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A Critical Review of Properties and Analytical Methods for the Determination of Docetaxel in Biological and Pharmaceutical Matrices

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ABSTRACT

Docetaxel (DTX) is an antineoplastic agent of the second generation of the taxoid family. It is a semi-synthetic drug prepared from a precursor extracted of the plant *Taxus baccata*. The commercial formulation of DTX, Taxotere®, employs the surfactant polysorbate 80, due to the low water solubility of the drug, causing several side effects. Therefore, there is a need to develop delivery systems to reduce the side effects of DTX. In addition, this drug has been qualitative and quantitatively analyzed in pharmaceutical formulations and biological samples. Thus, several techniques and analytical methods have been reported with the aim of optimizing the analytical signal, increasing sensitivity, selectivity and reducing the effects of interference. Herein, we highlight immunoassay, capillary electrophoresis and chromatographic methods. This review presents a summary of physicochemical and pharmacokinetics properties, mechanisms of action, drug delivery systems and analytical methods used in quantification of DTX in diverse matrices such as blood, plasma, oral fluid, urine, carcinoma cells, pharmaceutical formulations and delivery systems.

KEYWORDS

Docetaxel; physicochemical properties; drug delivery systems; analytical methods

Introduction

Docetaxel (DTX) is an antineoplastic drug of the taxoid family, obtained semi-synthetically from the natural compound 10-deacetylbaccarin III, a non-cytotoxic component of the Yew tree, *Taxus baccata*.[1–3] This drug is highly lipophilic and practically insoluble in water, which is a factor that compromises the pharmacokinetics profile. The commercial formulation, Taxotere®, employs the surfactant polysorbate 80 and ethanol to improve the solubility, although causing several side effects.[3–5]

The mechanism of action of DTX is related to the cytotoxic activity, consequence of β-tubulin binding, which causes inhibition of cell proliferation and mitotic progression due to inhibition of microtubule dynamics.[6] DTX was approved by the Food and Drug Administration (FDA) in 1996 for the treatment of anthracycline-refractory metastatic breast cancer. Afterwards, it was approved for treatment of platinum-refractory stage non-small-cell lung cancer.[7,8] Furthermore, the toxicity of both drug and formulations has stimulated the development of nanostructured delivery systems, with many advantages, including controlled DTX release and improved pharmacokinetics.[9,10]

The development and validation of analytical methods play an important role both on the research of DTX delivery systems and quality control. Many analytical methods for quantification of DTX have been published, particularly employing high-performance liquid chromatography (HPLC). Overall, those studies reported differences in the parameters of wavelength, mobile phase, stationary phase, and others, which will be addressed herein.[3,11,12] Moreover, other analytical methods reported for DTX quantification include immunoassay,[13,14] capillary electrophoresis (CE) [15] and ultraperformance liquid chromatography (UPLC), which presents many advantages, including the faster analytical run and the use of smaller volumes of solvents.[16–18] Another important issue regarding DTX analytical methods is the analytical matrix, which should not interfere in drug quantification. In this context, several studies have quantified DTX extracted from different matrices, including biological samples, such as blood, plasma, urine, and carcinoma cells [19–22] and also in drug delivery systems.[23–25]

In this review, our purpose is to present important physicochemical characteristics of DTX and also give the reader an overview of the drug's pharmacokinetics, the mechanism of action and summarize some strategies to load DTX into nanostructured delivery systems, highlighting the advantages. Finally, we will address the most commonly employed analytical methods for DTX quantification in various matrices, including formulations and biological samples, highlighting the analytical conditions employed.

Physicochemical and pharmacokinetics characteristics

DTX (CAS number: 114977-28-5, Figure 1) is a white to off-white crystalline powder with a molecular weight and formula corresponding to 807.89 Da and $C_{43}H_{53}NO_{14}$, respectively. Its solubility in water is $1.27.10^{-2}$ g/L and melting point is 232°C.

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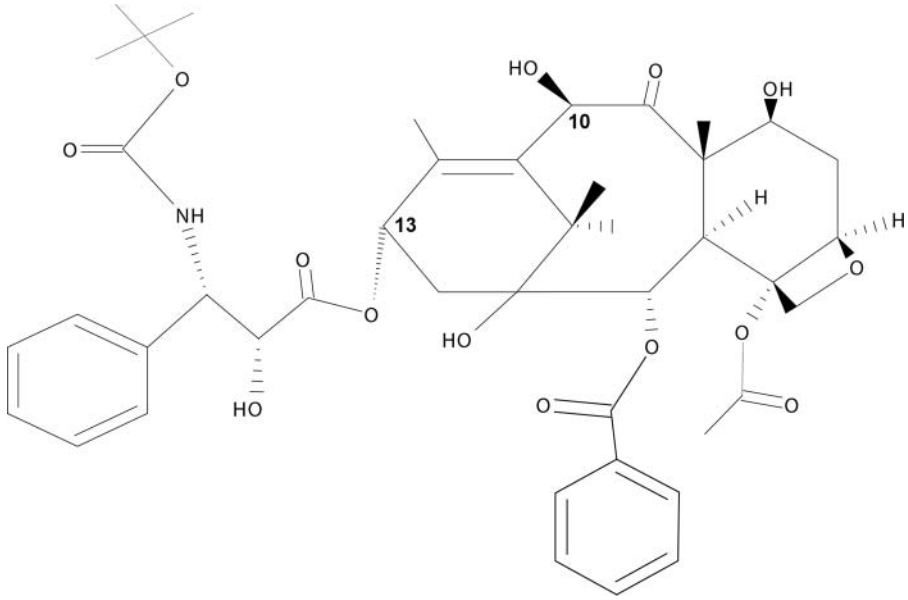

Figure 1. Chemical structure of docetaxel.

