

REVIEW

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A multiscale approach to targeted docetaxel formulations: combination therapy, nanotechnology, electrospinning and 3D printing—a review

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Abstract

Background: Cancer remains one of the leading causes of death worldwide. Docetaxel, first marketed as ‘Taxotere’, has been approved for use as a chemotherapeutic for management of gastric, breast, neck, head, non-small cell lung cancer and prostate cancer.

Main body: Taxotere, is a docetaxel formulation solubilized in tween 80 and 13% ethanol solution. It is effective as a chemotherapeutic agent but has numerous toxic effects due to the ethanol and polysorbate. Aside from this, challenges with administration during mixing of the docetaxel with the diluent exist. Poor mixing results in gel formation while addition of the drug mix to an infusion may result in micelle formation. These challenges have necessitated remodeling of the currently available docetaxel formulation, but none has made it to clinical setting as an alternative. Efforts have also been made to develop oral docetaxel formulation to ease administration of the drug. Attempts have also been made to develop other dosage forms, notably transdermal formulations and implants to target cancer cells while avoiding systemic side effects. Formulation methods such as nanoformulation, drug coupling with other active moieties, 3D fabrication as well as electrospinning have been employed.

Conclusions: Development of novel formulations of docetaxel for different chemotherapeutic needs appears promising with some formulations currently in clinical trials. Exploring other drug formulation techniques such as the use of 2D LDH may produce novel anticancer formulations in the future.

Keywords: Cancer, Metastatic cancer, Polymeric docetaxel nanoformulations, Combined chemotherapeutics, Targeted anticancer formulation, Electrospun fibers, 3D drug fabrication, Sustained-release chemotherapeutic drugs

Background

Docetaxel is an antineoplastic agent used in cancer chemotherapy. It belongs to the taxane class and is a semisynthetic form of paclitaxel, extracted from the needle of the European yew tree (*Taxus baccata L*) with higher

efficacy than paclitaxel (Bissery et al. 1991). It exerts its cytotoxicity by binding to β -tubulin, stabilizing microtubule structures and inhibiting the depolymerization of microtubules with subsequent inhibition of cell growth (Hwang 2012). Docetaxel is a tetracyclic diterpenoid is paclitaxel whose N-benzyloxycarbonyl group has been replaced by N-tert-butoxycarbonyl. There is also subsequent replacement at position 10 of an acetoxy group by a hydroxy group. It was originally thought to possess antimalarial properties, photosensitization and anti-neoplastic activities (National Center for Biotechnology

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Information 2022). Docetaxel has been used in chemotherapy of different kinds of cancers including hormone-refractory metastatic prostate cancer in which situation it exerts by preventing separation of cancerous cells into newer ones, hence blocking the growth of the tumor (Hoang et al. 2014). It was approved in the USA for the treatment of gastric, breast, neck, head, non-small cell lung cancer and prostate cancer and was registered under the name 'Taxotere' on the May 19, 2004, by Aventis pharmaceutical Inc.

FDA approved Taxotere is barely soluble in water and contains a high concentration of ethanol used to dissolve tween 80, utilized for its formulation. This results in the production of an efficacious product, with high cytotoxicity to normal noncancerous cells as well as side effects including peripheral neuropathy, hypersensitivity reaction, microsites, fluid accumulation in the body, mouth sores, anemia, hair loss, diarrhea, and nausea, among others (Rajappa et al. 2018; de Dosso and Berthold 2008). It is not compatible with polyvinyl chloride intravenous administration sets. These side effects have reduced its use in clinical settings despite its efficacy, necessitating researchers to implement more effective drug delivery strategies for docetaxel that increases efficacy minimizes side effects attributed to tween 80 and ethanol (Nasrolahi et al. 2016).

Over the years, scientists have employed numerous strategies to improve the currently available taxotere formulation. Such strategies include the use of novel combination therapy, nanoformulations, and of recent 3D fabrication and electrospinning with polymers (Yan et al. 2016). These drug delivery systems have been utilized as a tool for the development of targeting anti-neoplastic formulations such as mucoadhesive and transdermal patches, among others. However, only a few of such formulations make it to clinical trials or for use in clinical settings. This may be as a result of difficulty in transitioning from bench to large scale formulations (Campani et al. 2022). This review aims to highlight various attempts at development of novel, efficacious docetaxel formulations with little to no side effects for targeted delivery for chemotherapy in docetaxel responsive tumors.

Main text

Docetaxel (taxotere)

Docetaxel is the second drug from the taxane group of antineoplastic medications developed by researcher Pierre Potier (Zhang et al. 2019). The parent taxane 'paclitaxel' was extracted from a non-renewable source, whereas docetaxel was partly synthesized from a precursor obtained from the needles of *Taxus baccata*, making docetaxel more accessible than paclitaxel. Also docetaxel

has shown greater efficacy against cancer cells when compared with the parent taxane paclitaxel. Several studies have proven the efficacy of docetaxel against a wide array of cancer cells. Taxotere, a patent docetaxel formulation by Sanofi-aventis, is an antineoplastic approved for the management of non-small lung cancer, breast cancer, gastric adenocarcinoma, metastatic castration resistance prostate cancer, and squamous cell carcinoma of the neck and head (van Zuylen et al. 2001). Research to evaluate its efficacy in varying types of cancer has been carried out. Its use in the management of metastatic hormone refractory prostate cancer was established by Dominic et al. (2008). Taxotere was administered with prednisolone in 106 human subjects, and the results of the clinical trial demonstrated its superiority over mitoxantrone, which was the medication used prior to the study. The approved dose based on the outcome of the clinical trial was 75 mg/m² intravenous infusion transfused hourly every 21 days, administered with 5 mg prednisolone tablet every 12 h for 10 cycles (Dominic et al. 2008). Although the efficacy of this regimen has been proven in clinical settings, the mechanism of this chemotherapeutic success has not been clearly elucidated (Parker et al. 2015; Mottet et al. 2016; Puente et al. 2017).

