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REVIEW ARTICLE

Carbon nanotubes: An alternative for platinum-based drugs delivery systems

Daniel Salas-Trevino[1], Odila Saucedo-Cardenas[1,2], Maria de Jesus Loera-Arias[1], Edgar Gerardo De Casas-Ortiz[3], Humberto Rodriguez-Rocha[1], Aracely Garcia-Garcia[1], Roberto Montes-de-Oca-Luna[1], Adolfo Soto-Dominguez[1]

[1]Department of Histology, Faculty of Medicine, Autonomous University of Nuevo Leon, Monterrey, Nuevo Leon, Mexico; [2]Northeast Biomedical Research Center (CIBIN) of the IMSS, Monterrey, Nuevo Leon, Mexico; [3]Department of Advanced Materials, Applied Chemistry Research Center (CIQA), Saltillo, Coahuila, Mexico

Summary

Currently, nanomedicine is approaching the research of nanomaterials that could work as drug delivery systems, to increase the efficiency, specificity and safety of drugs reducing toxicity and side effects. In this regard, carbon nanotubes have acquired great interest due to their physicochemical properties. The use of platinum-based drugs is facing some troubles in the clinic due to their side effects such as nephrotoxicity, neutropenia, neurotoxicity, among others. In addition, cases of tumors resistant to these drugs have been recently observed. The goal of this review was to analyze the reports about the use of formulations of platinum-based drugs in carbon nanotubes, to know and establish the most functional and potential conditions for its use in cancer treatment, identifying perspectives and develop areas for the improvement of these nanomaterials in the application of cancer therapy.

Key words: *cancer, carbon nanotubes, drug delivery, chemotherapy, platinum-based drugs*

Introduction

In the early 1960's, Roserberg and colleagues discovered the antitumor activity of cisplatin in sarcoma models in rats [1]. This event was a turning point for oncology and cisplatin was established as the first drug of this type approved as an antineoplastic by FDA [2]. This compound is efficient to treat different types of cancer, such as testicular, ovarian, bladder, colorectal, lung, head and neck [1,2].

Cisplatin analogues, such as carboplatin and oxaliplatin, release platinum II (Pt II); this species forms intra and interchain linkages in the DNA [3], causing alterations in the transcription processes and activating apoptosis pathways [4].

However, the use of platinum-based drugs requires palliative medication because they can cause a series of important adverse effects such as nephrotoxicity, neutropenia, neurotoxicity, ototoxicity, alopecia, nausea, vomiting, among others [2,5]. In addition, it has recently been observed that tumors gradually develop platinum resistance after an initial response [2].

Correspondence to: Adolfo Soto-Domínguez, PhD. Autonomous University of Nuevo Leon, Faculty of Medicine, Department of Histology, Monterrey, 66460, Nuevo Leon, Mexico.
Fax: +52 82 8348 5477, E-mail: ibqasoto@yahoo.com.mx
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A quite important point in the chemotherapy based on platinum is the resistance or inactivation of its therapeutic effects by tumor cells. Also, it has been observed that the presence of nucleophilic protein efflux pumps in the membrane and the subexpression of copper transporter membrane (CTR1) are closely related to this type of drug resistance [4].

The toxicity profile and acquired resistance have caused great concern in clinical practice, so that structural variants have been developed, like carboplatin or oxaliplatin [1,2,6] and although these variants have milder toxic profiles, they are still not inert to the body [2]. It has also been noticed that the combined therapies of platinum drugs and new antineoplastic agents (third generation, e.g. doxorubicin, paclitaxel) increase the successful therapeutic ratio [5], however, the toxicity of platinum compounds is not reduced, and this can be due to their low specificity, which restricts the use of higher doses [7]. Another therapeutic option that has taken on considerable importance nowadays is nanotechnology, because of its great potential in diagnosis, imaging and treatment of various diseases, including cancer [8,9].

Nanomaterials are capable of delivering drugs, especially those with poor solubility and stability such as platinum drugs [9], moreover, they reduce their toxicity and improve their pharmacokinetics as well as their bioavailability to increase their therapeutic effect [4,9].

