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Review Article

A Comprehensive Review on the Nanocarrier–based Drug Delivery of Cabazitaxel

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ABSTRACT

Drug resistance significantly impacts the anticancer activity of several taxane-based formulations, i.e., docetaxel (DTX) and paclitaxel (PTX) formulations in clinical research. Cabazitaxel is a second-generation taxane with high anticancer efficacy than paclitaxel and docetaxel. The structure of cabazitaxel depicts low P-glycoprotein (p-gp) efflux pump affinity, which could help overcome the taxane resistance. Cabazitaxel's clinical use is limited to metastatic castration-resistant prostate cancer (mCRPC) who have progressed after the chemotherapy from the docetaxel because of its hydrophobicity and high toxicity as the less stability of its marketed formulation, Jevtana®. The nanomedicines of cabazitaxel have the potential to overcome the constraints of drug use and overcome taxane resistance. This review reports on the recent cabazitaxel-based drug delivery systems, explains the obstacles encountered in creating cabazitaxel nanoformulations and provides solutions to address these challenges.

Introduction

The first-generation taxanes, docetaxel and paclitaxel, have changed the treatment criterion for many tumours, including breast, lung, prostate, gastric, and ovarian cancers, since their initial approval in 1992.[1] Despite displaying solid anticancer activity in combination regimens or monotherapy, the taxanes of the first generation are typically insubstantial in clinical use due to innate or acquired resistance. The majority of patients with prostate cancer will develop docetaxel therapy resistance. Cabazitaxel was discovered throughout screening 450 compounds produced from 10-deacetylbaccatin-III to find a chemical that may be used to treat taxane-resistant and taxane-sensitive malignancies.[2] Cabazitaxel plus prednisone significantly improved overall survival in patients with prostate cancer who had been treated with a regimen containing docetaxel in the pivotal TROPIC trial (NCT00417079) of Phase III. Cabazitaxel was sanctioned in 2010 for treating patients who have hormone-refractory metastatic prostate cancer and who had docetaxel-based therapy in conjunction with prednisone. Cabazitaxel is a taxoid chemical, which is obtained from *Taxus supp.* Yew tree needles. It had been chosen for clinical development because of its therapeutic activity and pharmacological profile in a wide range of docetaxel-sensitive, resistant, and refractory tumour models.[3] This compound was found to penetrate the brain barrier more effectively than first-generation taxanes in a preclinical model. Cabazitaxel was developed as a docetaxel's dimethyloxy derivative, which has several benefits over its antecedent. The extra methyl

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groups have the principal benefit of eliminating the docetaxel P-gp affinity, allowing cabazitaxel to be beneficial against prostate cancer with docetaxel resistance.[4] Cabazitaxel has a complicated structure that consists of a natural product that has been synthetically changed and has two other methoxy groups added to the docetaxel structure. The chemical structure of cabazitaxel is shown in Fig. 1. RPR116258A, TXD258, and XRP6258 are some of its other names. Cabazitaxel was developed primarily to combat docetaxel resistance in preclinical model systems. Cabazitaxel was evaluated in cold-induced tubulin depolymerization experiments and was as effective as docetaxel in early mechanistic research.[5] However, it was shown that cabazitaxel was more successful than docetaxel in inhibiting growth in cell lines which show resistance to the docetaxel and other treatment therapies. In several *in-vitro* experiments, the cabazitaxel was shown to be a poor substrate for the PgP efflux pump (MDR1), which exhibited multidrug resistance. This may or may not be relevant to the mechanism of action. The MDR1 inhibitors lack therapeutic efficacy in earlier clinical phases,[6] and it's unclear whether MDR1 is pertinent in