Chemical structure of docetaxel

DTX (CAS number: 114977-28-5, Fig. 1) is a white to off-white crystalline powder with a molecular weight and formula corresponding to 807.89 Da and C₄₃H₅₃NO₁₄, respectively. Its solubility in water is 1.27.10⁻² g/L and melting point is 232°C. DTX is a highly lipophilic, semi-synthetically derived from 10-deacetylbaccatin III compound. (da Silva et al. 2018).

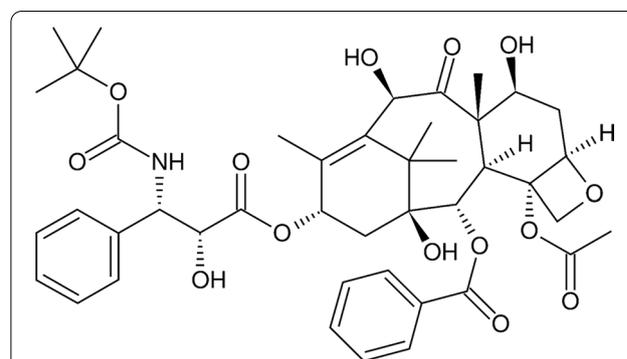


Fig. 1 Structure of docetaxel shows the presence of an hydroxyl functional group at C10 with a benzamide side chain (Wikipedia, accessed May 17, 2022)

Mechanisms of action

Docetaxel, a semisynthetic taxane thought to have a twofold antineoplastic action. Docetaxel has been discovered to decrease micro-tubular de-polymerization and to counteract the effects of bcl-2 and bcl-xL gene expression. The microtubules are the most essential components of the eukaryotic cytoskeleton, and they are known to play key roles in cell division, migration, signaling, and intracellular trafficking, making them crucial mediators of cancer cell proliferation and metastatic processes. During the polymerization process, tubulin heterodimers join noncovalently to form 25-nm-diameter hollow cylindrical filaments termed microtubules. They are highly dynamic structures that are responsible for the addition or removal of tubulin subunits at microtubule ends, allowing microtubules to alternate between phases of growth and shortening phase (Imran et al. 2020a, b). This phenomenon is known as "dynamic instability." Docetaxel most frequently acknowledged mode of action for microtubule stabilization is the binding of docetaxel to P-tubulin, which promotes polymerization, inhibiting the dynamic instability process as indicated in Fig. 2 (Du et al. 2018).

Pharmacokinetic profile

DTX pharmacokinetic profile is composed of three compartments having half-lives of 4.5 min, 38.3 min and 12.2 h for alpha, beta and gamma phases, respectively (Imran et al. 2020a, b). Intravenous administration is

followed by high concentrations of the drug in most of the tissues including liver, bile ducts, muscles, pancreas and stomach but lower deposition in testes and nervous system. The concentration of DTX is obviously higher in the cancer cells as compared to the normal healthy cells owing to their extensive binding to α -1 acid glycoprotein. The distribution of the drug takes place from the central to the peripheral compartments with a total volume of distribution of 22 L/h/m² in human body and having mean stationary distribution volume of about 113 L (Imran et al. 2020a, b).

Volume of distribution is dependent on a number of factors such as age, plasma protein binding, liver function, and body surface area. Studies have observed extensive binding of DTX to plasma proteins including albumin, α -1 acid glycoprotein (AAG) and lipoproteins. The binding varies up to 93–94% in vitro and about 70–95% in vivo. α -1 acid glycoprotein is more expressed in cancer patients, which explains the efficacy of docetaxel in cancer management. About 4–10% fraction of DTX has been reported to be unbound in plasma of patients that were treated with the drug, which is an indicative of extensive protein binding (da Silva et al. 2018).

DTX is metabolized by hepatic cytochrome P450 (CYP) 3 A isoforms CYP3A4 and CYP3A5 resulting in various pharmacologically inactive oxidation products. Biliary, renal and intestinal excretion has been established as the major pathways of the elimination of the

