoparticles

Since Kolliphor EL (Taxol®) and Tween 80 (Taxotere® and Jevtana®) are polymeric micelles, polymer-based formulations represent the most frequently investigated taxane delivery approach. Polymeric materials can have diverse compositions, physicochemical properties, and functionalities. Polymer-based taxane delivery systems often make use of non-ionic block copolymers with hydrophilic and hydrophobic domains. Typical polymeric micelles have low critical micelle concentrations (CMC) in aqueous media. Under these conditions, the

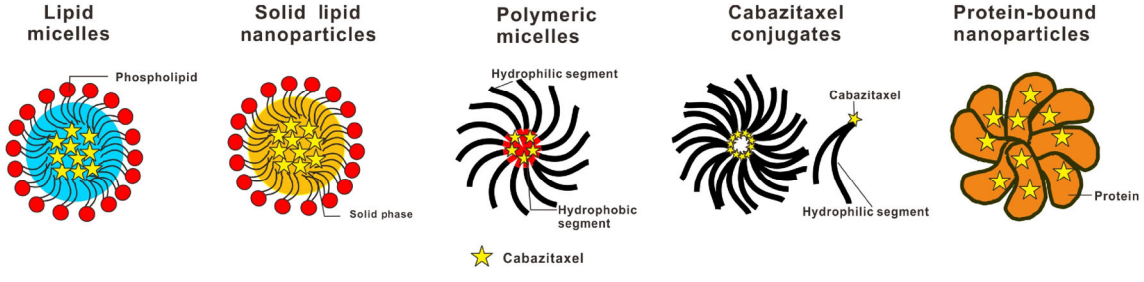

Figure 6 Schematic illustration of several novel cabazitaxel drug delivery platforms that have been demonstrated.

polymer will self-aggregate into 10–200 nm diameter micelle dispersions and incorporate hydrophobic drugs inside the core via hydrophobic interactions [129]. The size of the polymeric micelle may help the nanoparticle undergo tumor deposition through the EPR phenomenon [130]. In many cases, a PEG segment is used as the hydrophilic polymer component, and the hydrophobic component is represented by polyesters, polyethers, poly(amino acids), or other moieties [131, 132]. Many polymers used in drug delivery systems are biodegradable and biocompatible. Polymers such as poly (lactide) (PLA) and poly (lactic-co-glycolic acid) (PLGA) hydrolyze at the ester bond into small, non-toxic molecules [133, 134], releasing their drug cargo in the process. In addition, polymeric micelles can protect hydrophobic drugs against inactivation in the harsh biological environment of the gastrointestinal tract after oral administration [135].

Numerous methods exist to prepare polymeric nanoparticles, such as emulsion/solvent evaporation, nanoprecipitation, and interfacial deposition [136]. Different manufacturing methods result in different formulation properties, and formulation methods depend on the properties of the incorporated drug [136, 137]. Polymeric materials can be formed from a wide variety of polymer types, several of which can control the drug release rate to achieve specific objectives. PEG polymer segments reduce serum opsonization and delay uptake into the reticuloendothelial system, thereby slowing clearance rates [138]. Polymers can be actively targeted by conjugation with targeting ligands [139].

PLGA is a biodegradable and biocompatible copolymer. Cabazitaxel-loaded PLGA nanoparticles have been developed for treating bone metastases. Many types of cancer metastasize to specific locations in the body, including the bone [140]. Advanced-stage prostate cancer is associated with a high incidence of bone metastases, which cause substantial pain, have poor treatment options, and are associated with poor survival. Bone-targeted cabazitaxel-loaded PLGA nanoparticles were developed using an emulsion/solvent evaporation technique [141]. To achieve bone targeting, the micelle surface was modified non-covalently with an amino-bisphosphonate (alendronate), which has high affinity for the hydroxyapatite structure of the bone. A 56% encapsulation efficacy and a 5% drug: polymer ratio were achieved. The mean size was 236 nm following alendronate coating. Both targeted- and non-targeted nanoparticles had efficacy similar to the free drug in two-dimensional (2D) and three-dimensional (3D) *in vitro* prostate cancer cell cultures. However, treatment with the targeted nanoparticles better maintained bone structure integrity and reduced pain in tumor-bearing mouse limbs compared to treatment with the free drug.

PLA is another commonly used biodegradable polymer component. Poly(ethylene glycol)-block-poly(D,L-lactic acid) (PEG-b-PLA) is an FDA approved polymer excipient that has been used extensively in polymeric drug formulations. Nanoparticles formed with PEG-b-PLA can have long circulation times and high tumor uptake through the EPR effect [142]. Genexol-PM, mentioned above, is a successful example of a PEG-b-PLA micellar taxane formulation used for paclitaxel delivery. Cabazitaxel-loaded mPEG-PLA-derivative particles have been developed [143]. Cabazitaxel-loaded micelles formed from a mPEG-PLA polymer were found to be unstable. However, by conjugating N-t-butoxycarbonyl-L-phenylalanine (Boc-L-Phe) to the terminal hydroxyl group of the PLA segment, cabazitaxel-loaded nanoparticles were stabile for at least three weeks in aqueous dispersions without a size change upon dilution. In mice, the pharmacokinetic parameters AUC and C_{max} were increased 26-fold and 10-fold, respectively, compared to those of Jevtana®. Thus, innovations in polymer synthesis and formulation can yield improved cabazitaxel formulations.

Poly(caprolactone) (PCL) is another biocompatible, biodegradable polymer that is widely used for drug delivery. A dispersion method was developed using mPEG-PCL block copolymers to encapsulate cabazitaxel [144]. The nanoparticles not only showed high drug loading (11%) and encapsulation efficiency (99%), but also exhibited slow, sustained drug release. *In vivo* antitumor efficacy was assessed in Lewis lung carcinoma tumors. The mPEG-PCL cabazitaxel nanoparticles delayed tumor growth significantly more than a Tween 80 formulation.

Most polymers can be covalently modified with tumor-targeting ligands, and this strategy has been explored with polymeric cabazitaxel nanoparticles.

PEG-PCL nanoparticle targeting was explored by covalent conjugation of a tumor-metastasis-targeting (TMT) peptide [145]. The TMT peptide binds specifically to a series of metastatic tumors. Following treatment with TMT-modified nanoparticles, metastatic breast cancer cells had a higher rate of necrosis compared to those treated with non-targeted nanoparticles. Based on confocal microscopy, fluorescently labeled nanoparticles were taken up similarly by the non-metastatic MCF-7 cell line, regardless of the presence of the targeting ligand. However, the targeted particles exhibited significantly greater uptake in the MDA-MB-231 human metastatic breast cancer cell line compared to that of non-targeted particles.

PEG is frequently used in drug delivery systems to improve steric stability and prolong blood circulation *in vivo*. However, PEG has potential shortcomings. First, dehydrogenases can oxidize PEG to potentially toxic byproducts *in vivo* [146]. Second, repeated administration of PEG polymer or PEGylated nanoparticles may result in accelerated blood clearance owing to the induction of PEG antibodies [147, 148]. Alternatives to PEG have been investigated. One is poly(N-vinylpyrrolidone) (PVP) [149, 150]. Increasing the PVP block length can prolong circulation times and tumor drug delivery. Poly(N-vinylpyrrolidone)-block-poly(caprolactone) (PVP-b-PCL) colloidal micelles prepared via nanoprecipitation have been used to carry taxanes, with good drug loading, encapsulation efficacy, antitumor efficacy, and survival rates [151]. Self-assembling complexes have been prepared from adamantane-terminated PCL and β-cyclodextrins modified with 4 or 7 poly(N-vinylpyrrolidone) (Fig. 7)

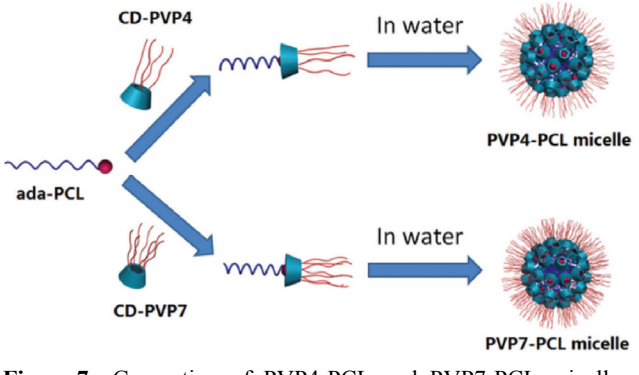

Figure 7 Generation of PVP4-PCL and PVP7-PCL micelles. Reproduced with permission from Ref. [152], © Royal Society of Chemistry 2015.

[152]. The 7-armed PVP supramolecular complex (PVP7-PCL) had greater stability and lower protein adsorption compared to the 4-armed PVP-cyclodextrin. PVP7-PCL complexes loaded with cabazitaxel showed greater cytotoxicity against a paclitaxel-resistant human ovarian cell line (A2780/T) compared to free paclitaxel or free cabazitaxel. In a biodistribution study, cabazitaxel-loaded PVP7-PCL particles produced 2-fold higher drug concentrations in tumors compared to free drug. They also induced greater tumor growth inhibition and survival compared to the free drug.

Polymer crosslinking can result in more stable nanoparticle size and improved cargo entrapment. Cross-linkable, acid-sensitive micelles have been developed for cabazitaxel delivery [153] (Fig. 8). The amphiphilic copolymer is comprised of three blocks: PEG as a hydrophilic segment, poly(methyl methacrylate) (PMMA) as a hydrophobic segment, and a central polyacrylic acid (PAA) block to crosslink and control the release of the drug. *In vitro* drug release studies showed that the non-crosslinked nanoparticles had a faster release rate compared to those of shell cross-linked micelles (SCLM). The release of cabazitaxel from SCLM in a 30 h period increased from 30% to 85% in response to mild acidic stimuli (pH 5.0). SCLM containing cabazitaxel exhibited high cytotoxicity in PC3 and C4-2B cancer cells.

To solubilize hydrophobic drugs for intravenous injection, surfactants such as Kolliphor EL or Tween 80 are commonly employed, but come with side-effects such as complement activation that alternative solubilization approaches may bypass [154].

Toward the goal of minimizing surfactant use, Zhang et al. demonstrated a unique Poloxamer Pluronic 127 (F127) tri-block copolymer drug delivery system, which could deliver numerous hydrophobic drugs including cabazitaxel [155, 156]. By lowering the formulation temperature below the Pluronic critical micelle temperature, unincorporated surfactants could be stripped away from the system by membrane filtration, leaving behind therapeutic micelles with high drug:surfactant ratios (Fig. 9). Cabazitaxel micelles produced in this fashion could be further stabilized with co-loading of other inert hydrophobic cargo (such as α-tocopherol) and by storage in a hypertonic saline solution. Surfactant-stripped cabazitaxel subs-