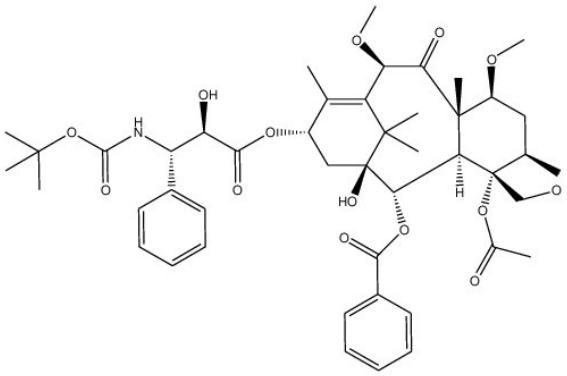

Fig. 1: Chemical structure of cabazitaxel; reprinted with permission from Mathrusri *et al.*[7]

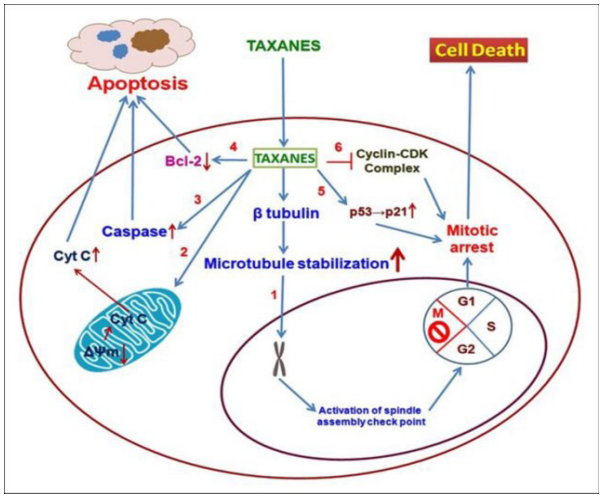

Fig. 2: Mechanism of action of taxanes; reprinted with permission from Sinha *et al.*[9]

describing cabazitaxel's clinical action. Cabazitaxel was proven highly active in an *in-vivo* mice xenograft model employing the prostate cancer cell line at a safe dose. The discovery that cabazitaxel is equally effective compared to docetaxel in "sensitive" models but more active as compared to docetaxel in "refractory" models led to the start of clinical phase trials for this new taxane.[4]

Mechanism of Action of Taxanes

Microtubule inhibitors, such as taxanes, cause cellular death by stabilizing microtubules. These are essential constituents of the cytoskeleton that play important parts in a range of cell-based activities such as cellular shape preservation, cell signalling, intracellular transport and division of the cell. Microtubules are a lead target for anticancer drugs because they are critical in mitosis. Microtubules are polymers that are constantly being assembled and disassembled within the cell. Taxanes attach to tubulin molecules, promote stabilize microtubules, polymerization, and inhibit their activity. Microtubule dynamics suppression causes a stop in mitosis and, as a result, tumour cell death.[8] The schematic representation of the mechanism of action of taxanes is represented in Fig. 2.[9]

Mechanisms of Resistance

Resistance to first-generation taxanes, innate or acquired, is common in several tumour types, resulting in therapeutic failure. In preclinical research, multiple putative pathways of resistance of taxane have been established, and some of these are likely to contribute to a resistant phenotype. In particular, two mechanisms have been linked to the evaluation of taxane resistance; hence, it is essential to note that they have to be verified in samples of patients, and their significance is unknown. The family of transporters' ATP-binding cassette has been overexpressed by the family of transporters, among which P-gP is encoded by the MDR1 gene (ATP-binding cassette, subfamily B [MDR/TAP], member 1; ABCB1), is the best cause of resistance in clinical research. P-glycoprotein is a substrate of docetaxel and paclitaxel, which works as an efflux pump of drugs that lower the cytotoxicity and intracellular drug levels.[10] Resistance may also develop due to naturally occurring tubulin mutations and taxane cell targets, resulting in changes in microtubule dynamics and tubulin binding sites. Additional mechanisms may also take part in the clinical data in taxane resistance, such as dysfunctional regulation of apoptotic and intracellular signalling, loss of functional p53, elevated expression of specific tubulin isotypes and binding of microtubule-regulatory proteins. The mitotic spindle checkpoint proteins synuclein-, MAD2, Aurora A, and BUBR1, as well as cell cycle proteins like BRCA1, have all been identified as possible prognostic markers for taxane resistance; nevertheless, clinical results have been mixed. Exploring other

medicines to overcome resistance from taxanes has attracted much interest.[11]

Challenges in Cabazitaxel

The dose of cabazitaxel is 20–25 mg/m^2 as concerned to safety data profile for 1-hour intravenous infusion every 3 weeks. The data on cabazitaxel dose was obtained from the phase I/II study when administered in combination with capecitabine during a phase I trial on patients with metastatic breast cancer and a phase II trial on patients with mCRPC.