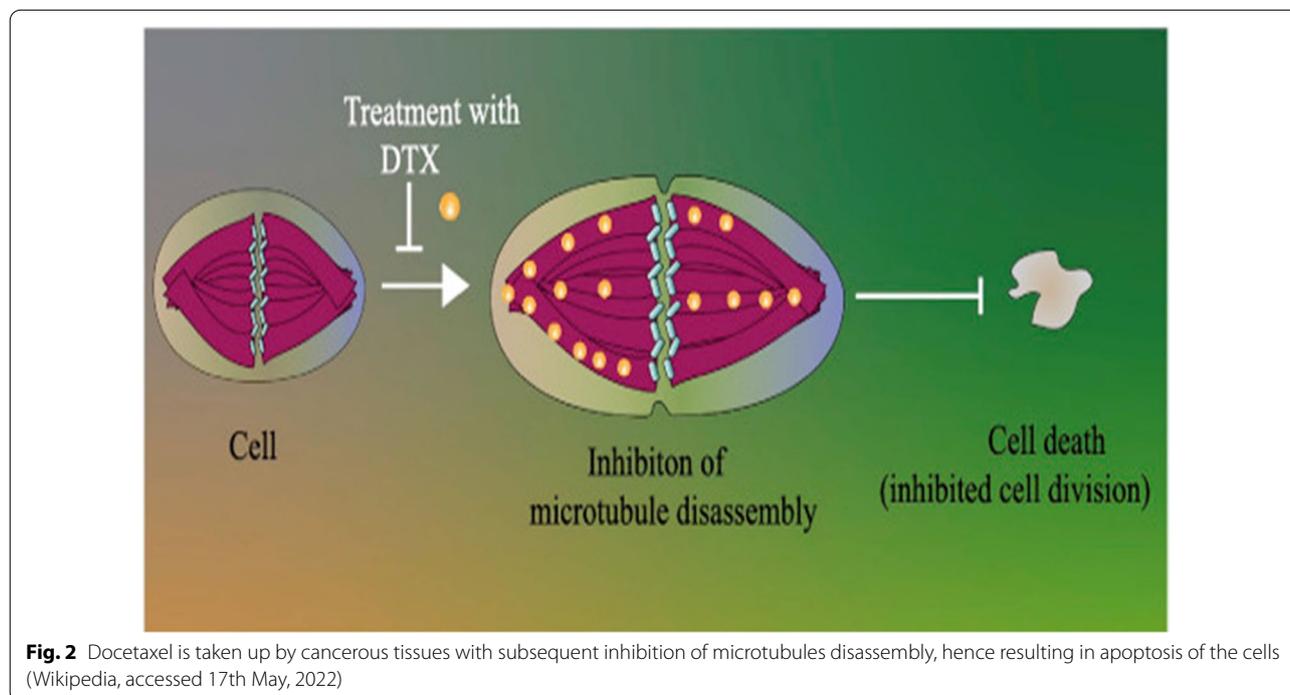


Fig. 2 Docetaxel is taken up by cancerous tissues with subsequent inhibition of microtubules disassembly, hence resulting in apoptosis of the cells (Wikipedia, accessed 17th May, 2022)

parent drug and the metabolites. After 7 days of administration, around 6% and 75% of the total amount of the drug is excreted in the urine and feces, respectively, with the highest elimination rates occurring during the first 48 h through fecal excretion (Sohail et al. 2018).

The evolution of docetaxel formulation

Taxotere was initially packaged in a two-vial presentation during the FDA approval period in 1995, with one vial containing docetaxel in polysorbate 80 at a 40 mg/ml concentration, whereas the second vial contained a 12% w/v ethanol/water diluent mixture. The addition of the whole diluent in the second vial to the first vial produces a 10 mg/ml solution of docetaxel which is subsequently added to an infusion of normal saline or 5% dextrose saline. Such infusions, if stored at 2 to 25 °C, are stable for only four hours as crystallization of the solution may occur in storage. Aside from the short storage period, poor mixing of the docetaxel may cause a gel phase to be formed, which when transferred to the infusion bag may result in micelle formation and subsequent precipitation of docetaxel. Efforts at improving the 2 vial taxotere formulation have led to the development of a single vial taxotere in 2010. The one vial formulation consists of a 20 mg/ml docetaxel solution prediluted in polysorbate 80 and ethanol at a concentration 50/50% v/v with the final docetaxel concentration remaining the same as in the two vial formulation. The single vial formulation offers numerous advantages over the former in terms of ease of administration. No premix solution is formed which eliminates the risk of crystallization with an improved storage time of seven days (Hart and Acott 2010).

Codelivery of docetaxel with other active moieties in chemotherapy

In an attempt to increase the bioavailability and efficacy of taxotere in the management of varying types of cancer, researchers have made attempts to combine docetaxel with other entities that may improve bioavailability or ensure targeted delivery to a specific site of action. Some scientists have attempted to combine docetaxel with P glycoprotein inhibitors such as ritonavir to produce an oral docetaxel formulation with high bioavailability. Others have attempted to combine two chemotherapeutic drugs to manage metastatic cancer. Table 1 summarizes notable, successful docetaxel combination attempts made by researchers in clinical trials. Utilization of ultrasound simulated microbubbles (USMB) to promote delivery of anticancer drugs into cancerous cells by improving the microvascular permeation of the medication was investigated by (Goertz et al. 2012). The combined use of intravenous injectable of antivascular USMB with docetaxel (taxotere) as a chemotherapeutic agent in mice with

induced prostate carcinoma has revealed an enhanced antineoplastic effect of USMB combined docetaxel when compared with taxotere. In vitro studies of the suspension of microbubbles with cancer cells resulted in an enhanced uptake of docetaxel intracellularly. The mechanism of this effect was attributed to the ability of USMB to preferentially significantly reduce blood flow within the tumor cells (Goertz et al. 2012). Another researcher formulated a liposome of docetaxel and siRNA and investigated its efficacy in lung cancer chemotherapy. A sustained release pattern of drug release with great regression of the tumor was observed in vivo. In a xenograft tumor model (Qu et al. 2014), synergism of all active moieties was observed with a 100% survival rate on A549 cells bearing xenografts.

In a phase II and subsequent phase III trial, Wolff et al. 2010 investigated the efficacy of combine docetaxel and liposomal doxorubicin (the doublet therapy) with or without trastuzumab for the management of metastatic breast cancer in a phase II and subsequent phase III trial. The doublet therapy was certified effective for use in the management of metastatic breast cancer with minimal risk of cardiac toxicity and a high risk of hand-foot syndrome. Although combined doxorubicin and docetaxel formulation is not yet available for clinical use, future use of the coformulation for metastatic cancer is certain (Wolff et al. 2010).

A coformulation of docetaxel and tanespimycin in hyaluronic acid and poly (lactic-co-glycolic acid) (PLGA) nanoparticles was formulated for management of metastatic cancers. Cytotoxicity studies revealed docetaxel and tanespimycin produced a synergistic effect in vivo, proving it's potential for management of advanced cancer in clinical settings (Pradhan et al. 2015).