DTX is a highly lipophilic, semi-synthetically derived from 10-deacetylbaccatin III compound. But, compared to paclitaxel (PTX), it is quickly absorbed, it is less toxic and the water solubility is better, due to differences in their chemical structures at two positions, the C-13 tert-butoxy group instead of the benzamide phenyl group and the C-10 hydroxy group replacing the acetyl group.[26–28]

The pharmacokinetic profile of DTX is well characterized, composed of three compartments, with half-lives of 4.5 min, 38.3 min, and 12.2 h for the alpha, beta, and gamma phases, respectively.[26] The standard dose varies according to the type of cancer and the treatment used, however the recommended dose is between 75 and 100 mg/m^2 with infusion once every 3 weeks for 1 h, unlike PTX whose recommended dose varies from 200 to 250 mg/m^2.[29,30]

The distribution of DTX occurs from the central compartments to the peripheral compartments. The total volume of distribution in the human body is approximately 22 L/h/m^2 and the mean stationary distribution volume is 113 L,[31] depending on the liver function, age, body surface area, and plasma proteins (for example, albumin, α-1-acid glycoprotein e lipoproteins).[32]

Previous studies reported DTX binding to plasma proteins, mainly albumin, α-1-acid glycoprotein and lipoproteins, about 90–95%, *in vitro*, and 70–95%, *in vivo*. α-1-acid glycoprotein is present in high levels in individuals with pathologies such as cancer and therefore becomes the major factor responsible for the total clearance of DTX. In addition, DTX bound to plasma proteins accounts for a 19% decrease in drug clearance.[28,33]

The tissue distribution of DTX is influenced by the route of administration and some authors consider the intravenous route as the best alternative. Preclinical studies in animals have demonstrated high concentrations in most tissues. The highest concentrations were initially found in the liver, stomach, bile ducts, pancreas, muscles, and hematopoietic tissues and after the initial period of administration, absorption by the nervous system and testes is limited. Compared with other tissues, tumors have elevated levels of DTX due to drug binding to the α-1-acid glycoprotein.[6,8,14]

The cytochrome P450 (CYP3A4 and CYP3A5) system plays an important role on the clearance and metabolism of the drug, resulting in various pharmacologically inactive oxidation products.[28,34,35] After the oxidative metabolism of the tert-butyl ester group, excretion occurs via the biliary, intestinal, and renal organs. At a time interval of 7 days, the urinary and fecal excretion is approximately 6% and 75% of the amount administered, respectively. The highest elimination rate occurs during the first 48 h through feces.[33,36]

Mechanisms of action

DTX acts on microtubules, which are hollow cylindrical fibrillar structures with an outer diameter of approximately 25 nm and a wall of about 5 nm thickness composed of α-tubulin and β-tubulin heterodimers firmly attached together by noncovalent bonds.[37,38] They are essential in cellular processes, such as transport, signaling and mitosis, in higher eukaryotic cells, and play an important role on the position of organelles and are responsible for removing the chromosomes in mitosis.[39]

Dynamic instability is one of the phenomena caused by microtubules through the loss or addition of heterodimers of alpha or beta tubulin from extremities. In cells, all microtubules originate from a microtubule organizing center.[40] Polymerization of tubulin dimers can be influenced by a number of factors, such as guanosine triphosphate (GTP), which binds to an exchangeable site on β-tubulin and a non-exchangeable site on α-tubulin and microtubule associated proteins (MAPs), which constitute a family of complex proteins responsible for the regulation of the polymerization and function of tubulin.[39,41]

The antimitotic agents such as colchicine, podophyllotoxin, and vinblastine have a locking function in the assembly of microtubules. However, DTX, which also acts on the cell cycle, has the opposite effect, provoking the stabilization of the microtubules (Figure 2).[42,43] DTX initially inhibits the