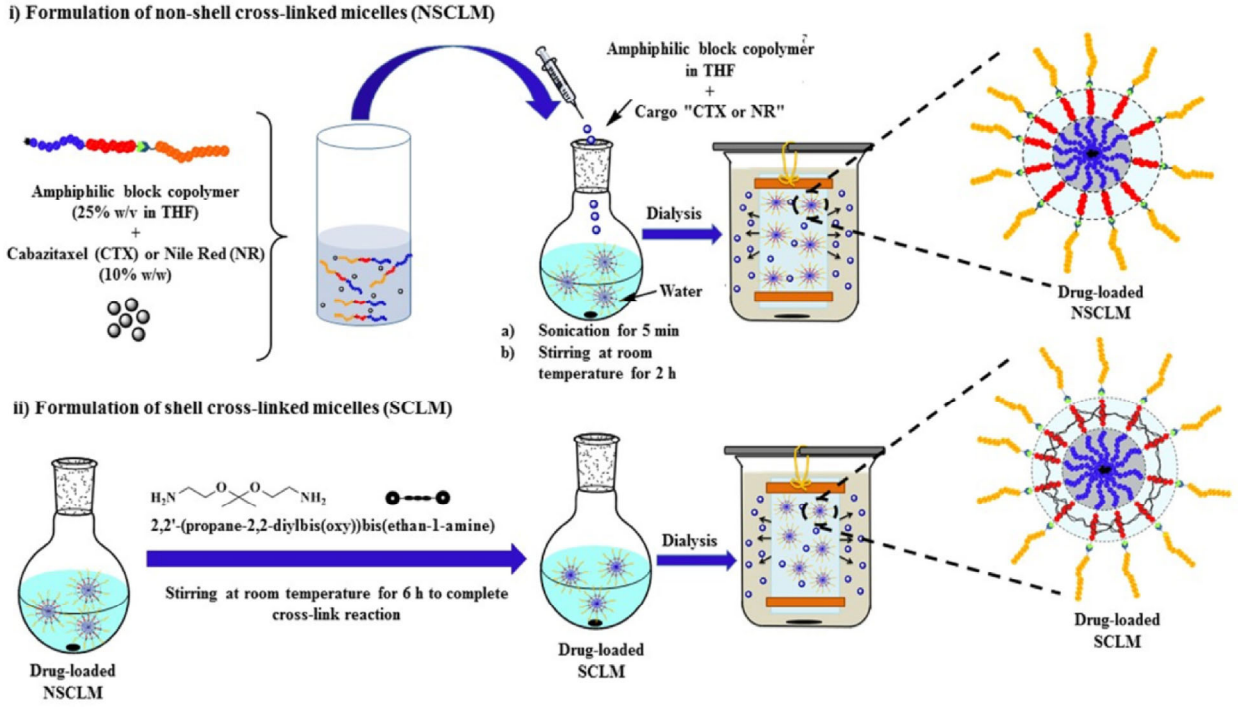

Figure 8 Formulation of polymers into acid-sensitive cross-linked micelles. Reproduced with permission from Ref. [153], © American Chemical Society 2016.

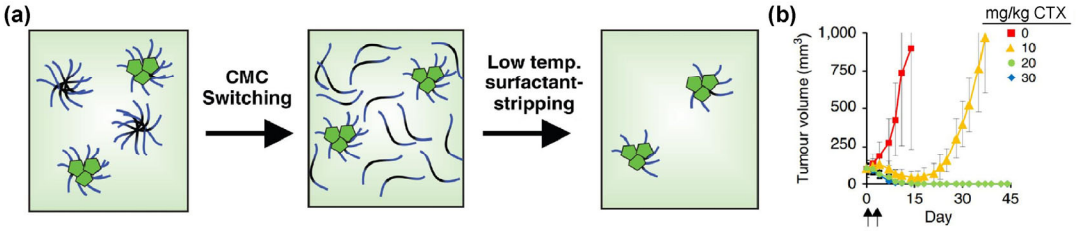

Figure 9 (a) Surfactant-stripped cabazitaxel micelles prepared by low-temperature surfactant stripping of Pluronic surfactant. (b) Anti-tumor efficacy of surfactant-stripped cabazitaxel following intravenous injection in nude mice bearing subcutaneous MIA Paca-2 tumors at the cabazitaxel doses indicated. Reproduced with permission from Ref. [155], © Zhang, Y. M., et al. 2016.

tantially delayed the growth of subcutaneous MIA PaCa-2 human pancreatic xenograft growth with intravenous cabazitaxel doses between 10–30 mg/kg, with no palpable tumors detected at higher dosing levels.

3.2 Lipid-based delivery systems

Liposomes are a common drug delivery system, and numerous liposomal taxane formulations have been developed. However, to the best of our knowledge, there have not yet been reports of liposomal cabazitaxel.

Lipid micelles consist of self-assembled low-molecular-weight lipids that surround a hydrophobic core [157]. Hydrophobic drugs can be encapsulated in the lipophilic inner core, with the hydrophilic lipid headgroups facing outward to the aqueous environment. Outward-facing hydrophilic lipid headgroups can be covalently modified by polymers such as PEG to extend blood circulation time or to attach targeting ligands to achieve better uptake in cancer cells. An intravenous lipid emulsion for cabazitaxel delivery was prepared using high-pressure homogenization [158]. The formulation was composed of medium-chain triglycerides, glycerin, and Pluronic F68. Pluronic F68 is an FDA-approved surfactant excipient for intravenous formulations. The addition of cholesterol was found to inhibit cabazitaxel

degradation; cholesterol protected drug from ester hydrolysis in the aqueous phase and oil phase. Compared to a formulation lacking cholesterol, cholesterol increased the cabazitaxel chemical stability from 134 to 831 days.

Cabazitaxel has been formulated for targeted delivery using a lipid-polymer hybrid surfactant system. Bombesin (BN) is a 14-amino-acid peptide that binds several receptors, including the neuromedin B and gastrin-releasing peptide (GRP) receptors [159, 160]. It was previously observed that conjugating bombesin to docetaxel-loaded PLGA nanoparticles conferred superior antitumor effects in breast cancer cells overexpressing the GRP receptor [161]. Using a similar approach, BN-polyethyleneglycol-1,2-distearoyl-sn-glycero-3-phosphoethanolamine (BN-PEG-DSPE) was synthesized and used to encapsulate cabazitaxel in hybrid lipid polymer nanoparticles [162]. *In vitro* and *in vivo* studies showed that these targeted nanoparticles had strong inhibitory activity in tumor cells that expressed the GRP receptor.

Cholesterol has been used to modify the behavior of polymer-based cabazitaxel delivery systems. Cholesterol was conjugated to Pluronic F68, and this hybrid lipid was used to encapsulate cabazitaxel via self-assembly (Fig. 10) [163]. After conjugation, the cholesterol-F68 copolymer had a relatively low CMC (10 μg/mL), which is 400-fold lower than the Pluronic F68 CMC, which conferred stability against precipitation upon dilution following intravenous injection into the bloodstream. The cabazitaxel-loaded cholesterol-F68 nanoparticles showed higher antitumor cytotoxicity against S180 cells compared to a Tween 80 formulation both *in vitro* and *in vivo*.

Solid lipid nanoparticles (SLNs) contain a solid lipid core and can be stabilized with surfactants such as Pluronic and lecithin [164]. Because of the reduced mobility of drugs in the lipid core, SLNs can control the release of the drug. SLNs can be prepared directly with methods such as high-pressure homogenization, providing potential for industrial-scale synthesis [165]. Cabazitaxel-loaded SLNs were developed and evaluated in antitumor studies [166]. The formulation was comprised of Compritol 888 ATO, didodecyldimethylammonium bromide, and tocopheryl polyethylene glycol succinate (TPGS). The outer shell was

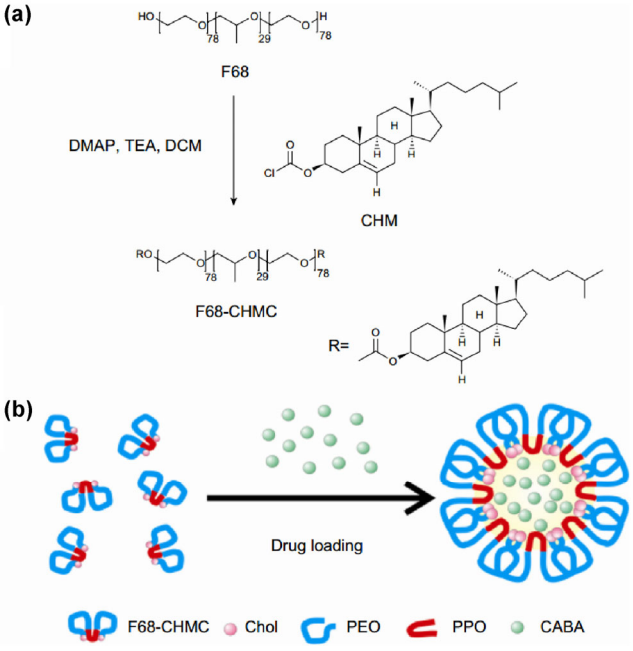

Figure 10 Synthesis and preparation of cholesterol-modified Pluronic F68 micelles. (a) Synthesis of F68-CHMC. (b) Preparation of cabazitaxel-loaded F68-CHMC micelles. Abbreviations: CABA: cabazitaxel; CHM, cholesteryl chloroformate; F68-CHMC, cholesterol-coupled F68; DMAP, 4-dimethylaminopyridine; TEA: triethylamine; DCM, dichloromethane; CHOL: cholesterol; PEO, poly(ethylene oxide); PPO, poly(propylene oxide). Reproduced with permission from Ref. [163], © Dove Medical Press 2014.

modified with hyaluronic acid (HA) as a targeting ligand for the CD44 receptor. HA is a biocompatible and biodegradable polysaccharide found in the extracellular matrix. Because many tumors overexpress HA receptors such as CD44 and hyaluronic-mediated motility receptor (RHAMM), HA has been used as a targeting agent for drug delivery systems. *In vitro* cell viability studies indicated that the nanoparticles had higher cytotoxicity than free drug and non-targeted nanoparticles in the human MCF-7 breast cancer cell line, which expresses the CD44 receptor.

3.3 Albumin

HSA is the most abundant plasma protein in blood (35–50 mg/mL in human serum), and it has been widely used for drug delivery. HSA is produced in the liver and has an average molecular weight of 66.6 kDa [167]. With a 19-day circulating half-life, HSA has potential to improve drug pharmacokinetic profiles. In addition to formulations of paclitaxel (as Abraxane®), HSA has also been explored as a carrier

for many compounds including penicillin, insulin, sulfonamides, and metals [167, 168].

Qu et al. examined two different methods to formulate cabazitaxel with HSA: high-pressure homogenization and salting-out [169, 170]. The salting-out method eliminates the need for organic solvents during preparation. The resulting HSA cabazitaxel nanoparticles (CTX-Nps) had no significant hemolytic activity compared to a Tween 80 formulation. The levels of blood urea nitrogen and serum creatinine in treated mice showed that CTX-Nps were less toxic to the kidneys than the Tween 80 formulation. CTX-Nps also showed prolonged blood circulation and greater cabazitaxel accumulation in tumor tissues compared to the Tween 80 formulation. CTX-Np activity was demonstrated in human PC3 (prostate), HCT116 (colorectal), and A549 (lung) cancer cell lines [169, 170].

Theranostic approaches frequently integrate imaging and therapeutic modalities into a single nanoparticle [171]. A near infrared light-absorbing photothermal agent, indocyanine green (ICG), was combined with cabazitaxel and HSA to generate ICG-HSA-CTX nanoparticles [172]. ICG is an FDA-approved, cyanine-based near-infrared organic dye with peak absorption at 805 nm. ICG can be therefore used as a light-absorbing contrast agent for photothermal therapy [173]. Administration of ICG-HSA-CTX nanoparticles, followed by tumor laser irradiation, resulted in tumor growth inhibition in a 4T1 tumor model.

3.4 Cabazitaxel conjugates

Covalent drug conjugation to carriers by chemical or enzymatic modification aims to achieve improved therapeutic properties compared to the parent drug. Carboxymethylcellulose is an FDA-approved cellulose derivative, used in medicine and manufacturing of food products including toothpaste, ice cream, and cosmetics [174, 175]. Because of its biocompatibility, it has been used in drug delivery applications. Cabazitaxel was conjugated to carboxymethylcellulose, resulting in a self-assembled, cellax-CTX polymer [176]. The cellax platform has also been demonstrated to effectively deliver a range of other anti-cancer hydrophobic drug conjugates, including docetaxel [177, 178]. Cellax-CTX nanoparticles exhibited sustained cabazitaxel release in serum. When mice were treated at the MTD, cellax-CTX induced limited neutropenia that was reversible, and no histological damage was observed. Cellax-CTX improved the survival rate in an mCRPC mouse model of bone metastasis to 120 days, which was 3-fold greater than that of free cabazitaxel (40 days). Cabazitaxel was also conjugated to a cellulose backbone together with PEG segments [179] to create nanoparticles with long-term stability and narrow polydispersity. A flash nanoprecipitation procedure was used, in which the cabazitaxel conjugate and an amphiphilic copolymer were dissolved in organic solvent, and rapidly mixed in a multi-inlet vortex mixer. The resulting cellax nanoparticles showed a size of 60 nm with narrow polydispersity, and were stable for over six months. The nanoparticles showed cytotoxic activity against the PC3 cancer cell line.