Due to ease of administration, various attempts to formulate oral docetaxel have been made. Such studies have highlighted that inhibition of P glycoprotein enhances oral absorption of docetaxel. Some researchers have coformulated docetaxel with ritonavir, a strong inhibitor of cytochrome P4503A4 and a minor inhibitor of P-glycoprotein. Studies in mice have indicated increased plasma levels after oral administration of DTX/RTV by 50 folds when compared with DTX alone (Bardelmeijer et al. 2002). Another study investigated the use of oral DTX with cyclosporine in an attempt to formulate an efficacious oral docetaxel formulation. This formulation in a phase II study was administered to patients with advanced solid malignancies. Apparent bioavailability (AUC ratio: AUC after oral administration divided by AUC after IV administration) of 90% was reached (Malingre et al. 2001). Another study was carried out in human subjects with solid tumors to determine the pharmacokinetic profile of the

Table 1 Drugs coadministered with docetaxel for optimized chemotherapeutic action

Tumor type	Coformulated drug(S)	Mode of administration	Clinical trial	Remark	References
Metastatic breast cancer	Trastuzumab	IV infusion	Phase II human study	Prolonged progression time with minimal toxicities	Esteva et al. (2002)
HER2 positive metastatic breast cancer	Trastuzumab	Intravenous infusion	Phase II human trials	Greater efficacy with minimal toxicity	Marty et al. (2005)
Prostate cancer	ABT 627	Intravenous infusion	Preclinical studies (in vivo and in vitro)	ABT 627 enhances sensitivity of tumor cells to docetaxel, hence enhancing docetaxel induced growth inhibition	Banerjee et al. (2007)
HER2 negative metastatic breast cancer	Bevacizumab	IV infusion	Phase III trials	Enhanced progression free survival with limited increase in toxicity	Miles et al. (2010)
HER2 Metastatic breast cancer	Pertuzumab and trastuzumab	IV infusion	Phase II human study	Prolonged survival with no disease progression when compared with trastuzumab/docetaxel only	Baselga et al. (2012)
Refractory tumors	Ritonavir	Oral	Phase II clinical trial	Comparable efficacy of combined drug in capsule and DTX/RTV separately	Moes et al. (2013)
Metastatic breast cancer	Capecitabine	Intravenous	Phase III human trials	Prolonged progression time with combination when compared with docetaxel alone	Glück et al. (2013)
Metastatic triple negative breast cancer	Cisplatin	Intravenous infusion	Phase II clinical trials	Cisplatin/DTX more effective than capecitabine/DTX	Fan et al. (2013)
Advanced recurrent non-small cell lung cancer	Ramucirumab	IV Infusion	Retrospective study in Human subject	Combination more effective, delays disease progression	Harada et al. (2019)
Advanced or metastatic solid tumors	Ritonavir	Oral	Phase 1 clinical trial	75% of subject did not experience toxic side effects. Twofold increase in Cmax when combined with RTV	Vermunt et al. (2021a, b)

coadministered medications. Such studies indicated that in subjects receiving oral doses of 100 mg docetaxel with 100 mg ritonavir simultaneously, the bioavailability of DTX/RTV was $131 \pm 90\%$ with an increase in the AUC. Koolen et al. (2010) suggest that bioavailability of over 100% suggests the inhibition of docetaxel elimination by ritonavir when co-administered orally. Hendriks et al., investigated concomitant use of oral docetaxel and paclitaxel with P-gp inhibitor elacridar, ritonavir and elacridar/ritonavir in mice. A fourfold and 10.7-fold increase in plasma concentration of docetaxel and paclitaxel, respectively, with coadministration with elacridar was observed. Coadministration with ritonavir resulted in a 7.3- and 2.5-fold increase in plasma concentration, while coadministration with elacridar/

ritonavir resulted in a 31.9- and 37.4-fold increment in paclitaxel and docetaxel plasma concentration, respectively (Hendriks et al. 2014). Research has also shown that the bioavailability of the taxane is enhanced when co-administered with a P-gp inhibitor. Co-administration of intravenous docetaxel with oral piperine, a potent inhibitor of CYP3A4 to a 6 week old mice has resulted in an increased AUC by 230%, a longer half-life of docetaxel from 0.44 to 1.14 h and a maximum concentration Cmax increased from 6808 ng/ml for docetaxel alone to 11,380 ng/ml docetaxel/piperine with no apparent increase in toxicity level (Kumar et al. 2018).

Another study that corroborated the use of formulated oral docetaxel and ritonavir, a formulation named 'ModraDoc006/r'. The bioavailability of oral docetaxel

formulation was impressive. However, the intake of a high fat meal strongly influences the bioavailability of the oral medication; hence, it is advised that patients should only take ModraDoc006/r an hour before and 2 h after consuming a highly fatty meal (Vermunt et al. 2021a, b).

Nanoformulations of docetaxel

Nanomedicine has been utilized to enhance the solubility of poorly soluble drugs in order to improve the drug's bioavailability as well as to deliver medications to specific sites of action. A number of nano-drug delivery systems have been employed for targeted chemotherapeutic drug delivery. Such drug delivery systems include the use of polymers as drug carriers, lipids (liposomes, micelles), inorganic drug delivery systems, and coupling of drugs with ligands attached to a nanocarrier as summarized in Table 2. The use of polymeric drug delivery systems has been widely employed in the development of antineoplastic medications. The physical and chemical properties of utilized polymers (particle size, hydrophobic nature of the polymer, surface charge) largely influence the pharmacokinetics of the polymeric nanoformulations (solubility of the polymeric formulation, blood circulation time, and biological compatibility) (Tan et al. 2012).