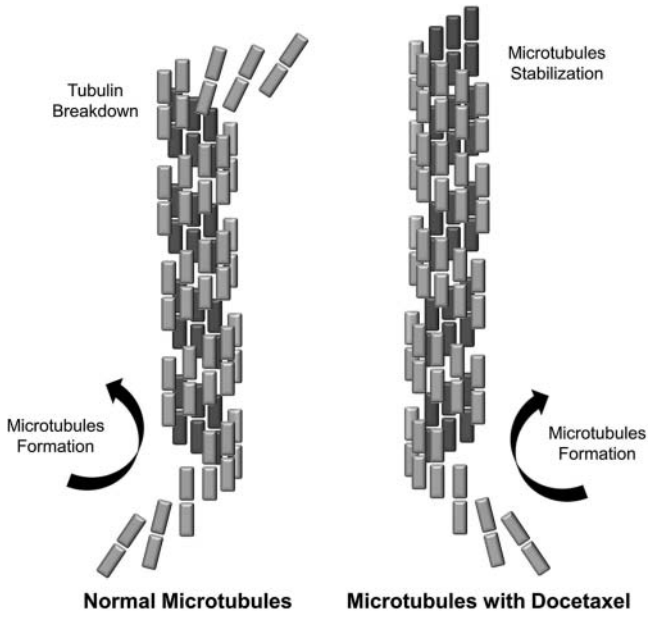

Figure 2. Effect of docetaxel on microtubules. Source: adapted from [45].

disassembly (disruption of microtubules) of the physiological microtubules by binding the β-tubulin subunit promoting the production of stable microtubule bundles and without normal function.[9,44]

The *in vitro* effects observed in tubulin polymerization by microtubule stabilizing agents (MSA) and DTX are similar to antiproliferative effects at the cellular level.[38] The MSAs and DTX suppress microtubule dynamics and stabilization, causing the interruption of mitosis by cell accumulation in G2/M phase of the cell cycle and subsequent blocking cell division and proliferation of tumor cells.[37,38]

As described in the literature, DTX is responsible for regulating microtubules upon binding to tubulin. Its action also involves other intracellular processes, such as binding to proteins of the Bcl2 family, causing phosphorylation, and inactivation and later apoptosis. Some authors described that DTX induces the expression of inhibitors of cyclin – cyclin-dependent kinase (CDK) complexes that cause cell cycle arrest at different stages of mitosis (p21, p27, and p53). Comparatively, DTX has some advantages when compared to PTX, for example, in tumor treatment it is more effective by binding β-tubulin with greater affinity, causing direct antitumor activity through the induction of apoptosis by phosphorylation of Bcl2. Furthermore, DTS has a longer retention time in tumor cells than PTX due to its structural characteristics. Thus, the various effects and mechanisms associated with DTX, such as regulation of microtubules, apoptosis, and action on genes related to the cell cycle, make it possible to treat various types of tumors.[9,26,37,41,46,47]

Drug delivery systems

DTX can be loaded into numerous nanostructured delivery systems, including liposomes, polymeric nanoparticles, lipid nanoparticles, micelles, dendrimers, and nanoemulsions.[9] Those systems offer several advantages over standard formulations, including better stability, the sustained drug release, improvement of the therapeutic effect of the drug and better pharmacokinetic profile, with longer circulation times.[10,48,49] Furthermore, nanostructured systems are used in the cancer therapy, since they promote the passive targeting of the drug to the tumor, through the enhanced permeability and retention (EPR) effect.[50]

Among the nanocarriers, liposomes, vesicular lipid systems, are the most commonly studied, owing to their biodegradability and low toxicity, compared to other nanocarriers such as nanoemulsions, dendrimers, liposomes, polymeric nanoparticles, and micelles.[51] Several liposomal characteristics are important for DTX delivery and the composition plays a central role, which is demonstrated in several reports in the literature.[52–55] For instance, Pereira *et al.* [56] evaluated the effect of different lipids, DOPC, DPPC, and DSPC, on both the purification of DTX-loaded liposomes and cytotoxicity on prostate cancer (PC3) spheroids. The results showed that the use of DOPC, the only unsaturated lipid, caused higher loading compared to more rigid liposomes, prepared with the saturated lipids DPPC and DSPC. Furthermore, DSPE-PEG2000 was also used in all formulations, since PEGylation increases the half-life of the liposome in systemic circulation and reduces the macrophage recognition and immunogenicity. The *in vitro* toxicity of the purified and non-purified liposomes was also determined, showing the importance of the purified liposomes effect on the therapeutic efficacy, since lipid composition improved DTX solubility and tissue penetration.

An alternative to the use of liposomes for DTX delivery is represented by solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC), which present improved colloidal stability compared to liposomes, because SLN are composed of a solid matrix, while NLC can be made with both solid and liquid lipids.[57] Liu *et al.* [58] designed a DTX-loaded nanostructured lipid carrier (DTX-NLC) with the aim of increasing drug therapeutic effect, compared to a regular DTX formulation, Duopafei®. The *in vitro* cytotoxicity was determined using human hepatocellular liver carcinoma (HepG2), ovary cancer cells (SKOV3), lung adenocarcinoma (A549), while the *in vivo* study was done with murine malignant melanoma (B16). Their results showed that DTX can be well loaded into the NLC, due to its physicochemical properties and lipid composition. In comparison to Duopafei®, the DTX-NLC formulation induced more apoptosis *in vitro* and had superior anticancer efficacy *in vivo*.