In addition to non-covalent drug adsorption (as in Abraxane®), HSA has also been used as a scaffold for covalent drug conjugation. Researchers previously demonstrated that paclitaxel or docetaxel conjugated to HSA (via succinic anhydride) shows improved tumor inhibition and reduced tissue cytotoxicity [180, 181]. This approach was adopted for cabazitaxel [182]. The linker designed for drug conjugation was composed of methacrylic acid and N-acetyl cysteine. Folic acid was also conjugated to HSA to impart targeting to cancer cells that overexpress the folate receptor. Compared to free cabazitaxel, the resulting targeted nanoparticles showed increased *in vitro* growth inhibition of cancer cells overexpressing the folate receptor.

A polymer's physical structure can influence the behavior and efficacy of drug conjugates [183, 184]. For example, the conjugation position of the active drug may change the properties of the resulting nanoparticles. PEG-PLA copolymers were prepared with cabazitaxel conjugated either between the PEG and PLA segments, creating a branched Y-shaped construct, or at the end of the PLA segment (Fig. 11) [185]. Y-shaped cabazitaxel had 2-fold faster drug release profile compared linear shaped particles, owing to greater accessibility for hydrolysis. Thus, the design of the conjugate can control key properties of the formulation.

Numerous strategies have been adopted for stimulus-triggered drug delivery [186–188]. Redox-sensitive drug

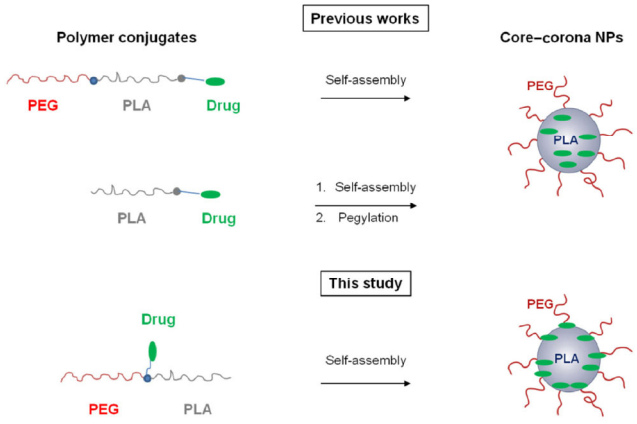

Figure 11 Various types of mPEG-PLA polymer/drug conjugates. Reproduced with permission from Ref. [185], © American Chemical Society 2013.

delivery strategies have been described to control drug release in the appropriate cancer cell microenvironments [189]. Redox-sensitive micelles usually contain disulfide linkages, which are stable in the mild oxidizing environment of blood but are sensitive to the intracellular reducing environment, as is observed for molecules such as glutathione (GSH) in tumor tissues [190]. The reducing environment leads to cleavage of the disulfide linkages, resulting in drug release. This approach has been applied with cabazitaxel-loaded micelles formed with redox- sensitive disulfide bonds [191]. In another approach, cabazitaxel was conjugated with citronellol via disulfide linkages (CIT-ss-CTX), and self-assembled in aqueous solution (Fig. 12) [192]. Citronellol is an FDA-approved, naturally-derived acyclic monoterpenoid that is widely used in food processing. The PEGylated phospholipid anchor DSPE-PEG_{2000} was added to the formulation as an emulsifier and to prolong blood circulation by reducing reticuloendothelial system clearance. The CIT-ss-CTX nanoparticle was stable and showed a higher drug loading ratio than alternative polymeric nanoparticles or micelles. Cancer cell toxicity of the conjugate was observed in PC3 and A549 cell lines. The CIT-ss-CTX construct could also carry hydrophobic dyes (6-coumarin and DiR) for theranostic applications, as well as other bioactive cargo (e.g. curcumin) [192].

Because anaerobic glycolysis is highly active in oxygen-deprived tumor cells, solid tumor microenvironments tend to be relatively acidic (pH 5.7–7.8, mean pH 7.0), whereas blood remains constantly neutral (pH 7.4) [193–195]. Cabazitaxel conjugation with a pH-sensitive bond provides a mechanism to release the drug in acidic tumor tissues and achieve localized drug release and activation. Cabazitaxel was attached to dextran via pH-sensitive ester linkers (succinate or glutarate), improving drug solubility 1,500-fold [196]. The cabazitaxel-succinate-dextran conjugate linkages were hydrolyzed in acidic conditions *in vitro* to release free cabazitaxel. The succinate-conjugated nanoparticles exhibited higher cytotoxicity in MCF-7 breast cancer cells compared to the free drug.

3.5 Comparison of cabazitaxel formulations

Beyond the Jevtana® formulation, most, if not all cabazitaxel formulations, are at very early stages of development, with no Phase I data reported yet.

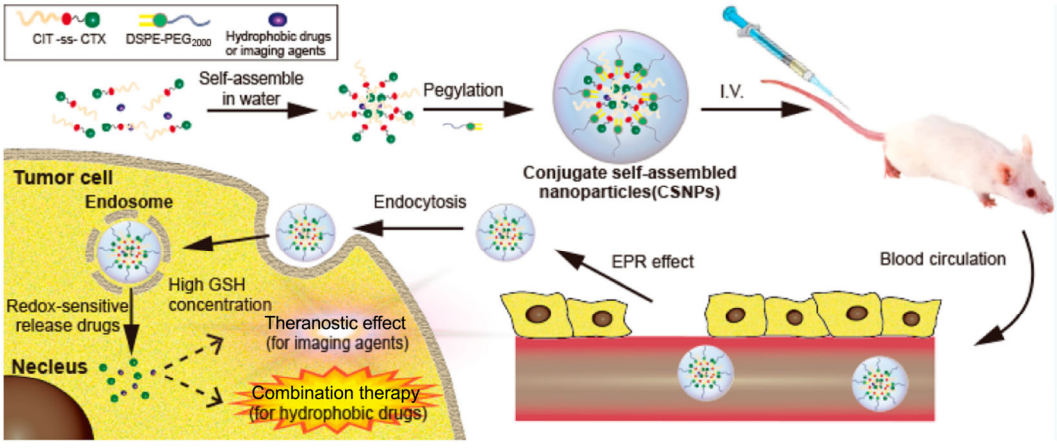

Figure 12 Illustration of CIT-ss-CTX nanoparticles and functionality. Reproduced with permission from Ref. [192], © American Chemical Society 2016.

Nevertheless, numerous drug delivery systems for cabazitaxel have been reported, as shown in Table 1. These include formulations with diverse polymeric materials, lipid micelles, albumin nanoparticles, and drug conjugates, and the use of active targeting moieties has been demonstrated. Numerous factors, such as ease and feasibility of scale-up and reproducibility of batch production, could impact the progression of some of the formulations. Production cost is another factor.

The *in vitro* and/or *in vivo* anti-tumor efficacy of several cabazitaxel formulations are shown in Table 2. Ultimately, the success and translation of these formulations will likely depend on reduced toxicity or compelling anti-tumor efficacy compared to Jevtana® and other established taxane formulations that are current standards of care. Most preclinical research has focused on prostate, lung, and breast cancer.

The pharmacokinetic parameters of various cabazitaxel formulations are shown in Table 3. Knowledge of these parameters is essential for understanding observed anti-tumor efficacy and toxicity.

Table 1 General summary of selected cabazitaxel nanoparticles

Platform	Material	Preparation	Drug loading (%)	EE (%)	Size (nm)	PDI	Ref.
Polymer micelles	mPEG-PCL	Solid dispersion	11	99	29	0.11	[144]
	TMT-PEG-PCL	Solvent evaporation		83	110	0.38	[145]
	PVP-PCL	Self-assembly	14	85	110		[152]
	PEG-PAA-PMMA	Dialysis	55		40–50		[153]
	mPEG-PLA-Phe	Solid dispersion–thin film hydration	5	98	17	0.020	[143]
	F127	Solvent evaporation			62	0.1	[197]
	PLGA	Solvent evaporation	4	56	200–250		[141]
Lipid micelles	F68-Cholesterol	Self-assembly	3	98	18		[163]
	Lipid microspheres	High-pressure homogenization		98	200		[197]
	Lipid emulsion with F68 and cholesterol	High-pressure homogenization		98	197		[158]
	BN-CTX-LPN	Nanoprecipitation	10	90	127	0.19	[162]
Solid lipid nanoparticles	Hyaluronic-acid targeted SLNs	Homogenization and sonication	4	72	210	0.13	[166]
Protein-bound	HSA	Self-assembly	5	97	240	0.13	[198]
	HSA	Salting out	5				[169]
	HSA	Self-assembly		53	170		[170]
	AN-ICG-CTX	High-pressure homogenization	8	91	171	0.16	[172]
Cabazitaxel-conjugates	CIT-ss-CTX	Nanoprecipitation	61		153	0.081	[192]
	Cellax	Nanoprecipitation	36		96	0.12	[176]
	Cellax	Flash nanoprecipitation			58	< 0.044	[179]
	Y-shape mPEG-PLA-CTX	Solvent evaporation	8		20–25	0.17	[185]
	Albumin-PEG-folate-CTX	Carbodiimide reactions	2		138	0.25	[182]
	Dextran-CTX-succinate, Dextran-CTX-glutarate	Self-assembly					[196]

Table 2 Antitumor efficacy of cabazitaxel nanoparticles *in vivo* and *in vitro*

Delivery system	*In vitro* cell line toxicity IC50	Tumor model	*In vivo* dose (mg/kg)	Note	Ref.
mPEG-PCL	0.6 μg/mL (Lewis lung carcinoma)	Lewis lung carcinoma	10 (day 6, 9, 12, 15)	Higher inhibition (85% vs. 65% free drug), longer median survival (45 vs. 36 days free drug)	[144]
TMT-PEG-PCL	MCF-7, MDA-MB-231	—	—	Metastatic MDA-MB-231 cells treated with targeted nanomicelles exhibited a increase in fluorescence	[145]
PVP-PCL	16 ng/mL (A549) 269 ng/mL (A2780)	H22	10	Prolonged survival compared to free drug	[152]
PEG-PAA-PMMA	NSCLM: 0.6 nM (PC-3); 2.7 nM (C4-2B). SCLM: 5.1 nM (PC-3); 2.7 nM (C4-2B)	—	—	—	[153]
mPEG-PLA-Phe	43 ng/mL (NCI-H460) Similar IC50 as Jevtana®	—	—	—	[143]
Surfactant-stripped micelles	—	MIA Paca-2	10, 20 or 30 (day 0, 4)	10 mg/kg delayed tumor growth, 20 and 30 mg/kg prevented tumor growth	[155]
PLGA	C4–2B, PC3	PC3	(day 7, 14, 21, 28)	Superior than free drug	[141]
F68-cholesterol	28 ng/mL (S180)	S180	5 (day 3, 6, 9, 12)	Superior than free drug	[163]
Bombesin lipid-polymer hybrid nanoparticles	0.6 μM (PC3)	PC3	—	Higher tumor growth inhibition ratio with targeting	[162]
Hyaluronic acid solid lipid nanoparticles	~ 1 μg/mL (MCF-7)	—	—	—	[166]
HSA	25 μg/mL (HCT116) 90 μg/mL (A549)	HCT116	10 (every 3 days)	—	[198]
HSA	—	Prostate cancer	8 (every 3 days)	Suppressed tumor growth	[169]
HSA	PC3, A549	—	—	—	[170]
AN-ICG	4T1	4T1	10 (day 0, 3, 6)	Higher tumor inhibition with laser treatment	[172]
CIT-ss-CTX	0.7 nM (PC3), 4 nM (A549)	—	—	—	[192]
Cellax		PC3	33, 41 or 55 (day1, 3, 6)	Prolonged survival by 70%	[176]
Cellax	1–2 nM (PC3)	—	—	—	[179]
Albumin-PEG-folate	10 nM (HT-29), 17 nM (MDA-MB-231)	—	—	—	[182]
Dextran-CTX-succinate, Dextran-CTX-glutarate	MCF-7	—	—	—	[196]

Table 3 Select pharmacokinetic parameters of cabazitaxel nanoparticles

Cabazitaxel formulation	Animal	CTX dose (mg/kg)	$AUC_{0\rightarrow\infty}$ (mg·h/L)	Half-life (h)	C_{max} (μg/mL)	Ref.
mPEG-PLA-Phe	Sprague−Dawley rats	5	12.1[a]	1.0	10	[143]
Jevtana®	Sprague−Dawley rats	5	0.5[a]	0.5	1	[143]
Lipid microspheres	Wistar rats	4	2.5	6.9	2.2[b]	[197]
Tween 80	Wistar rats	4	1.3	8.2	1.3[b]	[197]
HSA	Wistar rats	8	15.5	34.1	6.6	[169]
Tween 80	Wistar rats	8	11.7	10.9	3.1	[169]
Redox-sensitive citronellol conjugate	Sprague−Dawley rats	3	2.7	6.7	2[b]	[192]
Jevtana	Humans	25 (mg/m^2)	0.8	89	0.2	[32]

[a]0→24 h half-life reported; [b]estimated from cabazitaxel serum kinetic graph.