Liposomes and micellar formulations

Liposomes are made up of phospholipids of varying layers and cholesterol, forming a closed vesicle which is usually spherical and capable of enclosing hydrophilic compounds. It was introduced by Bangham in 1965 (Chang and Yeh 2012). Liposome can be used as a vehicles for delivery of drugs, vaccines, and other therapeutic or biological moieties (Akbarzadeh et al. 2013). It has been used for the delivery of various cytotoxic drug moieties for cancer management. Some of these drugs have been studied in vivo and in vitro and in some cases, in clinical trials (Deeken et al. 2013).

In an attempt to formulate an efficacious docetaxel formulation devoid of toxic side effects of tween 80 and ethanol, Lee et al., developed a nanomicellar formulation of docetaxel (Nanoxel-PM) using methoxy-poly (ethylene glycol)-block-poly (D,L-lactide) (mPEG-PDLLA). The average size was 10–50 nm in diameter and the follows a monodisperse unimodal pattern. Studies in mice, rats, and beagle dogs indicated pharmacokinetic profile of Nanoxel-PM was similar to taxotere. The chemotherapeutic efficacy of IV Nanoxel-PM in lung, ovary, and breast cancer cell lines as well as human lung cancer xenografts H-460 in nude mice was similar to taxotere, hence inferring bioequivalence of Nanoxel-PM and taxotere. However, fluid retention and hypersensitivity

reactions associated with taxotere were not observed with Nanoxel-PM (Lee et al. 2011).

Deeken et al., formulated a docetaxel liposome with lipids Dioleoyl-sn-glycero-3-phosphocholine (DOPC), cholesterol, cardiolipin, tetramyristoyl and alpha-tocopheryl acid succinate. The liposome measured 100 nm in mean diameter. A phase 1 trial was carried out to assess the efficacy, pharmacokinetics, clinical response, and toxicity of formulated docetaxel encapsulated in liposomes in patients with advanced solid tumor cancer. Twenty-four subjects with varying cancer types enrolled in the study, and results obtained indicated the formulation was well tolerated with minimal signs of anemia, fatigue, and neutropenia but no edema and neuropathy. 41% of the subjects benefitted and improved clinically with an intravenous dose of 85 mg/m² without G-CSF or 110 mg/m² with G-CSF (Deeken et al. 2013).

Ganta et al., attempted to develop a folate targeted nanoemulsion (NE) of docetaxel with incorporated imaging agent gadolinium and surface functionalized with folate for management of multi drug resistant ovarian cancer. The formulation had a particle size < 150 nm, was stable in parenteral fluids as well as dog plasma in vitro, for 24 h. Uptake of the intravenously administered docetaxel NE by ovarian tumor cells was significant, with an enhanced cytotoxic effect when compared with docetaxel alone. Studies in mice showed prolonged accumulation of folate targeted docetaxel NE in ovarian cancer cells when compared with the non-targeted NE, showing that folate targeting enhanced the ability to identify and permeate cancer cells by the theranostic docetaxel NE (Ganta et al. 2016).

While liposomes formulated with some phospholipids tend to facilitate drug release following intravenous use, some phospholipids tend to delay drug release for more sustained drug effect. Zawilska et al. 2021 formulated docetaxel liposomes using pegylated HSPC (hydrogenated soy PC) incorporated with 3-n-pentadecylphenol derivative—KW101, a synthetic stabilizing agent. In vitro evaluation of the efficacy of prepared liposome on MCF-7 and MDA-MB-231 breast cancer cell lines revealed similar cytotoxic effects when compared with docetaxel. Cytotoxicity in drug-resistant NCI/ADR-RES cell lines revealed a more efficacious liposome when compared with docetaxel. In vivo pharmacokinetic analysis reveals the liposome produced better pharmacokinetic parameters when compared with docetaxel (Zawilska et al. 2021).

Polymeric formulations

The encapsulation of drugs by polymers for targeted drug delivery ensures that encapsulated drugs are delivered to a specific site at a controlled rate. Polymeric

Table 2 Docetaxel nanoformulations and use for chemotherapy

Drug(s)	Formulation type	Formulation ingredients	Study type	Cancer type	Dosing and administration	Remarks	References
Docetaxel	Polymeric micelle	Poly (ethylene oxide)-block-poly (styrene oxide) (PEO-b-PSO) and PEO-b-poly (butylene oxide) (PEO-b-PBO)	In vitro	Prostate cancer cell line	Not specified	Solubilization was better with PSO than PBO copolymers	Elsabhy et al. (2007)
Docetaxel	Polymeric micelle	Poly(ethylene glycol)-b-poly(ε-caprolactone (PEG-b-PCL))	In vitro	Not specified	Not applicable	initial burst of drug release, followed by sustained release of docetaxel	Mikhail and Allen (2010)
Docetaxel	Solid dispersion	Polyvinylpyrrolidone, polyvinylpyrrolidone vinyl acetate copolymer, Tert-butanol, sodium lauryl sulfate and dimethyl sulfoxide, polysorbate 80, sorbitan monooleate, polyethylene glycol mPEG2000-DSPE	In vivo, in vitro and phase I study	Not specified	15 mg capsule daily by oral administration	Enhanced solubility and dissolution when compared with docetaxel	Moes et al. (2011)
Docetaxel	Polymeric micelle		In vitro and in vivo (mice)	Breast, ovarian and lung cancer	Intravenous	Similar antitumor activity in-vitro and enhanced cytotoxic effect in vivo when compared with taxotere	Tong et al. (2012)
Docetaxel	Polymeric micelle	Poly (lactic acid) (PLA)-polyethyleneglycol (PEG), folate	In vitro study	Not specified	Freeze dried products for various use	Sustained drug release, reduced cytotoxic effect compared with free docetaxel	Hami et al. (2014)
Docetaxel	Nano-lipid suspension	Soy phosphatidylcholine, sodium cholesteryl sulfate	Randomized human study	Metastatic breast cancer	I.V. Infusion of 75 mg/m ² administered over an hour	Greater therapeutic efficacy (35%) when compared with taxotere (26.3%)	Ahmad et al. (2014)
Docetaxel	Aqueous based nano-suspension	Soy phosphatidylcholine, Sodium Cholesteryl Sulfate, sodium citrate buffer, Sucrose solution	In vivo study	Advanced solid tumors	Albino mice at 5–15 mg/kg, and Sprague Dawley rats at 0.312 = 1.25 mg/kg,	Higher systemic bioavailability compared with taxotere	Ahmad et al. (2015)
Docetaxel	Nano-formulation	Dimethyl sulfoxide(DMSO) Calcium carbonate,	In vitro	Breast cancer	Suspension for various use	Sustained release at 7.4, cytotoxicity comparable with docetaxel	Hammadi et al. (2017)
Docetaxel	Polymeric micelle	Poly(styrene-maleic acid) (SMA), poly (amide-ether-ester-imide)-poly ethylene glycol (PAEEI-PEG)	In vivo study	Breast cancer	Intravenous	More stable formulation with high cytotoxicity and enhanced anticancer activity	Varshosaz et al. (2018)