The biodegradable and biocompatible properties of phosphatidylethanolamine (PE) are important characteristics for its use in some nanocarriers. For instance, Zhang *et al.* [59] prepared DTX loaded-lipid nanoparticles (DTX-LPNPs), based on PE. Their aim was to compare DTX-LPNPs with DTX-loaded nanoparticles (DTX-NPs), composed of a single chemical emulsifier, polyvinyl alcohol (PVA), instead of PE, and the commercial formulation, Duopafei®. Their results demonstrated that DTX was well-incorporated in the emulsified system, based on PE, causing better *in vitro* antitumor effect than DTX-NPs and Duopafei®.

Another potential nanostructure for drug delivery is represented by polymeric micelles, which are composed of amphiphilic copolymers. Raza *et al.* [60] explored the potential of a new DTX-loaded polymeric micelles, composed of tethered poly(lactic-co-glycolic acid) (PLGA) and dextran, a

biocompatible polysaccharide, which was chemically linked to PLGA, with advantages, such as immuno-neutrality and better pharmacokinetic profile. The *in vitro* study on MCF-7 and MDA-MB-231 cell lines demonstrated enhanced cytotoxicity of approximately 100%, in both cell cultures. Moreover, the pharmacokinetic profile study, evaluated in rats, demonstrated an increase in the biological half-life and bioavailability, by approximately 5 times compared to the pure drug.

Currently, aside from the passive targeting, there are numerous ways to offer active targeting. One of the most common strategies employ surface modification with folic acid (FA), peptides, dendrimers, and monoclonal antibodies.[61] This strategy is commonly reported to improve efficacy and reduce drug side effects. However, there are few reports regarding surface functionalization on DTX-loaded nanoparticles. For instance, Nateghian *et al.* [62] conjugated FA or biotin onto DTX-loaded albumin nanoparticles for active targeting to cancer cell lines that overexpress FA or biotin receptors, while Raju *et al.* [63] prepared D-α-tocopheryl polyethylene glycol 1,000 succinate (TPGS) loaded liposomes conjugated with trastuzumab for controlled and targeted delivery of DTX to cancer cells. Kulhari *et al.* [64] developed both DTX-loaded nanoparticles (DNP) and bombesin peptide (BBN) conjugated DTX-loaded nanoparticles (BDNP) for targeted delivery to MDA-MB-231 (breast cancer) cell line, which overexpresses gastrin-releasing peptide (GRP) receptor, for comparison with free DTX and the commercial formulation, Taxotere®. Their results demonstrated that DNP and, especially, BDNP had more *in vitro* cytotoxic effect than Taxotere® and free DTX, showing great potential for DTX delivery to GRP receptor-positive cancer cells.

Analytical methods

Much progress has been made in the last years in the development and validation of analytical methods for identification and quantification of drugs and other molecules of interest in different matrices. However, there is an increasing need to optimize many of these methods, in order to improve the analytical signal, reduce the analysis time, and consequently the consumption of reagents and solvents.[65,66]

Several analytical methods were developed for analysis of DTX, with the purpose of identification and quantification in biological samples (Table 1) and also in diverse matrices (Table 2), such as delivery systems, that were presented in the previous section of this review. These methods include, mostly, immunoassays,[13] CE assays, [15] and chromatographic assays.

The immunoassay methods consist of a competitive reaction using selective anti-DTX monoclonal antibodies-coated nanoparticles followed by the agglutination quantification reaction measured by the absorbance at 660 nm.[13,14] The technique was compared with LC–MS/MS for determination of the DTX concentration in human plasma by Geng *et al.* [14] The separation of DTX from plasma by LC–MS/MS utilized a C_{18} Diamonsil column (150 mm × 4.6 mm i.d. 5.0 μm particle size) with a mobile phase composed of 0.1% formic acid:acetonitrile (ACN) (40:60, v/v) and the mass spectrometry (MS) was performed in the positive ion multiple reaction monitoring (MRM) mode, with an ion transition of m/z 830.5>550.4, resulting in a retention time at 7.5 min. The immunoassay method was carried out according to the protocol presented by Cline *et al.* [13] and using the DTX reagent kit (Saladax MyDocetaxel assay reagent kit). The absorbance was determined by the difference between the reaction at cycle 27 and cycle 13 without subtraction of a blank reagent. Both methods were validated in accordance with FDA guidelines, including the assessment of specificity, matrix effect, recovery, linearity, accuracy, precision, and stability. However, the immunoassay method was regarded as far more cost-effective and had a better outcome in clinical drug monitoring.

CE is a separation technique based on the electrophoretic mobility of charged species (analytes) under an electric field in a capillary. CE is also used as a synonym of capillary zone electrophoresis (CZE), but there are other electromigration techniques such as micellar electrokinetic chromatography (MEKC), microemulsion electrokinetic chromatography (MEEKC), among others. The technique exhibits numerous advantages: (1) it can use a high voltage (up to 800 V/cm) due to the physical properties of fused silica capillaries; (2) requires small amounts of samples and buffer due to the small dimension of the capillaries; (3) contains a high number of theoretical plate (N)>10,000, which contribute to the high efficiency of separation; and (4) it can contain additives which interact with the analytes, altering their electrophoretic mobility and therefore improving separation process.[67]