Nanomedicine is the branch of nanotechnology that is dedicated to study the use of nanoscale materials in improving health [7]. A crucial part of nanomedicine is the research of nanomaterials that could work as drug delivery systems, in order to increase the specificity and security of the drug, thus reducing toxicity and side effects [10,11]. Diseases such as cancer, chronic or resistant infections have high expectations to implement their treatment with the use of these materials [12]. In this regard, nanomaterials offer many options to design intelligent transport systems for controlling the release of drugs [9,13,14]; they can also increase the solubility in water and the stability of the drug, as well as improve its pharmacokinetics in the body [8]. Among other uses, nanomaterials can carry antibiotics or anti-inflammatory drugs [15], or even antibody ligands, polymers, diagnostic probes, drugs or genetic material [16].

There are a variety of nanoparticles that have been used in recent years in order to deliver pharmaceutical molecules [17]. Nanomaterials such as liposomes and organic polymers are the most commonly used for their high biocompatibility, and in fact some have already been approved for clinical use [18]. Another nanomaterial that has recently generated much attention in the field of pharmaceutical research is the carbon nanotubes (CNTs) [4,19].

The CNTs are cylindrical nanostructures first described in 1991 [20]. They are an allotrope of carbon, the structure of which can be elucidated as a rolled sheet of graphene (condensed benzene rings) and are classified into two main groups: single wall carbon nanotubes (SWCNT) with only one sheet of graphene or multiwall carbon nanotubes (MWCNT) when two or more of a graphene sheets are used [21]. The diameter range of these nanotubes can be 0.4 to 2 nm for the SWCNT and 10 and 100 nm for the MWCNT, their length is in the order of microns (between 10 to 50 μm) [20], giving them a high aspect ratio, so they have been described as needle-like shape nanostructures, thus increasing their ability to cross cell membranes and attain cytoplasmic accumulation [21].

Recently, CNTs have drawn great interest in nanotechnology because of their great electrical, organic, physical and mechanical properties [22]. They are widely used in computers, aircraft structures, sporting goods and bicycles [23], while in the field of biology and nanomedicine they have been installed as a promising tool for the delivery of drugs, vaccines, biosensors or tissue scaffolds [24,25].

CNTs are especially functional in the transport of substances because of their unique physicochemical properties, their high dynamic range which increases their capacity to carry and detect molecules [26] like DNA, RNA, peptides or drugs [27]; these molecules can be encapsulated in their hollow interior or adsorbed to its external surface [4,11].

Functionalization (insertion of reactive functional groups, e.g. carboxyl, hydroxyl) to their walls makes it possible to form covalent and non-covalent bonds with hydrophobic or hydrophilic molecules [11,21]. It has been observed that Van der Waals forces and electrostatic interactions are responsible for the link between the CNTs and the molecules [20]. CNTs are able to enter the cell directly through membrane penetration causing endocytosis and this process depends on their morphology and chemical functionalization [11]. When CNTs enter through the intravenous route, they accumulate in the lungs over a period of 24 hrs, then they go to the liver and spleen to finally be eliminated mainly by the bile duct and to a lesser extent by urine [28].

Previous studies in cell and animal models have shown that CNTs without modifications or commonly known as “pristine”, can generate tox-

icity and pathogenicity due to their hydrophobic nature. They can bind to cellular proteins through hydrophobic interactions [11], damaging cell membranes and increasing oxidative stress, apoptosis, autophagy and inflammatory reactions [22,29-31].

Nowadays, CNTs safety for drug delivery is in controversy because their intrinsic toxicity is not known exactly. In this regard, several physical and chemical factors like purity of the material, its morphology, dose/concentration and route of administration have been proposed as crucial for the toxic profile of CNTs [9,32,33]. Toxicological data in murine models showed that CNTs without functionalization injected intraperitoneally behave as asbestos fibers producing mesothelioma [32,34] and through the intratracheal route they produce severe fibrosis and carcinoma *in situ* [35].

In order to diminish these disadvantages present in the pristine CNTs, many researchers were dedicated to finding ways to reduce their toxic effects. Studies have shown that the purification of CNTs by exposing them to high temperatures reduced the remains of catalytic metals used in their synthesis, increasing their biocompatibility and decreasing the toxicity levels [31]. Moreover, the functionalization of these nanocomposites substantially improves the biocompatibility of CNTs by increasing their dispersion in aqueous solutions [20,32], promoting interaction with biomolecules [36], reversing the hydrophobic nature to prevent the formation of toxic aggregates [21], adapting them to carry drugs and organic molecules such as proteins or nucleic acids [37], and enabling their passage through biological barriers to enter and accumulate in the cells [4]. Such modifications applied correctly, can make CNTs very potential candidates to be applied in the delivery of drugs, since they are able to encapsulate organic or inorganic molecules to protect them from degradation or premature inactivation [25,38].