Table 2 (continued)

Drug(s)	Formulation type	Formulation ingredients	Study type	Cancer type	Dosing and administration	Remarks	References
Docetaxel	Nano-formulation	Dimethyl sulfoxide(DMSO) Calcium carbonate,	In vitro	Not specified	Oral	Sustained drug release for up to 24 h	Kim et al. (2019)
Docetaxel	Polymeric micelle	N-(tert-butoxycarbonyl)-L-phenylalanine end-capped methoxy-poly(ethylene glycol)-block-poly (D, L-lactide) (mPEG-b-PLA-Phe(Boc))	In vitro and In vivo (mice) study	Non-small cell lung cancer	Intravenous	Targeted, sustained release formulation with greater efficacy than taxotere	Gong et al. (2020)
Docetaxel	Nano-liposome	Phosphatidylserine and cholesterol	In vitro	Breast, head, neck and gastric cancer	Injectable	Sustained drug release for up to 13 h	Harwalkar et al. (2020)
Docetaxel	Nano-emulsion	Low molecular weight methylcellulose, (DOCA) complexed with (DOTAP) (DOCA-yielding DOTAP [DA-TAP] complex)	In vivo (mice)	Not specified	Oral administration	Bioavailability increased by 249% when compared with taxotere	Jha et al. (2020)
Docetaxel	Nano-liposome	HSPC, mPEG, DSPE, Cholesterol, DPPG, DSPG	In vivo (mice)	Breast cancer	8 mg/kg body weight intravenously	Enhanced delivery to tumor with prolonged duration of action. High plasma stability was also observed	Vakili et al. (2020)
Docetaxel	Micelle	Polysorbate, retinoic acid	Phase I and II	Breast cancer	100 mg/m ² intravenous infusion administered for an hour	No prior administration of steroid necessary. Bioequivalence of micelles with taxotere was observed with similar safety profile	Joeger et al. (2020)
Docetaxel	Solid binary inclusion complex	dimethyl- β -cyclodextrin (DM- β -C)	In vitro	Not specified	Oral	Aqueous solubility enhanced by 76.04 and in vitro dissolution by 3.55-fold	Giri et al. (2021)

nanoformulations confer high solubility in otherwise poorly soluble drug moieties, and long duration of action, leading to a more efficacious anticancer effect. A polymeric docetaxel formulation CRLX301, comprising of a nanosized cyclodextrin-polyethylene glycol conjugated with docetaxel was studied in a phase I study in patient suffering from refractory solid tumors. Results obtained indicated higher efficacy and tolerability when compared with taxotere (Markman et al. 2016). Mukhtar et al. 2020 further employed microtubules to deliver CRXL301 to target cancer cells in patients with metastatic castration resistant prostate cancer with great success (Mukhtar et al. 2020).

Docetaxel was encapsulated in two polymer systems. Polyamidoamine-poly (γ -benzyl-L-glutamate)- α -tocopheryl polyethylene glycol 1000 succinate (PAM-PBLG-b-TPGS) and Polyamidoamine-poly (γ -benzyl-L-glutamate) (PAM-PBLG) using the nanoprecipitation technique for targeted breast cancer and cytotoxic effect investigated using the human breast cancer cell line and human cervical cell lines revealed the cytotoxicity of (PAM-PBLG-b-TPGS) was greater than PAM-PBLG. Also, uptake of PAM-PBLG-b-TPGS was 2.5 times higher than the other formulation. DTX-PAM-PBLG-b-TPGS was concluded to be an effective formulation for targeted ovarian and breast cancer (Wang et al. 2019). Another researcher formulated four polymeric nanoformulations of docetaxel with the poly(lactide)-vitamin E TPGS nanoparticles (PLA-TPGS NPs), poly(lactic-co-glycolic acid) nanoparticles (PLGA NPs), the poly(lactic-co-glycolic acid)-montmorillonite nanoparticles (PLGA/MMT NPs) and the poly(lactide)-vitamin E TPGS/montmorillonite nanoparticles (PLA-TPGS/MMT NPs) harnessing the encapsulation and emulsification effects of TPGS and detoxifying properties of montmorillonite. The prepared formulations showed greater efficacy than taxotere despite administering the formulations orally and taxotere intravenously, indicating a highly effective oral docetaxel dosage form (Feng et al. 2014). Docetaxel-loaded PLGA/TPGS/Poloxamer 235 was formulated for potential use for breast cancer management. The drug release pattern was biphasic when analyzed in vivo, with a significant cytotoxic effect on docetaxel resistant breast cancer (Tang et al. 2015).