Haematological Adverse Events

In any trials, haematological problems such as leukopenia and neutropenia were controllable and did not result in dose reductions or discontinuations. Approximately 64–82% of patients were observed to have grade 3 or 4 neutropenia. The incidence of febrile neutropenia and neutropenic infection was infrequent. Only one patient in four hundred and twenty-one had neutropenic colitis. Within 30 days of the last study drug dose, some patients treated with cabazitaxel died because of illness progression (5%), with 2% dying of neutropenia and its consequences. Mild to moderate severity was observed in the case of anaemia, whereas unusual effects were observed in the case of thrombocytopenia.[12,13]

Non-haematological Adverse Events

Fatigue, nausea, vomiting, and diarrhoea (approximately less than 5% each) are the standard grade 3 or 4 adverse events which are observed post-monotherapy. Less than 1% of patients were observed to have anaphylaxis and severe hypersensitivity reactions in the form of hypotension requiring treatment, syncope, bradycardia, etc. Almost 33% of patients are observed to have alopecia, whereas mild effects representing grade 1 or 2 are observed in the form of myalgia, arthralgia, stomatitis, mucositis, and peripheral oedema.[14] The Table 1 shows the adverse effects of cabazitaxel.[15]

Pharmacokinetics of Cabazitaxel

Cabazitaxel's pharmacokinetic qualities have been described in a phase I trial when used alone and in a study of phase I/II when used in conjunction with capecitabine. Cabazitaxel's pharmacokinetics were a proportionate dose of 10–25 mg/m^2 when given as the only drug in phase I research.[16] The drop in plasma cabazitaxel concentration was triphasic, with a rapid initial $t_{1/2}$ of 2.6 minutes, a short intermediate $t_{1/2}$ of 1.3 hours, and a protracted terminal phase of 77.3 hours. The average total body clearance (54 L/h/m^2) was high, accounting for 61% of the average hepatic blood flow. At a steady state, there was a high volume of distribution (2034 L/m^2), indicating that the drug is widely spread in the extravascular space. There was no sign of drug accumulation in plasma in patients who received multiple treatment cycles. When cabazitaxel is administered with capecitabine for atleast 14 days, there is no change in cabazitaxel and capcetabine pharmacokinetics. The metabolites of capcetabine were also not altered after the administration of cabazitaxel with them, suggesting no interaction between these two drugs.[17] Cabazitaxel is processed by cytochrome P450 (CYP) enzyme 2C8 and CYP 3A4/5 enzyme and also inhibits the CYP3A enzymes but no alter CYP enzymes. As a result, cabazitaxel may interact with CYP3A substrates *in-vivo*, but it is not likely to affect compounds processed by the other CYP enzymes.[15]

Cabazitaxel-based Drug Delivery Systems

Novel cabazitaxel formulation strategies are being researched due to the benefits of cabazitaxel, such as its increased potency and reduced sensitivity to P-gp efflux. This section will go through several different nanoplatforms that have been researched for cabazitaxel delivery. The ultimate goal is to give significant benefits compared to the currently available commercial cabazitaxel formulation i.e., Jevtana® and other well-known first-generation taxanes formulations. Increased antitumor effectiveness is the most critical area for improvement. Reduced toxicity could be an additional benefit. Mitigating toxicity has long been a critical technique for advancing nanomedicines into clinical trials.[18] Finally, because Jevtana® requires two different dilutions until delivery and is only stable for a short time after preparation intravenous the other new formulations could process drug administration technical difficulties. The different nanosystems have been depicted in Fig. 3.[19]