As mentioned earlier, platinum-based drugs tend to have high toxicities and low solubility, in

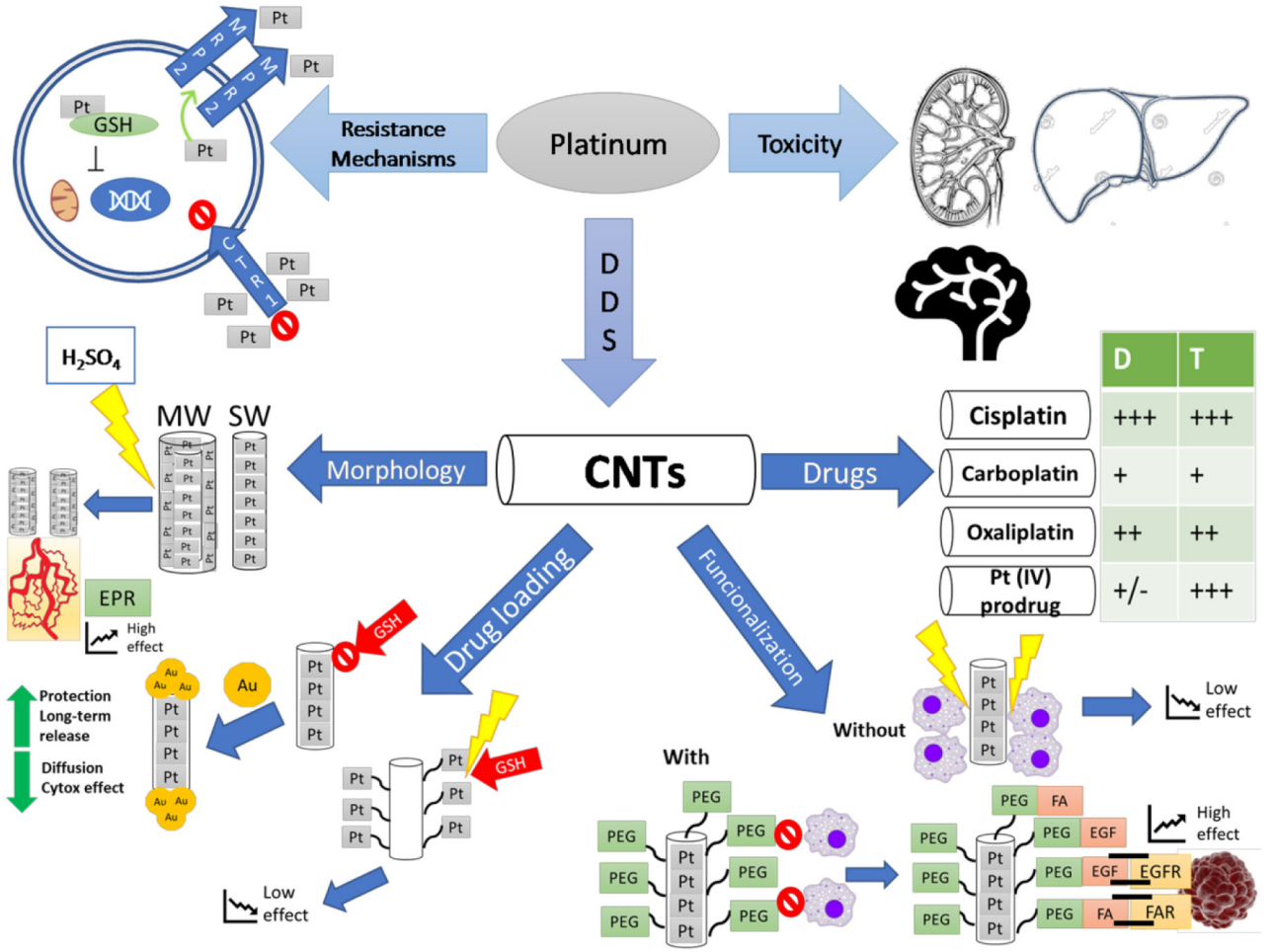

Figure 1. Carbon nanotubes (CNTs): some of their characteristics and potential applications for platinum-based drugs delivery systems. Pt: platinum, AU: gold nanoparticles, GSH: glutathione, EPR: enhanced permeability and retention, DDS: drug delivery system, D: disolution in cytoplasm, CTX: cytotoxicity, PEG: polyethylenglycol, EGF: epidermal growth factor, EGFR: epidermal growth factor receptor, FA: folic acid, FAR: folic acid receptor.