4 Future perspectives

Cabazitaxel is an effective second-generation taxane that has demonstrated activity in docetaxel-resistant tumors. Diminished affinity towards P-glycoprotein drug efflux transporters and better penetration of the blood-brain barrier have been proposed as potential clinical advantages of cabazitaxel over other taxanes. Taxol® (paclitaxel), Taxotere® (docetaxel), Abraxane® (paclitaxel), and now Jevtana® (cabazitaxel) have achieved clinical and commercial success, providing motivation for further development of cabazitaxel drug delivery systems. The numerous paclitaxel and docetaxel delivery systems that are approved or in various stages of clinical trials can provide insights for the design and production of cabazitaxel formulations having improved properties such as prolonged plasma circulation time or reduced side effects. Researchers have formulated cabazitaxel in various types of drug delivery systems. Even though many types of cabazitaxel drug delivery systems have been reported (e.g. Table 1), some formulation strategies that have been successful for other taxanes, such as liposomes, have not been reported yet. The breadth of taxane formulations that remain unexplored for cabazitaxel suggest additional and improved delivery systems may be devised in the future.

Acknowledgements

This work was supported by the National Institutes of Health (No. DP5OD017898). We thank Dr. Michael Smolinski for valuable discussion and feedback.

References

[1] Crown, J.; O'Leary, M. The taxanes: An update. *Lancet* **2000**, *355*, 1176–1178.

[2] Yared, J. A.; Tkaczuk, K. H. R. Update on taxane development: New analogs and new formulations. *Drug Des. Devel. Ther.* **2012**, *6*, 371–384.

[3] Zhao, P. X.; Astruc, D. Docetaxel nanotechnology in anticancer therapy. *ChemMedChem* **2012**, *7*, 952–972.

[4] Zhang, Z. P.; Mei, L.; Feng, S. S. Paclitaxel drug delivery systems. *Expert Opin. Drug Deliv.* **2013**, *10*, 325–340.

[5] Paller, C. J.; Antonarakis, E. S. Cabazitaxel: A novel second-line treatment for metastatic castration-resistant prostate cancer. *Drug Des. Devel. Ther.* **2011**, *5*, 117–124.

[6] Kartner, N.; Riordan, J. R.; Ling, V. Cell surface P-glycoprotein associated with multidrug resistance in mammalian cell lines. *Science* **1983**, *221*, 1285–1288.

[7] Vrignaud, P.; Sémiond, D.; Lejeune, P.; Bouchard, H.; Calvet, L.; Combeau, C.; Riou, J. F.; Commerçon, A.; Lavelle, F.; Bissery, M. C. Preclinical antitumor activity of cabazitaxel, a semisynthetic taxane active in taxane-resistant tumors. *Clin. Cancer Res.* **2013**, *19*, 2973–2983.

[8] De Bono, J. S.; Oudard, S.; Ozguroglu, M.; Hansen, S.; Machiels, J. P.; Kocak, I.; Gravis, G.; Bodrogi, I.; Mackenzie, M. J.; Shen, L. J. et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: A randomised open-label trial. *Lancet* **2010**, *376*, 1147–1154.

[9] Cragg, G. M. Paclitaxel (Taxol®): A success story with valuable lessons for natural product drug discovery and development. *Med. Res. Rev.* **1998**, *18*, 315–331.

[10] Cragg, G. M.; Newman, D. J. A tale of two tumor targets: Topoisomerase I and tubulin. The Wall and Wani contribution to cancer chemotherapy. *J. Nat. Prod.* **2004**, *67*, 232–244.

[11] Rowinsky, E. Paclitaxel pharmacology and other tumor types. *Semin. Oncol.* **1998**, *24*, S19-1–S19-12.

[12] Rowinsky, M.; Eric, K. The development and clinical utility of the taxane class of antimicrotubule chemotherapy agents. *Annu. Rev. Med.* **1997**, *48*, 353–374.

[13] Schiff, P. B.; Fant, J.; Horwitz, S. B. Promotion of microtubule assembly *in vitro* by taxol. *Nature* **1979**, *277*, 665–667.

[14] MacConnachie, A. Docetaxel (Taxotere, Rhone-Poulenc Rorer). *Intensive Crit. Care Nurs.* **1997**, *13*, 119–120.

[15] Guenard, D.; Gueritte-Voegelein, F.; Potier, P. Taxol and taxotere: Discovery, chemistry, and structure-activity relationships. *Acc. Chem. Res.* **1993**, *26*, 160–167.

[16] Diaz, J. F.; Andreu, J. M. Assembly of purified GDP-tubulin into microtubules induced by taxol and taxotere: Reversibility, ligand stoichiometry, and competition. *Biochemistry* **1993**, *32*, 2747–2755.

[17] Yusuf, R. Z.; Duan, Z.; Lamendola, D. E.; Penson, R. T.; Seiden, M. V. Paclitaxel resistance: Molecular mechanisms and pharmacologic manipulation. *Curr. Cancer Drug Targets* **2003**, *3*, 1–19.

[18] Jones, S. E.; Erban, J.; Overmoyer, B.; Budd, G. T.; Hutchins, L.; Lower, E.; Laufman, L.; Sundaram, S.; Urba, W. J.; Pritchard, K. I. et al. Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. *J. Clin. Oncol.* **2005**, *23*, 5542–5551.

[19] Lee, K. S.; Chung, H. C.; Im, S. A.; Park, Y. H.; Kim, C. S.; Kim, S. B.; Rha, S. Y.; Lee, M. Y.; Ro, J. Multicenter phase II trial of Genexol-PM, a cremophor-free, polymeric micelle

formulation of paclitaxel, in patients with metastatic breast cancer. *Breast Cancer Res. Treat.* **2008**, *108*, 241–250.

[20] Untch, M.; Untch, A.; Sevin, B. U.; Angioli, R.; Perras, J. P.; Koechli, O.; Averette, H. E. Comparison of paclitaxel and docetaxel (Taxotere) in gynecologic and breast cancer cell lines with the ATP-cell viability assay. *Anti-Cancer Drugs* **1994**, *5*, 24–30.

[21] Valero, V.; Jones, S. E.; Von Hoff, D. D.; Booser, D. J.; Mennel, R. G.; Ravdin, P. M.; Holmes, F. A.; Rahman, Z.; Schottstaedt, M. W.; Erban, J. K. et al. A phase II study of docetaxel in patients with paclitaxel-resistant metastatic breast cancer. *J. Clin. Oncol.* **1998**, *16*, 3362–3368.

[22] Verschraegen, C. F.; Sittisomwong, T.; Kudelka, A. P.; de Paula Guedes, E.; Steger, M.; Nelson-Taylor, T.; Vincent, M.; Rogers, R.; Atkinson, E. N.; Kavanagh, J. J. Docetaxel for patients with paclitaxel-resistant Mullerian carcinoma. *J. Clin. Oncol.* **2000**, *18*, 2733–2739.

[23] Horwitz, S. B.; Cohen, D.; Rao, S.; Ringel, I.; Shen, H. J.; Yang, C. P. Taxol: Mechanisms of action and resistance. *J. Natl. Cancer Inst. Monogr.* **1993**, 55–61.

[24] Lockhart, A. C.; Tirona, R. G.; Kim, R. B. Pharmacogenetics of ATP-binding cassette transporters in cancer and chemotherapy. *Mol. Cancer Ther.* **2003**, *2*, 685–698.

[25] Childs, S.; Yeh, R. L.; Hui, D.; Ling, V. Taxol resistance mediated by transfection of the liver-specific sister gene of P-glycoprotein. *Cancer Res.* **1998**, *58*, 4160–4167.

[26] Hopper-Borge, E.; Chen, Z. S.; Shchaveleva, I.; Belinsky, M. G.; Kruh, G. D. Analysis of the drug resistance profile of multidrug resistance protein 7 (ABCC10): Resistance to docetaxel. *Cancer Res.* **2004**, *64*, 4927–4930.

[27] Bradshaw, D. M.; Arceci, R. J. Clinical relevance of transmembrane drug efflux as a mechanism of multidrug resistance. *J. Clin. Oncol.* **1998**, *16*, 3674–3690.

[28] Fojo, T.; Menefee, M. Mechanisms of multidrug resistance: The potential role of microtubule-stabilizing agents. *Ann. Oncol.* **2007**, *18*, v3–v8.

[29] Perez, E. A. Microtubule inhibitors: Differentiating tubulin-inhibiting agents based on mechanisms of action, clinical activity, and resistance. *Mol. Cancer Ther.* **2009**, *8*, 2086–2095.

[30] Vrignaud, P.; Semiond, D.; Benning, V.; Beys, E.; Bouchard, H.; Gupta, S. Preclinical profile of cabazitaxel. *Drug Des. Devel. Ther.* **2014**, *8*, 1851–1867.

[31] Bouchard, H.; Semiond, D.; Risse, M. L.; Vrignaud, P. Novel taxanes: Cabazitaxel case study. In *Analogue-Based Drug Discovery III*; Fischer, J.; Ganellin, C. R.; Rotella, D. P., Eds.; Wiley-VCH: Weinheim, Germany, 2012; pp 319–341.

[32] Paller, C. J.; Antonarakis, E. S. Cabazitaxel: A novel second-line treatment for metastatic castration-resistant prostate cancer. *Drug Des. Devel. Ther.* **2011**, *5*, 117–124.

[33] Siegel, R. L.; Miller, K. D.; Jemal, A. Cancer statistics, 2016. *CA Cancer J. Clin.* **2016**, *66*, 7–30.

[34] De Bono, J. S.; Scher, H. I.; Montgomery, R. B.; Parker, C.; Miller, M. C.; Tissing, H.; Doyle, G. V.; Terstappen, L. W. W. M.; Pienta, K. J.; Raghavan, D. Circulating tumor cells predict survival benefit from treatment in metastatic castration-resistant prostate cancer. *Clin. Cancer Res.* **2008**, *14*, 6302–6309.

[35] Semenas, J.; Allegrucci, C.; A Boorjian, S. A.; Mongan, N. P.; Liao Persson, J. Overcoming drug resistance and treating advanced prostate cancer. *Curr. Drug Targets* **2012**, *13*, 1308–1323.