Inorganic nanoformulations

Multifunctional nanoparticles have found use in cancer diagnosis, imaging guided surgical procedures, and in chemotherapy. The formulation of docetaxel with magnetic manganese oxide (a fluorescence dye for targeted breast cancer chemotherapy) was carried out by Abbasi et al. Cytotoxicity studies revealed that the DTX/MnO exhibited a better sustained chemotherapeutic effect

at a low dose than free docetaxel (Abbasi et al. 2015). The use of functionalized gold as a delivery vehicle for docetaxel appears promising. This is largely because of the unique properties of its biocompatibility and ease of facile coupling with biological molecules. The unique shape, turnable size, and electro-optical properties of gold make it useful for targeted drug delivery, cancer diagnosis, tumor imaging, and photothermal therapy. Folic acid has also been utilized for targeted delivery of medications, largely because it interacts with folate receptors in cancer cell. Gold/docetaxel nanoformulation, was synthesized by citrate ion reduction, functionalized with thiol-PEG-amine and coupled with folic acid for targeting to the desired site. In vitro drug release studies and evaluation of anticancer effect in prostate cancer lines revealed a reduction in cancer cell viability to 40% and damage of prostate cancer cells (Thambiraj et al. 2021).

Mesoporous silica nanoformulations (MSN) have been utilized as vehicles for the delivery of anticancer medications. This is due largely to the high surface area and pore volume, which ensures a high concentration of drugs can be loaded. Drug loading into MSNs can be done during synthesis in situ, chemisorption, physio-sorption, and physical adsorption (Mamaeva et al. 2013). Pandita et al. formulated an optimized docetaxel formulation with albumin-coated hollow mesoporous silica nano-particles (A-HMSNs) and carried out in vitro drug release study and in vivo pharmacokinetic study in albino rats. Results indicated the sustained release of docetaxel for over 120 h with a maximum plasma concentration time of 6 h observed in in vivo studies (Pandita et al. 2021). Khosravian et al., also formulated docetaxel with MSM/folic acid and methionine for active targeting. In vivo studies in mice showed enhanced uptake by cancer cells, great cytotoxicity and apoptosis of cancer cells (Khosravian et al. 2016).

Mesoporous polydopamine (MPDA) has also gained attention as a vehicle for enhanced delivery of docetaxel as well as sustained release of the drug from the nanoformulations. This may be due to the properties of MPDA. It is biodegradable and compatible with biological tissue. It has great magnetic, optical and electrical properties. Docetaxel was formulated with an aptamer crosslinked with MPDA. In vitro and in vivo analysis of its efficacy for prostate cancer management revealed that the formulation targeted the prostate cancer cells and enhanced anticancer effects (Dai et al. 2021). Rivero-Buceta et al. 2019 also formulated docetaxel conjugated with antiprostata specific membrane antigen (PSMA) embedded on mesoporous silica nanoparticles. The prepared formulation was stable in physiological medium and showed specificity in targeting prostate cancer cells while sparing

non-cancerous cells. A twofold increase in cytotoxicity was observed when compared with non-targeted nanoparticles of docetaxel after an intraprostatic administration of the formulation.

Quantum dots have also been utilized for functionalization, imaging, and pharmacotherapy in cancer management. A quantum dot functionalized theranostic formulation of docetaxel with d-alpha-tocopheryl polyethylene glycol 1000 succinate mono-ester (TPGS) was developed and evaluated for cytotoxic effect using MCF-7 breast cancer cells. Better targeted cytotoxic effect was observed when compared with taxotere. High-resolution field emission transmission electron microscopy (FETEM) was used to assess quantum dots in the formulation and visualization by laser scanning microscopy confirms the suitability of the formulation for cancer imaging. Hence, the formulation serves dual purpose of imaging and chemotherapy (Muthu et al. 2012).

New technologies (electrospun and 3D fabricated docetaxel formulations)

Electrospinning of docetaxel

Electrospinning is a technology that has been recently employed to fabricate pharmacologically active moieties. It employs a high electric charge to produce an ultrafine fiber from a polymer solution or a hot melt (Garg et al. 2012). Electrospun fibers have been shown to possess great mechanical strength, high surface area, and capacity for high drug loading, great mucoadhesiveness, which makes this fiber an ideal choice for controlled drug delivery at the drug application sites. Singh et al., prepared nano-electrospun fibers of docetaxel in polyvinyl alcohol (PVA) for transdermal delivery. In vitro release studies revealed an initial burst release of 30.6% of docetaxel and a 97.1% release in total at 6 h post administration. The prepared formulation exerted higher cytotoxicity than docetaxel and permeation studies suggest maximum drug concentration at the application site, which diminishes the likelihood of systemic toxicity (Singh et al. 2015).

Docetaxel and zinc oxide have shown a synergistic cytotoxic effect. A formulation of electrospun fibers of DTX and zinc oxide (ZnO) incorporated into nanofibers of PCL for management of lung cancer and optimized with response surface methodology (RSM) confirmed the synergism of zinc oxide and docetaxel in the management of lung cancer. The prepared sustained release formulation targeted cancer cells in the lungs in an in vitro study against A549 lung cancer cells (Ekambaram et al. 2022).

Electrospun fibers of docetaxel for formulation of locally administered implants have been developed in an attempt to prevent recurrence of breast cancer. The

formulation was intended for local release of docetaxel to the desired site, thereby reducing systemic side effects. Ding et al., developed electrospun nanofibers of docetaxel in poly-D, L-lactide (PDLLA) and carried out an in vitro release study and a cytotoxicity study in 4T1 local breast tumor cells. In vivo antitumor evaluation in BALB/c mice with local breast tumors was also conducted. Recurrence rates were significantly reduced in subcutaneously transplanted mice when compared with mice administered systemic and locally administered doses. The formulation also showed great biocompatibility in mice implanted with it (Ding et al. 2016).