addition to reduced stability, which makes them ideal candidates for using nanotechnology in order to optimize their administration. In this regard, computational models have tested the potential of CNTs to encapsulate platinum drugs [39] and their efficacy to release them into cells [40]; furthermore, studies with *in vitro* or *in vivo* models have shown that drugs such as cisplatin [25], carboplatin [41] or oxaliplatin [42], as well as pro-drugs based in platinum [3] have been encapsulated and successfully tested in CNTs.

There is a series of considerable basic research studies on CNTs, however, it has not yet been possible to transfer them to a human application due to the differences in safety, functionality and efficiency data [37]. Besides, it is necessary to know better the efficiency in the loading of molecules as well as their load site and their release mechanisms [43] so we have taken on the task of collecting the most important studies in which CNTs have been used as a system of delivery of platinum-based antineoplastic drugs with *in vitro* (Table 1) and *in vivo* models (Table 2), due to the fact that these drugs are of major impact since they are the most used as a first line in chemotherapy and cause important toxic and side effects that affect directly the health of the treated patients.

The objective of this work was to analyze the reports regarding the use of formulations of platinum-based drugs in CNTs, their versatility in physical and chemical characteristics, as well as their efficiency and therapeutic safety, to know and establish the most functional and potential conditions for their use in cancer treatment and identify the perspectives and develop areas for the improvement of these nanomaterials (Figure 1).

Characteristics of delivery systems for platinum-plated antineoplastic drugs based on carbon nanotubes in cancer models

Structure: Diameter and length

As already mentioned, the diameter of a CNT depends directly on the amount of layers of graphene that form the wall of the material, while the length can be of the order of microns but can be reduced substantially using chemical treatments [19].

SWCNT were the first to be tested *in vivo* to carry cisplatin to a solid tumor, showing promising results [18], however, MWCNT are the best option to encapsulate platinum-based drugs because they have wider diameter compared to SWCNT [9,44]. Recent studies have shown that using CNTs with wider diameters may be more advantageous, because the platinum will be encapsulated with greater abundance, decreasing the possibility of escape from its hollow interior [3], and therefore, reducing the encapsulation time [25]. A study demonstrated the utility of MWCNT with long inner diameter (LID-MWCNT, 20 to 50 nm in diameter), to encapsulate cisplatin and functionalizing them with polyethylene glycol (PEG), achieving very high payload and good cytotoxicity in tumor cells [43]. Also, this year Yang et al. were able to conjugate this system with another antineoplastic agent (doxorubicin) by adhering it to the surface. Making the liberation dependent on pH, they observed a synergistic cytotoxic effect on breast cancer MCF-7 cells with greater efficiency at acid pH, which commonly occurs in the tumor microenvironment and simulating the double therapies that are currently usually applied in the clinic [45].

In regard to the length of CNTs, some authors have observed repercussion on the toxicity induced by long-CNTs based on the well-known pathogenicity caused by asbestos fibers, a compound quite chemically similar to CNTs [46]. In order to reverse this toxicity, it has been possible to reduce the length of these CNTs by chemical treatments to form ultra-short carbon nanotubes (US - Tubes) of approximately 30 to 80 nm long, coupling them to cisplatin and achieving good rates of *in vitro* toxicity against tumor cells [47]. In addition, due to its thermo-conductivity properties, it has been possible to activate them to release cisplatin by using radiofrequency to heat the material [48]. This same teamwork published this year the first study where a platinum drug is used, coupled to the US-tubes in an *in vivo* model of breast cancer, finding an increased suppression in tumor growth using CNTs with cisplatin compared to treatment with cisplatin alone [49].

Drug loading mechanism: Covalent bond in surface or encapsulated

The first approaches realized to load platinum-based drugs in CNTs were bonding covalently the drugs to the external surface in previously functionalized CNTs [50]. However, recent reports show that platinum-based drugs encapsulated in the CNTs are more efficient, since they prevent early loss or degradation, thus drugs are released for longer periods of time [4], discharging approximately 60% in the first 14 days of incubation in the culture medium [9] and causing a desired prolonged release.