[36] Pean, E.; Demolis, P.; Moreau, A.; Hemmings, R. J.; O'Connor, D.; Brown, D.; Shepard, T.; Abadie, E.; Pignatti, F. The European medicines agency review of cabazitaxel (Jevtana®) for the treatment of hormone-refractory metastatic prostate cancer: Summary of the scientific assessment of the committee for medicinal products for human use. *Oncologist* **2012**, *17*, 543–549.

[37] Galsky, M. D.; Dritselis, A.; Kirkpatrick, P.; Oh, W. K. Cabazitaxel. *Nat. Rev. Drug Discov.* **2010**, *9*, 677–678.

[38] Mahajan, M.; Kaur Khurana, R.; Shri Sahajpal, N.; Utreja, P.; Sankar, R.; Singh, B.; Kumar Jain, S. Emerging strategies and challenges for controlled delivery of taxanes: A comprehensive review. *Curr. Drug Metab.* **2015**, *16*, 453–473.

[39] Swain, S. M.; Arezzo, J. C. Neuropathy associated with microtubule inhibitors: Diagnosis, incidence, and management. *Clin. Adv. Hematol. Oncol.* **2008**, *6*, 455–467.

[40] Krebs, A.; Goldie, K. N.; Hoenger, A. Structural rearrangements in tubulin following microtubule formation. *EMBO Rep* **2005**, *6*, 227–232.

[41] Downing, K. H.; Nogales, E. Crystallographic structure of tubulin: Implications for dynamics and drug binding. *Cell Struct. Funct.* **1999**, *24*, 269–275.

[42] Abal, M.; Andreu, J.; Barasoain, I. Taxanes: Microtubule and centrosome targets, and cell cycle dependent mechanisms of action. *Curr. Cancer Drug Targets* **2003**, *3*, 193–203.

[43] Díaz, J. F.; Valpuesta, J. M.; Chacón, P.; Diakun, G.; Andreu, J. M. Changes in microtubule protofilament number induced by taxol binding to an easily accessible site: Internal microtubule dynamics. *J. Biol. Chem.* **1998**, *273*, 33803–33810.

[44] Montero, A.; Fossella, F.; Hortobagyi, G.; Valero, V. Docetaxel for treatment of solid tumours: A systematic review of clinical data. *Lancet Oncol.* **2005**, *6*, 229–239.

[45] Balasubramanian, S. V.; Alderfer, J. L.; Straubinger, R. M. Solvent- and concentration-dependent molecular interactions of taxol (paclitaxel). *J. Pharm. Sci.* **1994**, *83*, 1470–1476.

[46] Balasubramanian, S. V.; Straubinger, R. M. Taxol-lipid interactions: Taxol-dependent effects on the physical properties of model membranes. *Biochemistry* **1994**, *33*, 8941–8947.

[47] Sharma, A.; Straubinger, R. M. Novel taxol formulations: Preparation and characterization of taxol-containing liposomes. *Pharm. Res.* **1994**, *11*, 889–896.

[48] Campbell, R. B.; Balasubramanian, S. V.; Straubinger, R. M. Influence of cationic lipids on the stability and membrane properties of paclitaxel-containing liposomes. *J. Pharm. Sci.* **2001**, *90*, 1091–1105.

[49] Mu, L.; Feng, S. S. Fabrication, characterization and *in vitro* release of paclitaxel (Taxol®) loaded poly (lactic-co-glycolic acid) microspheres prepared by spray drying technique with lipid/cholesterol emulsifiers. *J. Control. Release* **2001**, *76*, 239–254.

[50] Lee, I. H.; Park, Y. T.; Roh, K.; Chung, H.; Kwon, I. C.; Jeong, S. Y. Stable paclitaxel formulations in oily contrast medium. *J. Control. Release* **2005**, *102*, 415–425.

[51] Straubinger, R. M.; Sharma, A.; Murray, M.; Mayhew, E. Novel taxol formulations: Taxol-containing liposomes. *J. Natl. Cancer Inst. Monogr.* **1993**, 69–78.

[52] Marupudi, N. I.; Han, J. E.; Li, K. W.; Renard, V. M.; Tyler, B. M.; Brem, H. Paclitaxel: A review of adverse toxicities and novel delivery strategies. *Expert Opin. Drug Saf.* **2007**, *6*, 609–621.

[53] Engels, F. K.; Mathot, R. A. A.; Verweij, J. Alternative drug formulations of docetaxel: A review. *Anti-Cancer Drugs* **2007**, *18*, 95–103.

[54] Nightingale, G.; Ryu, J. Cabazitaxel (jevtana): A novel agent for metastatic castration-resistant prostate cancer. *P. T.* **2012**, *37*, 440–448.

[55] Gelderblom, H.; Verweij, J.; Nooter, K.; Sparreboom, A. Cremophor EL: The drawbacks and advantages of vehicle selection for drug formulation. *Eur. J. Cancer* **2001**, *37*, 1590–1598.

[56] Sofias, A. M.; Dunne, M.; Storm, G.; Allen, C. The battle of "nano" paclitaxel. *Adv. Drug Deliv. Rev.* **2017**, *122*, 20–30.

[57] Carretta, R. M.; Eisenhauer, E.; Rozencweig, M. Methods for administration of taxol. U.S. Patents 5,641,803 A, June 24, 1997.

[58] Gradishar, W. J.; Tjulandin, S.; Davidson, N.; Shaw, H.; Desai, N.; Bhar, P.; Hawkins, M.; O'Shaughnessy, J. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. *J. Clin. Oncol.* **2005**, *23*, 7794–7803.

[59] Tamura, T.; Sasaki, Y.; Nishiwaki, Y.; Saijo, N. Phase I study of paclitaxel by three-hour infusion: Hypotension just after infusion is one of the major dose-limiting toxicities. *Jpn. J. Cancer Res.* **1995**, *86*, 1203–1209.

[60] Gotardo, M. A.; Monteiro, M. Migration of diethylhexyl phthalate from PVC bags into intravenous cyclosporine solutions. *J. Pharm. Biomed. Anal.* **2005**, *38*, 709–713.

[61] Venkataramanan, R.; Burckart, G. J.; Ptachcinski, R. J.; Blaha, R.; Logue, L. W.; Bahnson, A.; Giam, C. S.; Brady, J. E. Leaching of diethylhexyl phthalate from polyvinyl chloride bags into intravenous cyclosporine solution. *Am. J. Hosp. Pharm.* **1986**, *43*, 2800–2802.

[62] van Tellingen, O.; Beijnen, J. H.; Verweij, J.; Scherrenburg, E. J.; Nooijen, W. J.; Sparreboom, A. Rapid esterase-sensitive breakdown of polysorbate 80 and its impact on the plasma pharmacokinetics of docetaxel and metabolites in mice. *Clin. Cancer Res.* **1999**, *5*, 2918–2924.

[63] Sparreboom, A.; Verweij, J.; Van der Burg, M. E.; Loos, W. J.; Brouwer, E.; Viganò, L.; Locatelli, A.; de Vos, A. I.; Nooter, K.; Stoter, G. et al. Disposition of Cremophor EL in humans limits the potential for modulation of the multidrug resistance phenotype *in vivo*. *Clin. Cancer. Res.* **1998**, *4*, 1937–1942.

[64] Nannan Panday, V. R.; Huizing, M. T.; van Tellingen, O.; Hakvoort, R. A.; Willemse, P. H. B.; de Graeff, A.; Vermorken, J. B.; Beijnen, J. H. Pharmacologic study of Cremophor EL in cancer patients with impaired hepatic function receiving paclitaxel. *J. Oncol. Pharm. Pract.* **1999**, *5*, 83–86.

[65] Gelderblom, H.; Verweij, J.; Brouwer, E.; Pillay, M.; de Bruijn, P.; Nooter, K.; Stoter, G.; Sparreboom, A. Disposition of [G-^{3}H] paclitaxel and Cremophor EL in a patient with severely impaired renal function. *Drug Metab. Dispos.* **1999**, *27*, 1300–1305.

[66] Szebeni, J.; Alving, C. R.; Muggia, F. M. Complement activation by Cremophor EL as a possible contributor to hypersensitivity to paclitaxel: An *in vitro* study. *J. Natl. Cancer Inst.* **1998**, *90*, 300–306.

[67] Dye, D.; Watkins, J. Suspected anaphylactic reaction to Cremophor EL. *Br. Med. J.* **1980**, *280*, 1353.

[68] Weiss, R. B.; Donehower, R. C.; Wiernik, P. H.; Ohnuma, T.; Gralla, R. J.; Trump, D. L.; Baker, J. R., Jr.; Van Echo, D. A.; Von Hoff, D. D.; Leyland-Jones, B. Hypersensitivity reactions from taxol. *J. Clin. Oncol.* **1990**, *8*, 1263–1268.

[69] Szebeni, J. Complement activation-related pseudoallergy: A new class of drug-induced acute immune toxicity. *Toxicology* **2005**, *216*, 106–121.

[70] van Zuylen, L.; Gianni, L.; Verweij, J.; Mross, K.; Brouwer, E.; Loos, W. J.; Sparreboom, A. Inter-relationships of paclitaxel disposition, infusion duration and Cremophor EL kinetics in cancer patients. *Anti-Cancer Drugs* **2000**, *11*, 331–337.

[71] van Zuylen, L.; Verweij, J.; Sparreboom, A. Role of formulation vehicles in taxane pharmacology. *Invest. New*

Drugs **2001**, *19*, 125–141.

[72] Sparreboom, A.; van Zuylen, L.; Brouwer, E.; Loos, W. J.; de Bruijn, P.; Gelderblom, H.; Pillay, M.; Nooter, K.; Stoter, G.; Verweij, J. Cremophor EL-mediated alteration of paclitaxel distribution in human blood. *Cancer Res.* **1999**, *59*, 1454–1457.

[73] Kongshaug, M.; Cheng, L. S.; Moan, J.; Rimington, C. Interaction of Cremophor EL with human plasma. *Int. J. Biochem.* **1991**, *23*, 473–478.

[74] Sykes, E.; Woodburn, K.; Decker, D.; Kessel, D. Effects of Cremophor EL on distribution of Taxol to serum lipoproteins. *Br. J. Cancer* **1994**, *70*, 401–404.

[75] Expósito, O.; Bonfill, M.; Moyano, E.; Onrubia, M.; Mirjalili, M. H.; Cusido, R. M.; Palazon, J. Biotechnological production of taxol and related taxoids: Current state and prospects. *Anti-Cancer Agents Med. Chem.* **2009**, *9*, 109–121.

[76] Vasey, P. A.; Jayson, G. C.; Gordon, A.; Gabra, H.; Coleman, R.; Atkinson, R.; Parkin, D.; Paul, J.; Hay, A.; Kaye, S. B. Phase III randomized trial of docetaxel–carboplatin versus paclitaxel–carboplatin as first-line chemotherapy for ovarian carcinoma. *J. Natl. Cancer Inst.* **2004**, *96*, 1682–1691.

[77] Fossella, F. V.; DeVore, R.; Kerr, R. N.; Crawford, J.; Natale, R. R.; Dunphy, F.; Kalman, L.; Miller, V.; Lee, J. S.; Moore, M. et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. *J. Clin. Oncol.* **2000**, *18*, 2354–2362.

[78] Webster, L. K.; Linsenmeyer, M. E.; Rischin, D.; Urch, M. E.; Woodcock, D. M.; Millward, M. J. Plasma concentrations of polysorbate 80 measured in patients following administration of docetaxel or etoposide. *Cancer Chemother. Pharmacol.* **1997**, *39*, 557–560.

[79] Eisenhauer, E. A.; Trudeau, M. An overview of phase II studies of docetaxel in patients with metastatic breast cancer. *Eur. J. Cancer* **1995**, *31*, S11–S13.

[80] Green, M. R.; Manikhas, G. M.; Orlov, S.; Afanasyev, B.; Makhson, A. M.; Bhar, P.; Hawkins, M. J. Abraxane®, a novel Cremophor®-free, albumin-bound particle form of paclitaxel for the treatment of advanced non-small-cell lung cancer. *Ann. Oncol.* **2006**, *17*, 1263–1268.