Polymeric Nanoparticles

Polymer-coated nanoparticles are the widely researched taxanes administration strategy because of the Kolliphor EL and tween 80-based polymeric micelles. Polymeric materials are available in various compositions, physicochemical characteristics, and functions. The hydrophobic and hydrophilic non-ionic block copolymers are frequently used in polymer-based taxane delivery methods. In aqueous conditions, the polymeric micelles contain a low critical micellar concentration. The micellar dispersion of 10–200 nm will self-aggregate the polymer under these circumstances, and hydrophobic medicines will be incorporated via hydrophobic interactions into the core of the micelles.[20] The EPR phenomenon may enable the nanoparticle to undergo tumour deposition because of the polymeric micelle's particle size. In various cases, a PEG fragment is the hydrophilic polymer component, while polyethers, poly(amino acids), polyesters or other moieties serve as the hydrophobic polymer component. Biodegradable and biocompatible polymers are commonly employed in medication delivery systems. Polymers like poly (lactic-co-glycolic acid) (PLGA) and poly (lactide) (PLA) break up at the link of ester to form innocuous and tiny molecules, releasing their pharmacological payload.

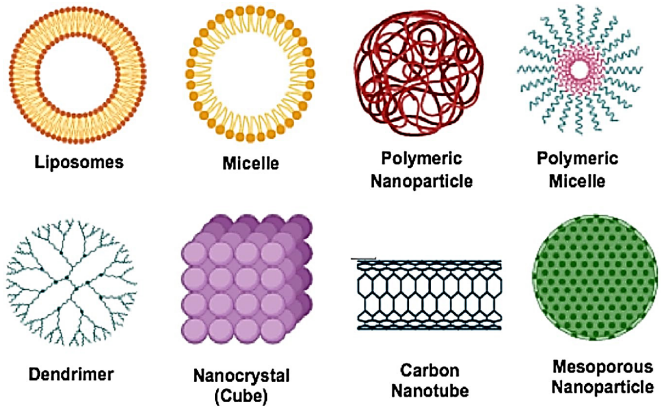

Fig. 3: Pictorial representation of various nanoparticles; reprinted with permission from Tayo *et al.*[19]