3D printing of docetaxel implanted formulations

3D printing allows for customization and gives the unique ability to fabricate drug designs, drug-loaded devices, as well as medical devices using imaging techniques. 3D printing of medications and medical devices offers numerous advantages. It is versatile and does not require lead time or tooling. Although implementation in clinical settings remains a challenge due to regulatory and logistic problems, researchers continue to explore 3D printing to fabricate drugs and medical devices. The utilization of continuous liquid interface production (CLIP) to manufacture functionalized drug-loaded devices capable of ensuring sustained release of implanted medications has been employed. This involves the incorporation of the active drug moiety in liquid resins and the subsequent formation of the device. Docetaxel and dexamethasone acetate were fabricated in 3D printed devices. Prepared formulations were analyzed for biocompatibility, rate of drug encapsulation, drug release rate, and pattern and degradation method. Results obtained were favorable and indicated great biocompatibility and drug loading. The release pattern was observed to be dependent on polymers used, but sustained release of docetaxel was generally observed. Degradation rate was generally slow but dependent on the polymers type. In vitro cytotoxic results were generally higher than 25% for formulations (Bloomquist et al. 2018). Other researchers developed a docetaxel laden 3D fabricated prostatic stent for localized sustained delivery of docetaxel (Jaworska et al. 2022). Zachkani et al. (2015) formulated a docetaxel laden cylindrical magnetic 3D device for drug delivery.

Although 3D fabricated anticancer medications have not made it to clinical settings or clinical trials, various research work geared toward 3D printed oral, transdermal medications and chemotherapy implants have been carried out with great success (Li et al. 2021; Chen et al. 2012; Maher et al. 2017; Ma et al. 2016, 2018).

Biocompatibility of 3D printed materials and safety remains a challenge in 3D drug fabrication. There is enormous potential for revolutionary inventions using the 3D technology for drug fabrication.

Future perspectives

2D material research and the use of layered double hydroxide are currently being explored as a functional drug delivery system. This system has brucite-like layers and a high charge density, which makes it attractive for use. Its high surface area for absorption makes it a choice drug delivery system for enhanced bioavailability of medications. 2D LDH has the advantage of diversity in chemical composition and choice of ions used, and intercalation of the ions enhances its potential for use as a sensor. It is a nanosheet capable of synergistic effects in hybrid structures and can serve as a nanofiller in polymers. It has been utilized as an electrode, a flame retardant and an anion scavenger. It has great biocompatibility in biological fluid and tissue and has antimicrobial properties (Ashtami et al. 2020). These unique properties have made 2D LDH widely used in drug development research. Although not much of its use has been documented in research geared toward the development of cytotoxic drugs, like 3D printing, there is enormous potential for the use of 2D LDH for the development of novel antineoplastic medications in the future.

Conclusions

Docetaxel is an evidently effective chemotherapeutic agent which has evolved in its formulation to enhance its efficacy and minimize its untoward effects. Various models are being explored in docetaxel drug development, most notably the use of nanotechnology to develop newer formulations, another area gaining interest is 3D printing and electrospinning formulations. 2D LDH is a novel formulation system with interesting potentials, the utilization 2D materials and layered double hydroxide as a drug delivery device is currently being researched. This model is very appealing owing to its brucite-like layers and a high charge density, also its large surface area for absorption increases medicine bioavailability. The 2D LDH offers the benefit of chemical variety and a wide range of ions to choose from, and intercalation of the ions increases its sensor potential. It is highly biocompatible in biological fluids and tissues and possesses antibacterial characteristics. Although not much of its application has been reported in research aimed at the production of cytotoxic pharmaceuticals, like as 3D printing, there is huge potential for the use of 2D LDH in the future development of innovative antineoplastic treatments.

Abbreviations

DTX: Docetaxel; RTV: Ritonavir; LDH: Layered double hydroxide; FDA: Food and drug administration; USMB: Utilization of ultrasound simulated microbubbles; PLGA: Poly (lactic-co-glycolic acid); mPEG-PDLLA: Methoxy-poly (ethylene glycol)-block-poly (D,L-lactide); NE: Nanoemulsion; PAM-PBLG-b-TPGS: Polyamidoamine)-poly (γ-benzyl-L-glutamate)-bd-α-tocopheryl polyethylene glycol 1000 succinate; PAM-PBLG: Polyamidoamine-poly (γ-benzyl-L-glutamate); MMT NPs: Montmorillonite nanoparticles; MnO: Manganese oxide; MSN: Mesoporous silica nanoformulations; MPDA: Mesoporous polydopamine; PSMA: Antiprostata specific membrane antigen; A-HMSNs: Albumin-coated hollow mesoporous silica nanoparticles; FETEM: Field emission transmission electron microscopy; PVA: Polyvinyl alcohol; CLIP: Continuous liquid interface production; ZnO: Zinc oxide; RSM: Response surface methodology; AUC: Area under curve; Cmax: Maximum concentration; mPEG2000-DSPE: 1,2-Distearoylsn-glycero-3 phosphoethanolamine-N-[methoxy (polyethylene glycol)-2000]; HSPC: Hydrogenated soy phosphatidylcholine; DSPG: 1,2-Distearoyl-sn-glycero-3-[Phospho-rac-(1-glycerol)] (Sodium Salt); DPPG: 1,2-Dipalmitoyl-sn-glycero-3-[Phospho-rac-(1-glycerol)] (Sodium Salt); CHOL: Cholesterol.

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Competing interests

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