[81] Desai, N.; Trieu, V.; Damascelli, B.; Soon-Shiong, P. SPARC expression correlates with tumor response to albumin-bound paclitaxel in head and neck cancer patients. *Transl. Oncol.* **2009**, *2*, 59–64.

[82] Gradishar, W. J.; Krasnojon, D.; Cheporov, S.; Makhson, A. N.; Manikhas, G. M.; Clawson, A.; Bhar, P. Significantly longer progression-free survival with nab-paclitaxel compared with docetaxel as first-line therapy for metastatic breast cancer. *J. Clin. Oncol.* **2009**, *27*, 3611–3619.

[83] Garlick, R. L.; Mazer, J. S. The principal site of nonenzymatic glycosylation of human serum albumin *in vivo*. *J. Biol. Chem.* **1983**, *258*, 6142–6146.

[84] Ait-Oudhia, S.; Straubinger, R. M.; Mager, D. E. Meta-analysis of nanoparticulate paclitaxel delivery system pharmacokinetics and model prediction of associated neutropenia. *Pharm. Res.* **2012**, *29*, 2833–2844.

[85] Matsumura, Y.; Maeda, H. A new concept for macro-molecular therapeutics in cancer chemotherapy: Mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. *Cancer Res.* **1986**, *46*, 6387–6392.

[86] Hawkins, M. J.; Soon-Shiong, P.; Desai, N. Protein nano-particles as drug carriers in clinical medicine. *Adv. Drug Deliv. Rev.* **2008**, *60*, 876–885.

[87] Sage, H.; Johnson, C.; Bornstein, P. Characterization of a novel serum albumin-binding glycoprotein secreted by endothelial cells in culture. *J. Biol. Chem.* **1984**, *259*, 3993–4007.

[88] Porter, P. L.; Sage, E. H.; Lane, T. F.; Funk, S. E.; Gown, A. M. Distribution of SPARC in normal and neoplastic human tissue. *J. Histochem. Cytochem.* **1995**, *43*, 791–800.

[89] Neesse, A.; Frese, K. K.; Chan, D. S.; Bapiro, T. E.; Howat, W. J.; Richards, F. M.; Ellenrieder, V.; Jodrell, D. I.; Tuveson, D. A. SPARC independent drug delivery and antitumour effects of nab-paclitaxel in genetically engineered mice. *Gut* **2014**, *63*, 974–983.

[90] Li, R.; Zheng, K.; Yuan, C.; Chen, Z.; Huang, M. D. Be active or not: The relative contribution of active and passive tumor targeting of nanomaterials. *Nanotheranostics* **2017**, *1*, 346–357.

[91] Kim, T. Y.; Kim, D. W.; Chung, J. Y.; Shin, S. G.; Kim, S. C.; Heo, D. S.; Kim, N. K.; Bang, Y. J. Phase I and pharmacokinetic study of Genexol-PM, a cremophor-free, polymeric micelle-formulated paclitaxel, in patients with advanced malignancies. *Clin. Cancer. Res.* **2004**, *10*, 3708–3716.

[92] Kim, D. W.; Kim, S. Y.; Kim, H. K.; Kim, S. W.; Shin, S. W.; Kim, J. S.; Park, K.; Lee, M. Y.; Heo, D. S. Multicenter phase II trial of Genexol-PM, a novel cremophor-free, polymeric micelle formulation of paclitaxel, with cisplatin in patients with advanced non-small-cell lung cancer. *Ann. Oncol.* **2007**, *18*, 2009–2014.

[93] Ventola, C. L. Progress in nanomedicine: Approved and investigational nanodrugs. *P. T.* **2017**, *42*, 742–755.

[94] Kato, K.; Chin, K.; Yoshikawa, T.; Yamaguchi, K.; Tsuji, Y.; Esaki, T.; Sakai, K.; Kimura, M.; Hamaguchi, T.; Shimada, Y. et al. Phase II study of NK105, a paclitaxel-incorporating micellar nanoparticle, for previously treated advanced or

recurrent gastric cancer. *Invest. New Drugs* **2012**, *30*, 1621–1627.

[95] Hamaguchi, T.; Kato, K.; Yasui, H.; Morizane, C.; Ikeda, M.; Ueno, H.; Muro, K.; Yamada, Y.; Okusaka, T.; Shirao, K. et al. A phase I and pharmacokinetic study of NK105, a paclitaxel-incorporating micellar nanoparticle formulation. *Br. J. Cancer* **2007**, *97*, 170–176.

[96] van der Meel, R.; Lammers, T.; Hennink, W. E. Cancer nanomedicines: Oversold or underappreciated? *Expert Opin. Drug Deliv.* **2017**, *14*, 1–5.

[97] Jain, M. M.; Gupte, S. U.; Patil, S. G.; Pathak, A. B.; Deshmukh, C. D.; Bhatt, N.; Haritha, C.; Babu, K. G.; Bondarde, S. A.; Digumarti, R. et al. Paclitaxel injection concentrate for nanodispersion versus nab-paclitaxel in women with metastatic breast cancer: A multicenter, randomized, comparative phase II/III study. *Breast Cancer Res. Treat.* **2016**, *156*, 125–134.

[98] Stylianopoulos, T.; Jain, R. K. Design considerations for nanotherapeutics in oncology. *Nanomed. Nanotechnol. Biol. Med.* **2015**, *11*, 1893–1907.

[99] Pattni, B. S.; Chupin, V. V.; Torchilin, V. P. New developments in liposomal drug delivery. *Chem. Rev.* **2015**, *115*, 10938–10966.

[100] Koudelka, Š.; Turánek, J. Liposomal paclitaxel formulations. *J. Control. Release* **2012**, *163*, 322–334.

[101] Zhang, Q.; Huang, X. E.; Gao, L. L. A clinical study on the premedication of paclitaxel liposome in the treatment of solid tumors. *Biomed. Pharmacother.* **2009**, *63*, 603–607.

[102] Ye, L.; He, J.; Hu, Z. P.; Dong, Q. J.; Wang, H. B.; Fu, F. H.; Tian, J. W. Antitumor effect and toxicity of Lipusu in rat ovarian cancer xenografts. *Food Chem. Toxicol.* **2013**, *52*, 200–206.

[103] ClinicalTrials.gov. *Pharmacokinetics Study of Liposomal Paclitaxel in Humans (LPSPK-H)* [Online]. https://www.clinicaltrials.gov/ct2/show/NCT00606515 (accessed Mar 23, 2018).

[104] Wang, X. H.; Zhou, J. C.; Wang, Y. S.; Zhu, Z. Y.; Lu, Y.; Wei, Y. Q.; Chen, L. J. A phase I clinical and pharmacokinetic study of paclitaxel liposome infused in non-small cell lung cancer patients with malignant pleural effusions. *Eur. J. Cancer* **2010**, *46*, 1474–1480.

[105] Fan, Y. C.; Zhang, Q. Development of liposomal formulations: From concept to clinical investigations. *Asian J. Pharm. Sci.* **2013**, *8*, 81–87.

[106] Zhang, J. A.; Anyarambhatla, G.; Ma, L.; Ugwu, S.; Xuan, T.; Sardone, T.; Ahmad, I. Development and characterization of a novel Cremophor® EL free liposome-based paclitaxel (LEP-ETU) formulation. *Eur. J. Pharm. Biopharm.* **2005**, *59*, 177–187.

[107] Fetterly, G. J.; Grasela, T. H.; Sherman, J. W.; Dul, J. L.; Grahn, A.; Lecomte, D.; Fiedler-Kelly, J.; Damjanov, N.; Fishman, M.; Kane, M. P. et al. Pharmacokinetic/pharmacodynamic modeling and simulation of neutropenia during phase I development of liposome-entrapped paclitaxel. *Clin. Cancer Res.* **2008**, *14*, 5856–5863.

[108] Slingerland, M.; Guchelaar, H. J.; Rosing, H.; Scheulen, M. E.; van Warmerdam, L. J. C.; Beijnen, J. H.; Gelderblom, H. Bioequivalence of liposome-entrapped paclitaxel easy-to-use (LEP-ETU) formulation and paclitaxel in polyethoxylated castor oil: A randomized, two-period crossover study in patients with advanced cancer. *Clin. Ther.* **2013**, *35*, 1946–1954.

[109] Fasol, U.; Frost, A.; Büchert, M.; Arends, J.; Fiedler, U.; Scharr, D.; Scheuenpflug, J.; Mross, K. Vascular and pharmacokinetic effects of EndoTAG-1 in patients with advanced cancer and liver metastasis. *Ann. Oncol.* **2012**, *23*, 1030–1036.

[110] Eichhorn, M. E.; Ischenko, I.; Luedemann, S.; Strieth, S.; Papyan, A.; Werner, A.; Bohnenkamp, H.; Guenzi, E.; Preissler, G.; Michaelis, U. et al. Vascular targeting by EndoTAG™-1 enhances therapeutic efficacy of conventional chemotherapy in lung and pancreatic cancer. *Int. J. Cancer* **2010**, *126*, 1235–1245.

[111] Bode, C.; Trojan, L.; Weiss, C.; Kraenzlin, B.; Michaelis, U.; Teifel, M.; Alken, P.; Michel, M. S. Paclitaxel encapsulated in cationic liposomes: A new option for neovascular targeting for the treatment of prostate cancer. *Oncol. Rep.* **2009**, *22*, 321–326.

[112] Thurston, G.; McLean, J. W.; Rizen, M.; Baluk, P.; Haskell, A.; Murphy, T. J.; Hanahan, D.; McDonald, D. M. Cationic liposomes target angiogenic endothelial cells in tumors and chronic inflammation in mice. *J. Clin. Invest.* **1998**, *101*, 1401–1413.

[113] Luo, D. D.; Geng, J. M.; Li, N. S.; Carter, K. A.; Shao, S.; Atilla-Gokcumen, G. E.; Lovell, J. F. Vessel-targeted chemophototherapy with cationic porphyrin-phospholipid liposomes. *Mol. Cancer Ther.* **2017**, *16*, 2452–2461.

[114] Löhr, J. M.; Haas, S. L.; Bechstein, W. O.; Bodoky, G.; Cwiertka, K.; Fischbach, W.; Fölsch, U. R.; Jäger, D.; Osinsky, D.; Prausova, J. et al. Cationic liposomal paclitaxel plus gemcitabine or gemcitabine alone in patients with advanced pancreatic cancer: A randomized controlled phase II trial. *Ann. Oncol.* **2012**, *23*, 1214–1222.

[115] Lee, I. H.; Hong, J. W.; Jang, Y.; Park, Y. T.; Chung, H. Development, optimization and absorption mechanism of DHP107, oral paclitaxel formulation for single-agent anticancer therapy. In *New Advances in the Basic and Clinical Gastroenterology*; Brzozowski, T., Ed.; INTECH

Open Access Publisher, 2012; pp 357–374.

[116] Hong, J. W.; Lee, I. H.; Kwak, Y. H.; Park, Y. T.; Sung, H. C.; Kwon, I. C.; Chung, H. Efficacy and tissue distribution of DHP107, an oral paclitaxel formulation. *Mol. Cancer Ther.* **2007**, *6*, 3239–3247.

[117] Hong, Y. S.; Kim, K. P.; Lim, H. S.; Bae, K. S.; Ryu, M. H.; Lee, J. L.; Chang, H. M.; Kang, Y. K.; Kim, H.; Kim, T. W. A phase I study of DHP107, a mucoadhesive lipid form of oral paclitaxel, in patients with advanced solid tumors: Crossover comparisons with intravenous paclitaxel. *Invest. New Drugs* **2013**, *31*, 616–622.

[118] Kang, Y. K.; Ryu, M. H.; Park, S. H.; Park, S. R.; Kim, J. G.; Kim, J. W.; Cho, S. H.; Park, Y. I.; Rha, S. Y.; Kang, M. J. Efficacy and safety findings from DREAM: A phase III study of DHP107 (oral paclitaxel) vs IV paclitaxel in patients with gastric cancer after failure of first-line chemotherapy. *Am. Soc. Clin. Oncol.* **2016**, *34*, 4016.