Shakalisava *et al.* [15] demonstrated the versatility of CE methods (CZE, MEKC, and MEEKC) for the separation of different types of anticancer drugs, anthracyclines (doxorubicin, daunorubicin, and epirubibin) and taxanes (PTX and DTX) simultaneously. Separation conditions employed UV detection at 230 nm, capillary of 56 cm (48 cm), 50 mm i.d., 20°C. The mobile phases were different according to the technique. For CZE, it corresponded to 20 mM pH 9 borate buffer, 70% ACN, 30 kV, with hydrodynamic injection of 6 s; while for MEKC it was composed of 25 mM pH 9 Tris-phosphate buffer, 70% methanol, 100% sodium dodecyl sulfate (SDS), 30 kV, with hydrodynamic injection of 12 s; and for MEEKC the mobile phase corresponded to 20 mM pH 2.5 phosphate buffer, 0.81% w/w octane, 3.31% w/w SDS, and 6.61% w/w butan-1-ol, 25% ACN, –25 kV, with hydrodynamic injection of 12 s. In conclusion, the methods showed high-speed, especially the MEEKC method, with a migration time less than 3 min and great potential for simultaneous monitoring of pharmacokinetics of anthracyclines and taxanes in plasma.

Among the most studied analytical methods, HPLC methods play a central role, with a variety of detectors, including the ultraviolet (UV) (225–232 nm), most commonly used, MS or tandem mass spectrometry (MS/MS), due to its higher sensitivity, resolution, and possibility to work with different matrices, as well as eliminating interference. HPLC technique is the standard method of the United States Pharmacopoeia (USP 35nd), which uses as mobile phase a mixture of water–ACN and UV detection at 232 nm.[68] In addition to HPLC, more recently, methods using UPLC with MS or MS/MS as detectors (Table 3) have received great attention, employing particles smaller than 2 μm in diameter to achieve superior resolution, speed, and sensitivity compared with HPLC.[69]

Table 1. HPLC analysis performed with biological samples.

Matrix	Detector	Column	Mobile Phase	Gradient Time	Gradient B	t_R (min.)	Ref.
Plasma	UV (227)	Supelcosil LC-18 (3 μm, 150 × 4.6 mm)	(A) 20mM phosphate buffer, pH 3 (B) ACN	45% (B)		< 15	[21]
	UV (230)	Updesphere ODSB (5 μm, 250 × 3 mm)	(A) methanol (B) water, pH 3	28% (B)		< 17	[75]
	MS/MS (808.2; 527.0)	Phenomenex Onyx C_{18} (5 μm, 50 × 3.0 mm)	0.1% formic acid (A) water (B) ACN	0 min 1.0 min 2.0 min	5% 25% 90%	< 3.0	[78]
	UV (227)	Nucleosil C_{18} (5 μm, 250 × 4.6 mm)	(A) ACN (B) 35mM ammonium acetate buffer, pH 5 (C) tetrahydrofuran	Isocratic 50% (B)		7.7	[79]
Plasma or urine	UV (227)	Waters Nova-Pack C_{18} (4 μm, 100 × 5 mm)	(A) 0.02M ammonium acetate buffer, pH 5 (B) ACN	Isocratic 43% (B)		< 10	[19]
Human plasma	MS/MS (808.5; 527.2)	Waters X-Terra MS (3.5 μm, 50 × 2.1 mm)	(A) water with 0.1% formic acid (B) ACN	Isocratic 80% (B)		~7	[80]
	MS/MS (808.4; 527.2)	SunFire C_{18} (3.5 μm, 100 × 2.1 mm)	(A) water, 0.1% acetic acid (B) ACN, 0.1% acetic acid	0 min 3.0 min 7.0 min	50% 60% 50%	< 10	[81]