Furthermore, after oral delivery. Polymeric micelles can protect the hydrophobic medicines against deactivation of the biological environment of the GI tract.[21] Nanoprecipitation, interfacial deposition and emulsion/solvent evaporation are some of the processes used to make polymeric nanoparticles. Manufacturing procedures influence formulation qualities, while the included medication's properties influence formulation methods. Polymeric materials are made up of a range of polymer kinds, some of which can control the rate at which drugs are released to achieve certain goals. PEG polymer segments inhibit clearance rates by reducing serum activity and delaying absorption towards the reticuloendothelial system.[22] Conjugation of polymers with targeting ligands can be used to target them actively. The PLGA copolymer is biocompatible and biodegradable. The bone metastases were treated by developing cabazitaxel-loaded PLGA nanoparticles. Many cancers can spread to specific body parts, including the bone. Bone metastases are frequent in advanced-stage prostate cancer, and they tenant significant pain, have limited therapeutic options and are linked to poor survival. An emulsion/solvent evaporation approach was used to create bone-targeted cabazitaxel-loaded PLGA nanoparticles. The covalent attachment of a tumour-metastasis-targeting (TMT) peptide to PEG-PCL nanoparticles was investigated. The TMT peptide binds to several different metastatic cancers. Metastatic breast cancer cells treated with TMT-modified nanoparticles had a higher rate of necrosis than those treated with non-targeted nanoparticles. Fluorescently labelled nanoparticles were taken up identically by the nonmetastatic MCF-7 cell line, regardless of the presence of the targeted ligand, according to confocal microscopy. However, compared to non-targeted particles, targeted particles showed much better absorption in the MDAMB-231 human metastatic breast cancer cell line. Cabazitaxel-loaded PVP7-PCL particles produced 2-fold higher drug concentrations in tumours than free drugs in a biodistribution investigation. Compared to the free medicine, they also caused more tumour growth inhibition and survival. Crosslinking polymers can lead to more stable nanoparticle sizes and better cargo entrapment. For cabazitaxel distribution, cross-linkable, acid-sensitive micelles have been created.[23] PEG as a hydrophilic segment, poly(methyl methacrylate) (PMMA) as a hydrophobic segment, and a central polyacrylic acid (PAA) block to cross-link and control drug release make up the amphiphilic copolymer. In vitro drug release experiments revealed that non-crosslinked nanoparticles released drugs more quickly than shell cross-linked micelles (SCLM). After responding to mild acidic stimuli, the release of cabazitaxel from SCLM increased from 30 to 85% in 30 hours (pH 5.0). In PC3 and C4-2B cancer cells, SCLM containing cabazitaxel showed significant cytotoxicity. Surfactants like Kolliphor EL or tween 80 are routinely used to solubilize hydrophobic medicines for intravenous administration. However, they have negative effects such as complement activation that alternate solubilization methods can avoid.[24] Gdowski *et al.* developed a brand-new cabazitaxel bone-targeted nanoparticle (NP) technology for enhanced bone microenvironment medication delivery. Poly(D, L-lactic-co-glycolic acid) and cabazitaxel were used to create nanoparticles, and the surface was conjugated with amino-bisphosphonates. The physicochemical properties of nanoparticles were optimized. Prostate cancer cell lines were used for in vitro testing, and an intraosseous metastatic prostate cancer model was used for in vivo testing. The tumour burden was significantly reduced using this bone-targeted cabazitaxel nanocarrier system, which also preserved the integrity of the bone structure and decreased pain in the mouse tumour limb. This clinically applicable evaluation method and bone microenvironment-targeted nanoparticle technology indicate a promising development for the treatment of metastatic bone cancer.[25]

Lipid-based Drug Delivery Systems

High-pressure homogenization was used to develop a cabazitaxel-loaded intravenous lipid emulsion. Glycerin, medium-chain triglycerides, and Pluronic F68 were included in the formulation. Pluronic F68 is a surfactant excipient for intravenous formulations that have received FDA approval. Adding cabazitaxel with cholesterol inhibited degradation and protected the medication against hydrolysis of esters in both the oil and water phases. The chemical stability of cabazitaxel has been enhanced from 134 to 831 days compared with the formulation without cholesterol. Cabazitaxel has been designed to form a surfactant system of a lipid-polymer hybrid for targeted distribution. The 14-amino-acid peptide bombesin (BN) interacts with a variety of receptors, including the gastrin-releasing peptide (GRP) receptors and neuromedin B.[24] Bombesin conjugated to docetaxel-loaded PLGA nanoparticles previously overexpressed the GRP receptor to show the higher