[119] Sparreboom, A.; Van Asperen, J.; Mayer, U.; Schinkel, A. H.; Smit, J. W.; Meijer, D. K.; Borst, P.; Nooijen, W. J.; Beijnen, J. H.; Van Tellingen, O. Limited oral bioavailability and active epithelial excretion of paclitaxel (Taxol) caused by P-glycoprotein in the intestine. *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 2031–2035.

[120] Paek, I. B.; Ji, H. Y.; Lee, G. S.; Lee, H. S. Simultaneous determination of paclitaxel and a new P-glycoprotein inhibitor HM-30181 in rat plasma by liquid chromatography with tandem mass spectrometry. *J. Sep. Sci.* **2006**, *29*, 628–634.

[121] Lee, K. W.; Lee, K. H.; Zang, D. Y.; Park, Y. I.; Shin, D. B.; Kim, J. W.; Im, S. A.; Koh, S. A.; Yu, K. S.; Cho, J. Y. et al. Phase I/II study of weekly oraxol for the second-line treatment of patients with metastatic or recurrent gastric cancer. *Oncologist* **2015**, *20*, 896–897.

[122] Rautio, J.; Kumpulainen, H.; Heimbach, T.; Oliyai, R.; Oh, D.; Järvinen, T.; Savolainen, J. Prodrugs: Design and clinical applications. *Nat. Rev. Drug Discov.* **2008**, *7*, 255–270.

[123] Skwarczynski, M.; Hayashi, Y.; Kiso, Y. Paclitaxel prodrugs: Toward smarter delivery of anticancer agents. *J. Med. Chem.* **2006**, *49*, 7253–7269.

[124] Terwogt, J. M. M.; ten Bokkel Huinink, W. W.; Schellens, J. H. M.; Schot, M.; Mandjes, I. A. M.; Zurlo, M. G.; Rocchetti, M.; Rosing, H.; Koopman, F. J.; Beijnen, J. H. Phase I clinical and pharmacokinetic study of PNU166945, a novel water-soluble polymer-conjugated prodrug of paclitaxel. *Anti-Cancer Drugs* **2001**, *12*, 315–323.

[125] Fracasso, P. M.; Picus, J.; Wildi, J. D.; Goodner, S. A.; Creekmore, A. N.; Gao, F.; Govindan, R.; Ellis, M. J.; Tan, B. R.; Linette, G. P. et al. Phase 1 and pharmacokinetic study of weekly docosahexaenoic acid-paclitaxel, Taxoprexin®, in resistant solid tumor malignancies. *Cancer Chemother. Pharmacol.* **2009**, *63*, 451–458.

[126] Homsi, J.; Bedikian, A. Y.; Papadopoulos, N. E.; Kim, K. B.; Hwu, W. J.; Mahoney, S. L.; Hwu, P. Phase 2 open-label study of weekly docosahexaenoic acid–paclitaxel in patients with metastatic uveal melanoma. *Melanoma Res.* **2010**, *20*, 507–510.

[127] Jones, R. J.; Hawkins, R. E.; Eatock, M. M.; Ferry, D. R.; Eskens, F. A. L. M.; Wilke, H.; Evans, T. J. J. A phase II open-label study of DHA-paclitaxel (Taxoprexin) by 2-h intravenous infusion in previously untreated patients with locally advanced or metastatic gastric or oesophageal adenocarcinoma. *Cancer Chemother. Pharmacol.* **2008**, *61*, 435–441.

[128] Luo, D. D.; Carter, K. A.; Lovell, J. F. Nanomedical engineering: Shaping future nanomedicines. *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.* **2015**, *7*, 169–188.

[129] Adams, M. L.; Lavasanifar, A.; Kwon, G. S. Amphiphilic block copolymers for drug delivery. *J. Pharm. Sci.* **2003**, *92*, 1343–1355.

[130] Maeda, H. Tumor-selective delivery of macromolecular drugs via the EPR effect: Background and future prospects. *Bioconjugate Chem.* **2010**, *21*, 797–802.

[131] Sutton, D.; Nasongkla, N.; Blanco, E.; Gao, J. M. Functionalized micellar systems for cancer targeted drug delivery. *Pharm. Res.* **2007**, *24*, 1029–1046.

[132] Gaucher, G.; Dufresne, M. H.; Sant, V. P.; Kang, N.; Maysinger, D.; Leroux, J. C. Block copolymer micelles: Preparation, characterization and application in drug delivery. *J. Control. Release* **2005**, *109*, 169–188.

[133] Li, J.; Stayshich, R. M.; Meyer, T. Y. Exploiting sequence to control the hydrolysis behavior of biodegradable PLGA copolymers. *J. Am. Chem. Soc.* **2011**, *133*, 6910–6913.

[134] Makadia, H. K.; Siegel, S. J. Poly lactic-co-glycolic acid (PLGA) as biodegradable controlled drug delivery carrier. *Polymers* **2011**, *3*, 1377–1397.

[135] Kedar, U.; Phutane, P.; Shidhaye, S.; Kadam, V. Advances in polymeric micelles for drug delivery and tumor targeting. *Nanomed. Nanotechnol. Biol. Med.* **2010**, *6*, 714–729.

[136] Kumari, A.; Yadav, S. K.; Yadav, S. C. Biodegradable polymeric nanoparticles based drug delivery systems. *Colloids Surf. B: Biointerfaces* **2010**, *75*, 1–18.

[137] Jain, R. A. The manufacturing techniques of various drug loaded biodegradable poly (lactide-co-glycolide) (PLGA) devices. *Biomaterials* **2000**, *21*, 2475–2490.

[138] Esmaeili, F.; Ghahremani, M. H.; Esmaeili, B.; Khoshayand, M. R.; Atyabi, F.; Dinarvand, R. PLGA nanoparticles of different surface properties: Preparation and evaluation of

their body distribution. *Int. J. Pharm.* **2008**, *349*, 249–255.

[139] Oerlemans, C.; Bult, W.; Bos, M.; Storm, G.; Nijsen, J. F. W.; Hennink, W. E. Polymeric micelles in anticancer therapy: Targeting, imaging and triggered release. *Pharm. Res.* **2010**, *27*, 2569–2589.

[140] Coleman, R. E. Clinical features of metastatic bone disease and risk of skeletal morbidity. *Clin. Cancer Res.* **2006**, *12*, 6243s–6249s.

[141] Gdowski, A. S.; Ranjan, A.; Sarker, M. R.; Vishwanatha, J. K. Bone-targeted cabazitaxel nanoparticles for metastatic prostate cancer skeletal lesions and pain. *Nanomedicine* **2017**, *12*, 2083–2095.

[142] Zhang, Z.; Xiong, X. Q.; Wan, J. L.; Xiao, L.; Gan, L.; Feng, Y. M.; Xu, H. B.; Yang, X. L. Cellular uptake and intracellular trafficking of PEG-b-PLA polymeric micelles. *Biomaterials* **2012**, *33*, 7233–7240.

[143] Han, X. X.; Chen, D.; Sun, J.; Zhou, J. S.; Li, D.; Gong, F. R.; Shen, Y. L. A novel cabazitaxel-loaded polymeric micelle system with superior *in vitro* stability and long blood circulation time. *J. Biomater. Sci., Polym. Ed.* **2016**, *27*, 626–642.

[144] Zhuang, B.; Du, L.; Xu, H. X.; Xu, X. L.; Wang, C.; Fan, Y. F.; Cong, M. Y.; Yin, J. Q.; Li, H. X.; Guan, H. S. Self-assembled micelle loading cabazitaxel for therapy of lung cancer. *Int. J. Pharm.* **2016**, *499*, 146–155.

[145] Mahdaviani, P.; Bahadorikhalili, S.; Navaei-Nigjeh, M.; Vafaei, S. Y.; Esfandyari-Manesh, M.; Abdolghaffari, A. H.; Daman, Z.; Atyabi, F.; Ghahremani, M. H.; Amini, M. et al. Peptide functionalized poly ethylene glycol-poly caprolactone nanomicelles for specific cabazitaxel delivery to metastatic breast cancer cells. *Mater. Sci. Eng. C* **2017**, *80*, 301–312.

[146] Herold, D. A.; Keil, K.; Bruns, D. E. Oxidation of polyethylene glycols by alcohol dehydrogenase. *Biochem. Pharmacol.* **1989**, *38*, 73–76.

[147] Garay, R. P.; Labaune, J. P. Immunogenicity of polyethylene glycol (PEG). *Open Conf. Proc. J.* **2011**, *2*, 104–107.

[148] Cheng, T. L.; Wu, P. Y.; Wu, M. F.; Chern, J. W.; Roffler, S. R. Accelerated clearance of polyethylene glycol-modified proteins by anti-polyethylene glycol IgM. *Bioconjugate Chem.* **1999**, *10*, 520–528.

[149] Yang, Q.; Wang, K.; Nie, J. J.; Du, B. Y.; Tang, G. P. Poly(N-vinylpyrrolidinone) microgels: Preparation, biocompatibility, and potential application as drug carriers. *Biomacromolecules* **2014**, *15*, 2285–2293.

[150] Bailly, N.; Thomas, M.; Klumperman, B. Poly(N-vinylpyrrolidone)-block-poly(vinyl acetate) as a drug delivery vehicle for hydrophobic drugs. *Biomacromolecules* **2012**, *13*, 4109–4117.

[151] Zhu, Z. S.; Li, Y.; Li, X. L.; Li, R. T.; Jia, Z. J.; Liu, B. R.; Guo, W. H.; Wu, W.; Jiang, X. Q. Paclitaxel-loaded poly(N-vinylpyrrolidone)-b-poly(ε-caprolactone) nanoparticles: Preparation and antitumor activity *in vivo*. *J. Control. Release* **2010**, *142*, 438–446.

[152] Xie, C.; Zhang, P.; Zhang, Z. K.; Yang, C. C.; Zhang, J. L.; Wu, W.; Jiang, X. Q. Drug-loaded pseudo-block copolymer micelles with a multi-armed star polymer as the micellar exterior. *Nanoscale* **2015**, *7*, 12572–12580.

[153] Aydin, O.; Youssef, I.; Yuksel Durmaz, Y.; Tiruchinapally, G.; ElSayed, M. E. H. Formulation of acid-sensitive micelles for delivery of cabazitaxel into prostate cancer cells. *Mol. Pharm.* **2016**, *13*, 1413–1429.

[154] Weiszhár, Z.; Czúcz, J.; Révész, C.; Rosivall, L.; Szebeni, J.; Rozsnyay, Z. Complement activation by polyethoxylated pharmaceutical surfactants: Cremophor-EL, Tween-80 and Tween-20. *Eur. J. Pharm. Sci.* **2012**, *45*, 492–498.

[155] Zhang, Y. M.; Song, W. T.; Geng, J. M.; Chitgupi, U.; Unsal, H.; Federizon, J.; Rzayev, J.; Sukumaran, D. K.; Alexandridis, P.; Lovell, J. F. Therapeutic surfactant-stripped frozen micelles. *Nat. Commun.* **2016**, *7*, 11649.

[156] Zhang, Y. M.; Wang, D. P.; Goel, S.; Sun, B. Y.; Chitgupi, U.; Geng, J. M.; Sun, H. Y.; Barnhart, T. E.; Cai, W. B.; Xia, J. et al. Surfactant-stripped frozen pheophytin micelles for multimodal gut imaging. *Adv. Mater.* **2016**, *28*, 8524–8530.

[157] Torchilin, V. P. Micellar nanocarriers: Pharmaceutical perspectives. *Pharm. Res.* **2007**, *24*, 1.

[158] Shao, Y. J.; Zhang, C. G.; Yao, Q.; Wang, Y. Q.; Tian, B.; Tang, X.; Wang, Y. J. Improving cabazitaxel chemical stability in parenteral lipid emulsions using cholesterol. *Eur. J. Pharm. Sci.* **2014**, *52*, 1–11.