	MS/MS (808; 527)	Zorbax C_{18} (5 μm, 150 × 2.1 mm)	(A) Methanol (B) 10 mM NH_4OH	Isocratic – 9 min 30% B		4.4	[82]
	MS/MS (808; 527)	Zorbax Extend C_{18} (5 μm, 150 × 2.1 mm)	(A) 10mM ammonium acetate (B) methanol	70%		7.5	[83]
	UV (230)	Inertsil ODS-80A (5 μm, 150 × 4.6 mm)	(A) water (B) methanol (C) tetrahydrofuran (D) ammonium hydroxide	60% (B)		8.5	[84]
	UV (225)	Supelcosil LC-18 (3 μm, 150 × 4.6 mm)	(A) 0.3% orthophosphoric acid (B) methanol (C) tetrahydrofuran	Isocratic 57.5% (B)		9.2	[85]
Human plasma	MS (808.1)	Hypersil ODS C_{18} (5 μm, 100 × 2.0 mm)	0.1% formic acid (A) methanol (B) water	Isocratic 30% (B)		3.7	[86]
	MS/MS (808.5; 527.1)	Thermo Betaseal C-18 (5 μm, 150 × 4.6 mm)	(A) 10mM ammonium acetate, 0.1% formic acid (B) ACN	40% (B)		1.25	[76]
	UV (227)	APEX-Octyl (5 μm, 150 × 4.6 mm)	(A) ACN (B) 0.02M ammonium acetate, pH 5	63.2% (B)		11.2	[87]
	UV (227)	CSC-Nucleosil C_8 (5 μm, 150 × 4.6 mm)	(A) 30mM phosphate buffer, pH 3 (B) ACN	53% (B)		7.2	[88]
	UV (225)	Spherosil C_{18} (5 μm, 250 × 4.6 mm)	(A) methanol (B) 0.3% orthophosphoric acid	32.5% (B)		< 12	[89]
	MS/MS (808.0; 527.0)	Eclipse XDB-C_8 (5 μm, 50 × 2.1 mm)	(A) water, 0.1% formic acid (B) ACN	Isocratic 60% (B)		1.56	[90]
	MS/MS (808; 527)	TSKgel ODS-100V (3 μm, 50 × 2.0 mm)	(A) ACN (B) water (C) methanol (D) formic acid	45% (B)		3.6	[91]
Human plasma and oral fluid	MS/MS (808.4; 526.9)	Merck Purospher Star (3 μm, 55 × 2.0 mm)	(A) 2mM acetic acid/0.2mM ammonium acetate in water (B) 2mM acetic acid/0.2mM ammonium acetate in methanol	0 min 1.8 min 2.0 min 3.0 min	63% 73% 95% 95%	3.5	[72]
Whole blood and human plasma	MS/MS (830.3; 599.1)	Zorbax Eclipse XDB-C_8 (5 μm, 150 × 4.6 mm)	(A) water, 0.1% formic acid (B) methanol, 0.1% formic acid	5% (B)		4.7	[22]
Human breast carcinoma cell lines	UV (227)	Nucleosil 100–5 C_{18} (5 μm, 250 × 4 mm)	(A) 0.02M ammonium acetate buffer, pH 5 (B) ACN	43% (B)		—	[20]
Mouse plasma	MS/MS (808.2; 527.05)	Waters X-Terra MS (3.5 μm, 50 × 2.1 mm)	(A) water, 0.1% formic acid (B) ACN, 0.1% formic acid	Linear gradient 20–100% – 5min		< 5.0	[92]
Rat plasma	MS/MS (830.3; 549.1)	Cosmosil-C_{18} (5 μm, 150 × 2.0 mm)	(A) water, 0.1% formic acid (B) methanol	0 min 1.8 min 2.0 min 6.5 min 6.7 min 9.0 min	40% 40% 95% 95% 40% 40%	6.1	[93]
Rat plasma	UV (230)	Capcell Pak C_8 (5 μm, 150 × 4.6 mm)	(A) water (B) ACN	Isocratic 40% (B)		14.25	[70]
Rat plasma and peritoneal fluid	UV (227)	Dynamax 300A (5 μm, 250 × 4.6 mm)	(A) 0.1% phosphoric acid (B) water	Isocratic 50% (B)		—	[94]
Rabbit plasma	UV (227)	Dikma Platisil C_{18} (5 μm, 150 × 4.6 mm)	(A) ACN (B) 35nM ammonium acetate, pH 5 (C) tetrahydrofuran	48% (B)		5.3	[95]
	UV (230)	Phenomenex LUNA C_{18} (5 μm, 250 × 4.6 mm)	(A) ACN (B) methanol (C) ammonium acetate buffer, pH 5	47.5% (B)		~15	[96]