anticancer effects. The cabazitaxel-loaded lipid-polymer hybrid nanoparticles were synthesized using BN-PEG-DSPE. These nanoparticles displayed considerable inhibitory action in GRP receptor-expressed tumour cells, according to *in-vitro* and *in-vivo* experiments. Cholesterol has been utilized to alter the behaviour of cabazitaxel nanosystems based on polymers. Conjugation of cholesterol with Pluronic F68, the resulting hybrid lipid, was employed as self-assemble cabazitaxel.[26] After conjugation, the CMC of cholesterol-F68 copolymer was low (10 g/mL) which was 400 times lower than the Pluronic F68 CMC, which provided stability against precipitation after intravenous administration into the bloodstream. In vitro and in vivo studies of cabazitaxel-loaded Tween 80 formulation showed lower antitumor activity compared to cabazitaxel-loaded cholesterol-F68 nanoparticles, which displayed better antitumor cytotoxicity against S180 cells. Surfactants like Pluronic and lecithin can stabilize solid lipid nanoparticles (SLNs), which have a solid lipid core. SLNs can control the release of medications due to the restricted mobility of pharmaceuticals in the lipid core. SLNs can be made directly using processes like high-pressure homogenization, allowing for industrial-scale production. Antitumor experiments with Cabazitaxel-loaded SLNs have been conducted.[27] Compritol 888 ATO, didodecyldimethylammonium bromide, and tocopheryl polyethylene glycol succinate were used in the composition (TPGS). Hyaluronic acid (HA) was added to the outer shell as a CD44 receptor targeting ligand. The extracellular matrix contains HA, a biocompatible and biodegradable carbohydrate. Many cancer cells have HA receptors such as CD44 and hyaluronic-mediated motility receptor (RHAMM), so we can use HA as a targeted agent for drug delivery systems. In vitro cell viability experiments on the human MCF-7 breast cancer cell line, which has the CD44 receptor, showed that the nanoparticles had more cytotoxicity than free drug and non-targeted nanoparticles. Liposomes and nanoparticles (NPs) were created as effective nanotherapeutics for the administration of the very hydrophobic medication CBZ. The generated NPs and liposomes have spherical shapes and diameters less than 110 nm, which is advantageous for EPR targeting. The formulation may be stabilized using CBZ liposomes with a negative zeta potential (24.351.2 mV) and CBZ NPs with a positive zeta potential (+45.731.65 mV). Compared to CBZ liposomes, which had 10%w/wdrug loading(entrapment efficiency: 88%), the proportion of drug loading for CBZ NPs was approximately 20%w/w(entrapment efficiency: 98%). According to *in-vitro* drug release tests, persistent CBZ release from liposomes (60%) and NPs (41%) in 28 days is more advantageous for long-term breast cancer treatment. *In-vitro* cytotoxicity tests on the MCF-7 and MDA-MB-231 cell lines showed that NPs and liposomes are more effective than a CBZ micellar solution; this may be because nanocarriers internalize quickly through the cell lines' endothelium, as seen in CLSM pictures. A cell cycle study showed that CBZ liposomes and NPs on both cell lines exhibit higher G2/M phase cell arrest than the CBZ micellar solution. According to an assay for apoptosis, NPs generated necrosis in both cell lines, while CBZ micellar solution and CBZ liposomes caused apoptosis and necrosis, which resulted in cell death. CBZ liposomes, as opposed to CBZ NPs and the micellar CBZ solution, induced greater apoptosis, which is better for treating breast cancer. The *in-vitro* hemolysis investigation suggested that NPs (2.7-fold, 13.09%) and liposomes (8.7-fold, 5.03%) were less harmful to RBC than a micellar CBZ solution based on surfactants (48.88%). Additionally, at a concentration of 20 g/mL, CBZ liposomes demonstrated a 1.6-fold decrease in hemolysis compared to CBZ NPs. Liposomes and NPs, two surfactant-free nanotherapeutics, reduced neutrophil count by 0.6 and 1.4 folds, respectively, when compared to control, but micellar CBZ solution reduced neutrophil count by 24.7 folds. The micellar CBZsolution and NPs displayed a more neutropenic impact than CBZ liposomes. Pharmacokinetic measurements showed increased MRT and $t_{1/2}$ of produced formulations, resulting in a sustained drug release and decreased dose frequency. Compared to CBZNPs, CBZ liposomes exhibit longer $t_{1/2}$ (7.6 hours) and MRT (8.9 hours). In conclusion, newly created CBZ liposomes have the potential to serve as less hazardous delivery vehicles for the treatment of breast cancer. The effectiveness of the created CBZ-loaded NPs and liposomes will be assessed soon in a breast cancer model.[28]

Cabazitaxel Conjugates

The goal of chemical or enzymatic drug conjugation to carriers is to gain better therapeutic qualities over

Table 1: Haemolytic and non-haemolytic adverse event of grade 3–4 related to clinical trials of cabazitaxel.