[159] Ananias, H. J. K.; De Jong, I. J.; Dierckx, R. A.; van de Wiele, C.; Helfrich, W.; Elsinga, P. H. Nuclear imaging of prostate cancer with gastrin-releasing-peptide- receptor targeted radiopharmaceuticals. *Curr. Pharm. Des.* **2008**, *14*, 3033–3047.

[160] Safavy, A.; Khazaeli, M. B.; Qin, H. Y.; Buchsbaum, D. J. Synthesis of bombesin analogues for radiolabeling with rhenium-188. *Cancer* **1997**, *80*, 2354–2359.

[161] Kulhari, H.; Pooja, D.; Shrivastava, S.; V.G.M, N.; Sistla, R. Peptide conjugated polymeric nanoparticles as a carrier for targeted delivery of docetaxel. *Colloids Surf. B: Biointerfaces* **2014**, *117*, 166–173.

[162] Chen, W. J.; Guo, M.; Wang, S. L. Anti prostate cancer using PEGylated bombesin containing, cabazitaxel loading nano-sized drug delivery system. *Drug Dev. Ind. Pharm.* **2016**, *42*, 1968–1976.

[163] Song, Y.; Tian, Q.; Huang, Z.; Fan, D.; She, Z.; Liu, X.;

Cheng, X.; Yu, B.; Deng, Y. Self-assembled micelles of novel amphiphilic copolymer cholesterol-coupled F68 containing cabazitaxel as a drug delivery system. *Int. J. Nanomedicine* **2014**, *9*, 2307–2317.

[164] Shahgaldian, P.; Da Silva, E.; Coleman, A. W.; Rather, B.; Zaworotko, M. J. Para-acyl-calix-arene based solid lipid nanoparticles (SLNs): A detailed study of preparation and stability parameters. *Int. J. Pharm.* **2003**, *253*, 23–38.

[165] Qi, J. P.; Lu, Y.; Wu, W. Absorption, disposition and pharmacokinetics of solid lipid nanoparticles. *Curr. Drug Metab.* **2012**, *13*, 418–428.

[166] Zhu, C. J.; An, C. G. Enhanced antitumor activity of cabazitaxel targeting CD44+ receptor in breast cancer cell line via surface functionalized lipid nanocarriers. *Trop. J. Pharm. Res.* **2017**, *16*, 1383–1390.

[167] Kratz, F. Albumin as a drug carrier: Design of prodrugs, drug conjugates and nanoparticles. *J. Control. Release* **2008**, *132*, 171–183.

[168] Kratz, F. A clinical update of using albumin as a drug vehicle—A commentary. *J. Control. Release* **2014**, *190*, 331–336.

[169] Qu, N.; Lee, R. J.; Sun, Y.; Cai, G.; Wang, J.; Wang, M.; Lu, J.; Meng, Q.; Teng, L.; Wang, D. et al. Cabazitaxel-loaded human serum albumin nanoparticles as a therapeutic agent against prostate cancer. *Int. J. Nanomed.* **2016**, *11*, 3451–3459.

[170] Qu, N.; Sun, Y. T.; Xie, J.; Teng, L. S. Preparation and evaluation of *in vitro* self-assembling HSA nanoparticles for cabazitaxel. *Anti-Cancer Agents Med. Chem.* **2017**, *17*, 294–300.

[171] Huang, H. Y.; Lovell, J. F. Advanced functional nanomaterials for theranostics. *Adv. Funct. Mater.* **2017**, *27*, 1603524.

[172] Tai, X. W.; Wang, Y.; Zhang, L.; Yang, Y. T.; Shi, K. R.; Ruan, S. B.; Liu, Y. Y.; Gao, H. L.; Zhang, Z. R.; He, Q. Cabazitaxel and indocyanine green co-delivery tumor-targeting nanoparticle for improved antitumor efficacy and minimized drug toxicity. *J. Drug Target.* **2017**, *25*, 179–187.

[173] Shafirstein, G.; Bäumler, W.; Hennings, L. J.; Siegel, E. R.; Friedman, R.; Moreno, M. A.; Webber, J.; Jackson, C.; Griffin, R. J. Indocyanine green enhanced near-infrared laser treatment of murine mammary carcinoma. *Int. J. Cancer* **2012**, *130*, 1208–1215.

[174] Reza, A. T.; Nicoll, S. B. Characterization of novel photocrosslinked carboxymethylcellulose hydrogels for encapsulation of nucleus pulposus cells. *Acta Biomater.* **2010**, *6*, 179–186.

[175] Toğrul, H.; Arslan, N. Production of carboxymethyl cellulose from sugar beet pulp cellulose and rheological behaviour of carboxymethyl cellulose. *Carbohydr. Polym.* **2003**, *54*, 73–82.

[176] Hoang, B.; Ernsting, M. J.; Tang, W. H. S.; Bteich, J.; Undzys, E.; Kiyota, T.; Li, S. D. Cabazitaxel-conjugated nanoparticles for docetaxel-resistant and bone metastatic prostate cancer. *Cancer Lett.* **2017**, *410*, 169–179.

[177] Ernsting, M. J.; Murakami, M.; Undzys, E.; Aman, A.; Press, B.; Li, S. D. A docetaxel-carboxymethylcellulose nanoparticle outperforms the approved taxane nanoformulation, Abraxane, in mouse tumor models with significant control of metastases. *J. Control. Release* **2012**, *162*, 575–581.

[178] Ernsting, M. J.; Tang, W. L.; MacCallum, N. W.; Li, S. D. Preclinical pharmacokinetic, biodistribution, and anti-cancer efficacy studies of a docetaxel-carboxymethylcellulose nanoparticle in mouse models. *Biomaterials* **2012**, *33*, 1445–1454.

[179] Bteich, J.; McManus, S. A.; Ernsting, M. J.; Mohammed, M. Z.; Prud'homme, R. K.; Sokoll, K. K. Using flash nanoprecipitation to produce highly potent and stable cellax nanoparticles from amphiphilic polymers derived from carboxymethyl cellulose, polyethylene glycol, and cabazitaxel. *Mol. Pharm.* **2017**, *14*, 3998–4007.

[180] Müller, R. H.; Mäder, K.; Gohla, S. Solid lipid nanoparticles (SLN) for controlled drug delivery—A review of the state of the art. *Eur. J. Pharm. Biopharm.* **2000**, *50*, 161–177.

[181] Kan, P.; Chen, Z. B.; Lee, C. J.; Chu, I. M. Development of nonionic surfactant/phospholipid o/w emulsion as a paclitaxel delivery system. *J. Control. Release* **1999**, *58*, 271–278.

[182] Khoeeniha, M. K.; Esfandyari-Manesh, M.; Behrouz, H.; Amini, M.; Varnamkhasti, B. S.; Atyabi, F.; Dinarvand, R. Targeted delivery of cabazitaxel by conjugation to albumin-PEG-folate nanoparticles using a cysteine-acrylate linker and simple synthesis conditions. *Curr. Drug Deliv.* **2017**, *14*, 1120–1129.

[183] Schacher, F. H.; Rupar, P. A.; Manners, I. Functional block copolymers: Nanostructured materials with emerging applications. *Angew. Chem., Int. Ed.* **2012**, *51*, 7898–7921.

[184] Gu, F.; Zhang, L. F.; Teply, B. A.; Mann, N.; Wang, A.; Radovic-Moreno, A. F.; Langer, R.; Farokhzad, O. C. Precise engineering of targeted nanoparticles by using self-assembled biointegrated block copolymers. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 2586–2591.

[185] Bensaid, F.; Thillaye du Boullay, O.; Amgoune, A.; Pradel, C.; Harivardhan Reddy, L.; Didier, E.; Sablé, S.; Louit, G.; Bazile, D.; Bourissou, D. Y-shaped mPEG-PLA cabazitaxel conjugates: Well-controlled synthesis by organocatalytic

approach and self-assembly into interface drug-loaded core–corona nanoparticles. *Biomacromolecules* **2013**, *14*, 1189–1198.

[186] Ganta, S.; Devalapally, H.; Shahiwala, A.; Amiji, M. A review of stimuli-responsive nanocarriers for drug and gene delivery. *J. Control. Release* **2008**, *126*, 187–204.

[187] Mura, S.; Nicolas, J.; Couvreur, P. Stimuli-responsive nanocarriers for drug delivery. *Nat. Mater.* **2013**, *12*, 991–1003.

[188] Miranda, D.; Lovell, J. F. Mechanisms of light-induced liposome permeabilization. *Bioeng. Transl. Med.* **2016**, *1*, 267–276.

[189] Meng, F. H.; Hennink, W. E.; Zhong, Z. Y. Reduction-sensitive polymers and bioconjugates for biomedical applications. *Biomaterials* **2009**, *30*, 2180–2198.

[190] Brülisauer, L.; Gauthier, M. A.; Leroux, J. C. Disulfide-containing parenteral delivery systems and their redox-biological fate. *J. Control. Release* **2014**, *195*, 147–154.

[191] Han, X. X.; Gong, F. R.; Sun, J.; Li, Y. Q.; Liu, X. F.; Chen, D.; Liu, J. W.; Shen, Y. L. Glutathione-responsive core cross-linked micelles for controlled cabazitaxel delivery. *J. Nanopart. Res.* **2018**, *20*, 42.

[192] Xue, P.; Liu, D.; Wang, J.; Zhang, N.; Zhou, J. H.; Li, L.; Guo, W. L.; Sun, M. C.; Han, X. F.; Wang, Y. J. Redox-sensitive citronellol–cabazitaxel conjugate: Maintained *in vitro* cytotoxicity and self-assembled as multifunctional nanomedicine. *Bioconjugate Chem.* **2016**, *27*, 1360–1372.

[193] Engin, K.; Leeper, D. B.; Cater, J. R.; Thistlethwaite, A. J.; Tupchong, L.; McFarlane, J. D. Extracellular pH distribution in human tumours. *Int. J. Hyperthermia* **1995**, *11*, 211–216.

[194] Van Sluis, R.; Bhujwalla, Z. M.; Raghunand, N.; Ballesteros, P.; Alvarez, J.; Cerdán, S.; Galons, J. P.; Gillies, R. J. *In vivo* imaging of extracellular pH using ^{1}H MRSI. *Magn. Reson. Med.* **1999**, *41*, 743–750.

[195] Ojugo, A. S. E.; McSheehy, P. M. J.; McIntyre, D. J. O.; McCoy, C.; Stubbs, M.; Leach, M. O.; Judson, I. R.; Griffiths, J. R. Measurement of the extracellular pH of solid tumours in mice by magnetic resonance spectroscopy: A comparison of exogenous ^{19}F and ^{31}P probes. *NMR Biomed.* **1999**, *12*, 495–504.

[196] Parhizkar, E.; Ahmadi, F.; Daneshamouz, S.; Mohammadi-Samani, S.; Sakhteman, A.; Parhizgar, G. Synthesis and characterization of water-soluble conjugates of cabazitaxel hemiesters-dextran. *Anticancer Agents Med. Chem.* **2017**, *17*, 1555–1562.

[197] Shao, Y. J.; Li, S.; Tian, B.; Su, L. L.; Zhang, C. G.; Wang, Y. Q.; Tang, X.; Wang, Y. Evaluation of the stability and pharmacokinetics of cabazitaxel-loaded intravenous lipid microspheres: Beneficial effect of cholesterol. *Eur. J. Lipid Sci. Technol.* **2015**, *117*, 460–470.

[198] Zhou, G. M.; Jin, X. Y.; Zhu, P.; Yao, J.; Zhang, Y. X.; Teng, L. S.; Lee, R. J.; Zhang, X. M.; Hong, W. Human serum albumin nanoparticles as a novel delivery system for cabazitaxel. *Anticancer Res.* **2016**, *36*, 1649–1656.