Table 2. HPLC analysis performed with diverse matrices.

Matrix	Detector	Column	Mobile Phase	Gradient		t_R (min.)	Ref.
				Time	B		
Docetaxel pure drug	UV (225)	Devenosil C_{18} (5 μm, 150 × 4.6 mm)	(A) phosphate buffer, pH 4.2 (B) ACN	Isocratic 70% (B)		3.19	[97]
Docetaxel pure drug and formulation	UV (230)	YMC pack ODS-A C_{18} (5 μm, 150 × 3.9 mm)	(A) 60:40 water:ACN (B) ACN	0 min 26 min 66 min 67 min 71 min 72 min	0% 0% 83% 100% 100% 0%	~21	[98]
Docetaxel in parenteral dosage form	UV (230)	Unison YMC C_{18} (5 μm, 250 × 4.6 mm)	(A) 0.02 M ammonium acetate, pH 4.5 (B) ACN	45% (B)		5.8	[99]
Docetaxel pure drug and injection	UV (232)	Packing L1 (3.5 μm, 150 × 4.6 mm)	(A) water (B) ACN	0 min 9 min 39 min 39.1 min 49 min 49.1 min 60 min	28% 28% 72% 100% 100% 28% 28%	–	[68]
Docetaxel and impurities	UV and MS (230) (807; 527)	Hypersil BDS C_{18} (5 μm, 250 × 4.6mm)	(A) 0.02 M ammonium acetate, pH 4.5 (B) ACN	40% (B)		26.6	[11]
	UV (230)	YMC Pack ODS-A (3 μm, 150 × 4.6 mm)	(A) 50:20:30 water:ACN:methanol (B) 20:80 water:ACN	0 min 25 min 26 min 35 min	5% 60% 5% 5%	< 45	[77]
Docetaxel and degradation products	UV (230)	Hichrom RPB (5 μm, 250 × 4.6 mm)	(A) water (B) ACN	0 min 15 min 25 min 30 min 35 min 39 min 40 min	35% 65% 75% 95% 100% 100% 35%	< 15	[3]
Docetaxel nanocrystals surface modified with transferrin	UV (230)	Intersil OSD-3 C_{18} (5 μm, 150 × 4.6 mm)	(A) water (B) ACN	70% (B)		–	[100]
Polymeric micelles	UV (232)	Waters Nova-Pack C_{18} (4 μm, 300 × 3.9 mm)	(A) water (B) ACN (C) methanol	Isocratic 48% (B)		–	[101]
	UV (230)	Symmetry C_{18} (3.5 μm, 150 × 4.6 mm)	(A) water (B) ACN	55% (B)		< 5	[23]
	UV (230)	Dikma Dimansil C_{18} (5 μm, 150 × 4.6 mm)	(A) water (B) ACN	47% (B)		–	[24]
Docetaxel-loaded micelles	UV (232)	Kromasil C_{18} (3.5 μm, 150 × 4.6 mm)	(A) ammonium acetate (B) ACN	45% (B)		–	[25]
Docetaxel-loaded mixed micelles	UV (230)	Elite ODS C_{18} (5 μm, 250 × 4.6 mm)	(A) water (B) ACN	45 (B)		–	[102]
	UV (230)	Capcell pak C_{18} MG (5 μm, 250 × 4.6 mm)	(A) water (B) ACN	65% (B)		–	[103]
Docetaxel-loaded Polysorbate 80/ Phospholipid mixed micelles	UV (230)	Diamonsil C_{18} (5 μm, 250 × 4.6 mm)	(A) water (B) ACN	55% (B)		< 13	[104]
Docetaxel-loaded solid lipid nanoparticles	UV (230)	Symmetry C_{18} (5 μm, 250 × 4.5 mm)	(A) 0.2% triethylamine, pH 6.4 (B) ACN	Isocratic 48% (B)		11.4	[74]
	UV (230)	Diamond C_{18} (5 μm, 150 × 4.6 mm)	(A) water (B) ACN	50% (B)		–	[105]
Docetaxel-loaded lipid nanoparticles	UV (230)	Inertsil ODS-3 (4 μm, 150 × 4.6 mm)	(A) 2-propanol (B) ACN (C) water	55% (B)		25	[106]
Docetaxel-loaded liposomes	UV (230)	Eclipse XDB-C_{18} (5 μm, 250 × 4.6 mm)	(A) water (B) ACN	50% (B)		–	[107]
Docetaxel-loaded folate-conjugated PEG-liposomes	UV (230)	Hypersil C_{18} (5 μm, 150 × 4.6 mm)	(A) water (B) ACN	48% (B)		–	[108]
Dual docetaxel/ superparamagnetic iron oxide loaded nanoparticles	UV (229)	Inertsil ODS-3 (5 μm, 150 × 4.6 mm)	(A) water (B) ACN	50% (B)		–	[109]
Docetaxel-loaded folic acid conjugated nanoparticles	UV (230)	Inertsil ODS-3 (5 μm, 150 × 4.6 mm)	(A) water (B) ACN	50% (B)		–	[110]
Docetaxel-loaded TPGS-cisplatin prodrug nanoparticles	UV (230)	Eclipse XDB-C_{18} (5 μm, 150 × 4.6 mm)	(A) water (B) ACN	50% (B)		–	[111]

Table 3. UPLC analysis performed with biological samples.

Matrix	Detector	Column	Mobile Phase	Gradient		t_R (min.)	Ref.
				Time	B		
Human plasma	MS/MS (808.3; 527.1)	Acquity BEH C_{18} (1.7 μm, 50 × 2.1 mm)	(A) 0.5% formic acid/water, pH 2.23 (B) 0.5% formic acid/ACN, pH 2.24	0 min 0.9 min 1.6 min 1.7 min	10% 100% 10% 10%	1.35	[16]
	MS/MS (808.3; 527.1)	Acquity BEH C_{18} (1.7 μm, 50 × 2.1 mm)	(A) water/0.2% formic acid (B) ACN/0.2% formic acid	0 min 0.9 min 1.6 min	10% 100% 10%	1.32	[17]
Rat plasma	MS/MS (808.48; 527.3)	Acquity BEH C_{18} (1.7 μm, 50 × 2.1 mm)	0.1% formic acid (A) ACN (B) water	0 min 1.6 min 2.5 min 3.0 min	50% 35% 50% 50%	1.89	[112]
	MS/MS (830.8; 549.6)	Waters C_{18} (1.8 μm, 50 × 2.1 mm)	0.1% formic acid (A) water (B) methanol	0 min 1.5 min 2.5 min	30% 80% 30%	~1.65	[113]
	MS/MS (830.5; 549.3)	Venusil MP C_{18} (3.0 μm, 100 × 2.1 mm)	(A) water (B) methanol	0 min 2.5 min 2.51 min	75% 80% 75%	< 2.5	[114]
Dog plasma	MS/MS (808.25; 527.17)	Acquity BEH C_{18} (1.7 μm, 50 × 2.1 mm)	(A) ACN (B) 5 mM ammonium acetate/water	0 min 0.9 min 2.3 min	50% 10% 50%	~1.4	[115]
Rabbit plasma	MS/MS (808.4; 226.2)	Acquity BEH C_{18} (1.7 μm, 50 × 2.1 mm)	(A) 0.1% formic acid (B) 49.95:49.95:0.1 methanol:ACN:formic acid	0 min 0.3 min 1.5 min 1.7 min 1.71 min	10% 10% 95% 10% 10%	1.54	[18]