Through electron microscopy it has been possible to determine the amount and position of platinum atoms that are found in the CNTs. These

characteristics are clearly related to the physicochemical properties, loading methods and concentration of the drug [51].

Another novel approach used to decrease the rapid release of the encapsulated platinum-based drug is to "cap" the ends of the CNTs through inorganic nanoparticles once encapsulated. This succeeded in increasing the intracellular delivery of platinum and optimizing its action by avoiding losses to nonspecific tissue [25]. One of these studies tested gold nanoparticles as "caps" coupled to the ends of the CNTs, and found an important decrease in the early release of the drug by up to 40% and increase of the cytotoxicity in a colon cancer cell line [52].

Functionalization

Both SWCNT and MWCNT have properties to bond molecules to their wall, however, in the latter, this process is more easy and does not compromise the integrity of the interior walls [9], keeping the encapsulated molecules stable and protected.

The compounds most commonly used to functionalize CNTs are water-soluble organic polymers, such as PEG or chitosan [18,27]. The use of these polymers has substantially increased the water dispersion and biocompatibility of CNTs, life span in blood flow, improves renal and biliary excretion, prevents opsonization, and therefore phagocytosis and inflammatory response [27]. However, most of the studies are short-term, and therefore immune response caused by chronic exposure to CNTs should be evaluated more extensively in the future.

Another advantage of functionalization in CNTs is to provide them with directing molecules towards specific organelles such as mitochondria, increasing their uptake rate through receptor-mediated endocytosis and elevate their cellular retention, as well as their performance and cytotoxicity [21]. It has been shown that using molecules such as rhodamine-123 (positively charged) attached to CNTs requires a significantly lower concentration of platinum to affect ovarian tumor cells (A2780) [44], thus the use of rhodamine significantly increases the retention of the system in cells.

Moreover, a quite effective strategy to increase the specificity of drug delivery against neoplastic tissues is to functionalize it with ligand molecules to bind with their receptors that are overexpressed in these tissues. In fact, clinically validated platinum delivery systems actually use molecules such as folates or other peptides [3]. Previous *in vivo* studies with CNTs loaded with platinum-based drugs showed that several directing molecules like EGF [18] and folic acid [53], increase the efficiency to deliver the drug due to the induced receptor-mediated endocytosis of the CNTs, increasing thus the cytotoxicity in tumor cells, which have the receptor on the surface.

Platinum-based drug loaded

Cisplatin, as the first platinum drug approved by the FDA for the treatment of tumors, was also the first to be encapsulated in CNTs in 2005, getting promising results by showing a prolonged release (72 hrs) in a hydrophilic solution and increased cytotoxicity *in vitro* against tumor cells [54], demonstrating the potential that CNTs had as delivery systems. Based on this finding, a large variety of studies have been conducted, testing different configurations of CNT-based drug delivery systems coupled to cisplatin [25,49,55]. Recently, studies have also been performed with *in vivo* models to determine the biodistribution of cisplatin-coupled MWCNT administered intravenously [56], finding that the organ where this conjugate is mostly present is the lung (which could be of potential use for aggressive non-small cell cancer), while its presence in the liver and kidneys was reduced, examples of main organs that are typically affected by this drug.

Analogous molecules of cisplatin, such as carboplatin, have also been coupled to functionalized CNTs, generating high levels of toxicity in different tumor cells [11,57,58]. This effect occurs both in long-length CNTs (carbon nanofibers) and in MWCNT, being more predominant in the first [55] and it has been determined that the toxicity produced apoptosis and inhibition of proliferation [59]. On the other hand, oxaliplatin has been coupled to MWCNT wrapped in PEG and tested *in vitro* in HT29 cells, showing increased cytotoxicity in a period of 48 to 96 hrs, producing high amount of crosslinks in the DNA [60].

A novel strategy is this regard is the encapsulation of hydrophobic platinum (IV) prodrugs, which upon entering the cell use the local reducing molecules that react with them to produce the active form of platinum (II) which is capable of bind to DNA [3,50,53]. This approach has the ability the lower the solubility that the prodrug will have in an aqueous solution, remaining within the CNTs until it is internalized in the cell and reduced, changing its structure to a more hydrophilic one releasing reactive platinum species. Other atypical platinum drugs synthetized and designed *de novo* have been conjugated in the walls of MWCNT, showing good cytotoxic effects that are enhanced by applying heat in the tumor areas, activating the nanomaterials and increasing their selective release [61].