Cabazitaxel alone (20 mg/m^3)	*Cabazitaxel alone (25 mg/m^3)*	*Adverse events*
55	68	Leukopenia
4	4	Thrombocytopenia
0	2/2	Nausea/vomiting
0	0	Anorexia
1	6	Diarrhoea
73	82	Neutropenia
3	11	Anaemia

the original medication. An FDA-approved cellulose derivative is the carboxymethylcellulose that is utilized in drug formulations and the production of food products such as toothpaste, ice cream, and cosmetics.[29] It has been used in medication delivery applications because of its biocompatibility. Cabazitaxel was attached to carboxymethylcellulose, yielding a cellax-CTX polymer that self-assembled. Other anticancer hydrophobic drug conjugates, such as docetaxel, have also been successfully delivered using the cellax platform. In serum, Cellax-CTX nanoparticles released cabazitaxel over time. When mice were given cellax-CTX at the MTD, it caused reversible neutropenia with no histological damage. In a mCRPC mice model of bone metastases, Cellax-CTX increased the survival rate to 120 days, three times higher than free cabazitaxel (40 days). Redox-sensitive drug delivery techniques have been described to restrain medication release in the proper tumour cell microenvironment.[30] Disulfide linkages are common in redox-sensitive micelles, which are steady in the moderate oxidizing blood environment but susceptible to the intracellular commuting environment, as seen in compounds like glutathione (GSH) in tumour cells. The disulfide bonds are cleaved in the reducing environment, resulting in drug release. This method was used to make micelles of cabazitaxel containing disulfide linkages. Cabazitaxel in conjugation with the citronellol using disulfide linkages (CIT-ss-CTX) got self-assembled in an aqueous solution. Citronellol is a naturally produced monoterpenoid frequently employed in food products and is FDA authorized. The PEGylated phospholipid anchor DSPEPEG2000 has been a PEGyltaed anchor of phospholipid and acts as an emulsifier to the formulation to reduce reticuloendothelial system clearance to prolong blood circulation. The prepared nanoparticles remained stabilized and had a more excellent drug loading ratio than other micelles or polymeric nanoparticles. The conjugation was found to be hazardous to cancer cells in the PC3 and A549 cell lines. The hydrophobic dyes such as DiR and 6-coumarin and other cargo like curcumin have been used for theranostic applications, which might be carried by the CIT-ss-CTX construct.[31] Solid tumour microenvironments are acidic because, in oxygen-deprived tumour cells, the anaerobic glycolysis is very active, whereas blood is always neutral. Cabazitaxel is conjugated with the dextran-loaded pH-sensitive ester linkers to provide a mechanism for drug release in the acidic tumour tissues, which results in the 1500-fold enhancement of drug solubility.[32] The cabazitaxel-dextran conjugate linkages were hydrolyzed to release free cabazitaxel under acidic conditions after in-vitro studies using MCF-7 breast cancer cells revealed that the succinate conjugated nanoparticles had more significant cytotoxicity than the free drug.[33]

Conclusion

Cabazitaxel is a taxane of second-generation that has shown efficacy in cancers resistant to docetaxel. Cabazitaxel has clinical advantages over other taxanes, which have been suggested as a reduced affinity for Pg drug efflux transporters and greater blood-brain barrier penetration. Clinical and commercial success for all the taxanes, i.e., Taxotere® (docetaxel), Taxol® (paclitaxel), Abraxane® (paclitaxel), and now Jevtana® (cabazitaxel), has inspired further improvement in the development of cabazitaxel loaded nanocarriers. There are several approved methods, and some are in the clinical trial phase of paclitaxel and docetaxel, which could give hope for the production and synthesis of cabazitaxel-loaded nanoformulations with better features such as less adverse effects and prolonged plasma circulation time. Cabazitaxel has been developed for use in a variety of medication delivery systems. Even though many different forms of cabazitaxel nanoformulations have been described, several formulation tactics that could be proven successful for further taxanes like liposomes have yet to be explored. The wide range of taxane nanosystems that have yet to be investigated for cabazitaxel suggests that new and effective delivery strategies may be developed in the nearest future.

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