Some methods have been developed for the simultaneous determination of DTX in presence of other drugs by HPLC and UPLC. For instance, Kim *et al.* [70] developed a RP-HPLC method for the simultaneous determination of DTX and curcumin in rat plasma, using as mobile phase a mixture of ACN–water (40:60, v/v) in isocratic elution mode with UV detection at 230 nm, simultaneously for curcumin and DTX, resulting in retention times of 10.47 and 14.26 min, respectively. The method was validated and proved to be selective, sensitive, linear, precise, accurate, robust, and reproducible.

In this same line, da Silva *et al.* [71] developed an UPLC–MS/MS method for the simultaneous determination of DTX, cyclophosphamide, doxorubicin, and 5-fluorouracil in order to evaluate the contact of workers exposed to these antineoplastic drugs. Chromatographic separation was done using a SHIM-PACK XR-ODC-C_{18} column (100 mm × 3.0 mm i.d. 2.2 μm particle size; Shimadzu, Kyoto, Japan), using a mobile phase composed of a mixture of 0.1% FA and ACN. MS/MS was performed on a triple quadrupole instrument in the MRM mode with transitions at *m/z* 129.1>42.1 for 5-fluorouracil, 544.1>396.9 for doxorubicin, 261.0>140.0 for cyclophosphamide, and 830.3>304.0 for DTX.

It has also become common the development of methods for analysis in diverse biological samples, because such complex matrices can interfere with the analyte, requiring a more efficient separation and more sensitive detectors. Therefore, Mortier *et al.* [72] reported an HPLC–MS/MS method for quantification of DTX and PTX in human plasma and oral fluid (saliva). They used a Merck Purospher Star RP-18 column (55 mm × 2.0 mm i.d. 3.0 μm particle size; VWR, Leuven, Belgium) and a mobile phase composed of a mixture of (A) 2 mM acetic acid/0.2 mM ammonium acetate in water and (B) 2 mM acetic acid/0.2 mM ammonium acetate in methanol. The MRM transition used was 808.4>526.9 m/z and the retention time was 3.5 min. In conclusion, they obtained a sensitive and robust method to quantify taxanes.

Ferrando-Climent *et al.*[73] on the other hand, innovated and developed a solid-phase extraction (SPE)–UPLC–MS/MS method for the determination of 10 anticancer drugs, among them DTX, in hospital effluents and wastewater treatment plants (WWTPs), using a method for the screening of human metabolites assisted by information-dependent acquisition (IDA) tool. Chromatographic separation was carried out using an Acquity HSS T3 column (50 mm × 2.1 mm i.d. 1.7 μm particle size; Waters Corp. Milford, USA). The MS/MS parameters were optimized by MRM positive ionization with transitions at *m/z* 808>509. DTX was found in one hospital effluent and one urban WWTP influent, at concentrations of 97.7 ± 21.0 ng L^{-1} and 175.1 ± 21.0 ng L^{-1}, respectively.

Most analytical studies with HPLC employed C_{18} or C_8 reverse phase analytical columns and a water–ACN mixture as the mobile phase, with pH variations between 3.0 and 6.4,[74,75] associated or not with some organic additives such as buffers, acids or bases, to improve selectivity and separation. The gradient elution system was more frequently used than the isocratic elution and the retention times ranged from 1.25 to over 40 min.[76,77] Altogether, these factors contributed to greater selectivity, better resolution and decreased elution time. However, most studies using delivery systems do not provide all the analytical information, for instance, retention times. And, finally, most analytical studies with UPLC employed C_{18} columns, commonly with gradient mobile phase composed of ACN, water or methanol, leading to DTX retention times lower than those obtained by HPLC.

Conclusion

DTX is an anticancer drug widely used for the treatment of a variety of tumors. As discussed, some physicochemical characteristics, particularly poor water solubility, compromise its pharmacokinetics. As an alternative, herein it was shown a variety of nanocarriers for DTX delivery, which in general, led to better *in vitro* and *in vivo* anticancer activity. In this review, we presented several analytical methods for DTX quantification in a variety of matrices, including delivery systems, and biological samples, representing an important step both during formulation development and quality control. Among these methods, immunoassays showed good sensitivity and selectivity, however, the need to use expensive kits limits its use. CE has the advantage of using reduced quantities of samples and solvents, besides having great sensitivity and selectivity, with reduced time of analysis, mostly with the MEEKC method. Despite various methods have been described in this review, the most commonly used method is the reverse phase liquid chromatography, with UV or MS detectors, employing a variety of columns and mobile phases. Finally, the UPLC has gained recent highlight for DTX quantification due to the reduction of mobile phase use and faster analysis.

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