Table 1. *In vitro* studies of CNTs as a platinum-based drug delivery system

Author, year [ref.no.]	*CNTs type*	*Platinum – based drug*	*Functionalization*	*Cell line type used*	*Result*
Sui et al, 2014 [43]	LID – MWCNT	Cisplatin (encapsulation)	Polyethylene glycol (PEG)	CAL – 27 (Human tongue squamous carcinoma)	IC50: 13.1 μM of drug
Ajima et al, 2005 [54]	SWCNT	Cisplatin (Encapsulation)	None	NCI-H460 (Human lung cancer)	IC50: 2.5 μM
Feazell et al, 2007 [50]	SWCNT	Platinum (IV) prodrug (covalently outer surface)	Phospholipids conjugated with PEG and with amino ends	NTera-2 (testicular carcinoma)	IC50: 0.02 μM
Dhar et al, 2008 [53]	SWCNT	Platinum (IV) prodrug (covalently outer surface)	Phospholipids conjugated with PEG and with amino ends that bind folic acid covalently	KB (Human nasopharyngeal epidermoid carcinoma, FR=+) JAR (choriocarcinoma, FR=+) NTera – 2 (Human testicular cáncer, FR=-)	IC50 KB: 0.019 μM IC50 JAR: 0.01 μM IC50 NTera-2: 0.048 μM
Bhirde et al, 2009 [18]	SWCNT	Cisplatin (Encapsulated)	Epidermal growth factor (EGF)	HN12 (Head and neck squamous cell carcinoma)	IC50: 1.3 μM
Arlt et al, 2010 [9]	MWCNT	Carboplatin (Encapsulated)	None	DU145 (Prostate carcinoma) PC – 3 (Prostate carcinoma)	RP DU145: 8% at 5 μg/ml RP PC-03:21% at 5 μg/ml
Haase et al, 2011 [57]	MWCNT	Carboplatin (Encapsulated)	None	EJ28 (bladder carcinoma)	RP EJ28: 5% at 0.5 μg/μl of DDS
Guven et al, 2012 [47]	SWCNT (ultra -short)	Cisplatin (Encapsulated)	Plucoronic-F108 surfactant	MCF – 7 MDA – MB – 231 (Human breast carcinoma)	RP MCF–7: 40% at 10 μM RP: MDA–MB–231: 50% at 10 μM
Li et al, 2012 [25]	MWCNT	Cisplatin (Encapsulated)	Gold nanoparticles w/ octadecanethiol (as caps)	MCF – 7 (Human breast carcinoma)	IC50: 7.74 μM
Raoof et al, 2013 [48]	SWCNT (ultra – short)	Cisplatin (Encapsulated)	Plucoronic F108 – Radiofrequency used to activate	Hep3B, HepG2. (Human liver carcinoma)	IC50: 2.5 μM
Wu et al, 2013 [60]	MWCNT	Oxaliplatin (Encapsulated)	Polyethylene glycol	HT-29 (colon adenocarcinoma)	RP 24h: 50% at 32 μM RP 48 h: 50% at 6 μM
Ringel et al, 2014 [55]	MWCNT	Cisplatin and Carboplatin (encapsulated)	None	DU-145 (prostate carcinoma) PC-3 (prostate carcinoma) EJ28 (bladder carcinoma)	RP DU-145: CNT-CDDP: 36.1% at 0.25 μg/ml CNT-CP: 43.3% at 7.5 μg/ml RP PC-3: CNT-CDDP: 30.8% at 0.35 μg/ml CNT-CP: 42.4% at 5.0 μg/ml RP EJ28: CNT-CDDP: 32.0% at 0.70 μg/ml CNT-CP: 34.3% at 10.0 μg/ml
Yoong et al, 2014 [44]	MWCNT	Prodrug platinum (IV) w/ 3-bromopyruvate (encapsulated)	TEG - Rhodamine 110	MCF – 7 (Human breast carcinoma) A2780/A2780CisR (Human ovarian carcinoma) IMR90 (Human fetal lung fibroblast)	IC50 MCF-7: 0.39 μM IC50 A2780: 0.17 μM IC A2780CisR: 0.71 μM IC50 IMR90: >2 μM
Li et al, 2015 [52]	MWCNT	Cisplatin (encapsulated)	Functionalized gold nanoparticles	HCT 116 (Human colon adenocarcinoma)	RP: 40% at 30 μM
Farenholtz et al, 2016 [61]	MWCNT	Non-common platinum compound (P3A1)	Polyethylene glycol	MDA – MB – 231 (Human breast carcinoma)	IC50: 10 μM of DDS

Continued on the next page

Table 1. *In vitro* studies of CNTs as a platinum-based drug delivery system

Author, year [ref.no.]	*CNTs type*	*Platinum – based drug*	*Functionalization*	*Cell line type used*	*Result*
Balas et al, 2016 [11]	MWCNT	Carboplatin (encapsulated)	Oxidized and aminated	MDA – MB – 231 (Human breast carcinoma)	RP CNT–NH2–CP: 41% at 0.6 μg/ml RP CNT–COOH–CP: 71% at 0.6 μg/ml
Irannejad et al, 2016 [58]	SWCNT	Diaminedicarboxy platinum (II) drug (surface)	None	HeLa (cervical carcinoma)	IC50: 13 μg/ml of DDS
Yang et al, 2017 [45]	LID – MWCNT	Cisplatin (encapsulated)	Doxorubicin (non-covalently) PEG and folic acid	MCF-7 (Human breast carcinoma)	IC50: 10 μg/ml of DDS in pH 6.5.

LID: Long inner diameter, IC_{50}: Half maximal inhibitory concentration, RP: Relative proliferation

Table 2. *In vivo* studies of CNTs as a platinum-based drug delivery system

Author, year [ref.no.]	*CNTs type*	*Platinum – based drug*	*Functionalization*	*Tumor cell type*	*Result*
Bhirde et al, 2009 [18]	SWCNT	Cisplatin (Covalently bonded)	Epidermal growth factor	HN12 (Head and neck squamous cell carcinoma)	Tumor volume (mg): w/EGF: 500 w/o EGF: 2200
Bhirde et al, 2010 [27]	SWCNT	Cisplatin (covalently bonded)	Polyethylene glycol and EGF	HN12 (Head and neck squamous cell carcinoma)	Tumor volume growth: w/EGF:6.25% w/o EGF: 55% Dose reduced at 1.33 μM w/PEG
Guven et al, 2017 [49]	US-SWCNT (Ultra short)	Cisplatin (encapsulated)	None	MCF – 7 MDA – MB – 231 BCM – 4272 (Human breast carcinoma xenografts in nude mice)	Mean fold increase in tumor volume: MCF-7: 1.0 MDA – MB – 231: 7.45 BCM – 4272: 2.57

Conclusion

CNTs represent a potential effective option as delivery system for drugs with poor stability, low retention and increased toxicity, such as platinum antineoplastic drugs, due to their favorable physicochemical properties, such as their large surface area, good aspect ratio, functionalization and hollow core. It has been observed that these drugs obtain greater loading capacity, better biodistribution and pharmacokinetics, as well as increased cytotoxic effects against tumor cells *in vitro* and *in vivo* when conjugated with these nanomaterials compared to drug therapy alone.

The morphology of CNTs has an important impact on the efficacy and safety of these materials, so it is important to consider the diameter and length to design platinum antineoplastic delivery systems. In this regard, we emphasize that the use of MWCNT (higher diameter) has been shown to be more efficient due to its high protection and increased drug loading, the encapsulation of the drug turns out to be the optimal loading method, and moreover it is possible to attach another drug to the surface covalently, creating a double delivery system and simulating a bivalent therapy, which is commonly used in the clinic. On the other hand, the length of the CNTs causes toxicity and inflammatory response in the lungs proportionally to its dimension, thus, it is safer to work with short CNTs.

The functionalization of the CNTs' surface is crucial to increase its aqueous dispersion and biocompatibility, and hydrophilic linear polymers such as PEG or chitosan are ideal for this purpose. Coupled with this, the use of specific molecules of tumor tissue such as the folic acid is quite useful to reduce side effects and toxicity in healthy organs.

In general, any type of platinum drug is optimized by the use of these systems, however, prodrugs represent a novel option to increase delivery and effect of the drug due to the necessary reaction with reductases in the cell, thus, its activation is more efficient in the cell than in the extracellular spaces.

In conclusion, the above characteristics are, to date, those that have shown better performance in terms of therapeutic efficiency and safety, so they can be considered as a starting point when designing a platinum drug delivery system based on CNTs for future pharmacological formulations, with the goal of obtaining the maximum potential of the use of this nanomaterial in this area.

Conflict of interests

The authors declare no conflict of interests.

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