Journal of Drug Delivery Science and Technology 59 (2020) 101855

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

journal homepage: www.elsevier.com/locate/jddst

Review article

An overview of recent development in therapeutic drug carrier system using carbon nanotubes

M.A. Saleemi [a], Y.L. Kong [b], P.V.C. Yong [a], E.H. Wong [c,*]

[a] School of Biosciences, Faculty of Health and Medical Sciences, Taylor's University Lakeside Campus, Subang Jaya, Selangor Darul Ehsan, 47500, Malaysia
[b] Department of Engineering and Applied Sciences, American Degree Program, Taylor's University Lakeside Campus, Subang Jaya, Selangor Darul Ehsan, 47500, Malaysia
[c] School of Medicine, Faculty of Health and Medical Sciences, Taylor's University Lakeside Campus, Subang Jaya, Selangor Darul Ehsan, 47500, Malaysia

ARTICLE INFO

Keywords:
Carbon nanotubes
Drug delivery carrier
Drug-loading capacity
Cytotoxicity

ABSTRACT

Carbon nanotubes (CNTs) provide a promising platform in therapeutic agent delivery system due to its unified and distinct physicochemical properties. On account of its immense potential, CNTs have been widely utilized as a proficient transport system of various therapeutic active agents, ranging from anti-infectives, anti-neoplastic agents, cardiovascular drugs to genes, and anti-inflammatory molecules. In the context of its large promise, this literature is devoted to understanding the biochemistry and functionalization of CNTs. Herein, we discuss comprehensively the characteristics of CNTs, including their mechanisms behavior, cellular uptake and drug-loading capacity. Consequently, the literature has surveyed the current patents to highlight the recent application status of CNTs in the biomedical field. The potential application of CNTs as distinct therapeutic carrier in the drug delivery system, together with their toxicology/biosafety profiles, and the approaches to overcome the cytotoxicity of CNTs are also investigated with further perspective in this work.

1. Introduction

In general, the word "therapeutic drugs" refers to natural or synthetic products designed to prevent or cure certain ailments or medical disorders. Their main mechanism of action is to prevent impaired biological development, which helps to restore the physiological activities of the body. The therapeutic effect begins with the administration of a drug, followed by drug circulation inside the body. The main challenges of current drug administration techniques include: (1) delivery to both normal and abnormal tissues, (2) excretion from the body, and (3) degradation of the drugs before reaching targeted organs, which significantly reduce the overall therapeutic effects. Administration of a higher dose of therapeutic drugs might overcome the problems mentioned above, but only a minor fraction of the drugs could reach the targeted organs in intact form. Moreover, exposure of the body to the surplus of drugs may result in more risky side effects [1].

In recent years, many pharmaceutical companies have invested hugely in medical research to formulate newly improved therapeutic drugs which produce minimal toxicity and higher physisorption into the targeted cells. The main research interest is to investigate the interaction of drugs with the surrounding tissues and cells. However, the development of new reliable drugs which often involves complicated *in-vivo*, *in-vitro* experiments and high-throughput screening (HTS) that are costly and time-consumed. Thus, the current researchers are drawing more attention to implement a highly effective drug delivery system with the vision of producing tailored drugs using a carrier or drug vehicle [2]. This approach enables the control of the dosage amount as well as releasing rate of the drugs [3].

Over the years, CNTs have been gaining attention from various fields due to its aspect ratio, electrical, mechanical, and physicochemical properties. In the biomedical field, CNTs have been used broadly as nanocarriers to deliver several peptides, proteins, plasmid DNAs, siRNAs [4,5]. Along with the notion of drug delivery system, this work is reviewing on the functionalized CNTs as reliable drug carriers in therapeutic system in the past decade. In addition, various biomedical applications of functionalized CNTs through different routes of administration will be reviewed. Last but not least, the interaction behavior of CNTs with cellular cells, toxicology and biosafety profile history, current research trend and the future development potentials of CNTs will be investigated in this work.

In this context, certain other reason behind our dependency on novel drug delivery systems are: (1) to avoid the severe loss of APIs through

* Corresponding author.
E-mail address: EngHwa.Wong@taylors.edu.my (E.H. Wong).

https://doi.org/10.1016/j.jddst.2020.101855
Received 17 March 2020; Received in revised form 7 May 2020; Accepted 19 May 2020
Available online 23 June 2020

Table 1
Encapsulation of drugs in CNTs.

Drugs	Types of CNTs	Process of immobilization	Study
Pregabalin (PRE)	SWCNTs	Encapsulation	[21]
Doxorubicin (DOX)	*Armchair* and *zigzag* CNTs	Adsorption and encapsulation	[22]
Ifosfamide	*Armchair* SWCNTs	Encapsulation	[23]
Paclitaxel (PLX)	f- MWCNTs	Encapsulation	[24]
Doxorubicin (DOX)	Covalent f-MWCNTs	Adsorption and encapsulation	[25]
Cisplatin (CDDP)	Carboxyl f-WWCNTs	Encapsulation	[26]
Doxorubicin (DOX)	Folic acid-modified MWCNTs	Encapsulation	[27]
Ciprofloxacin	PEG-MWCNTs/ gelatin-chitosan	Incorporated into nanocomposite matrix	[28]
Doxorubicin (DOX) and Paclitaxel (PLX)	f-SWCNTs	Encapsulation	[29]

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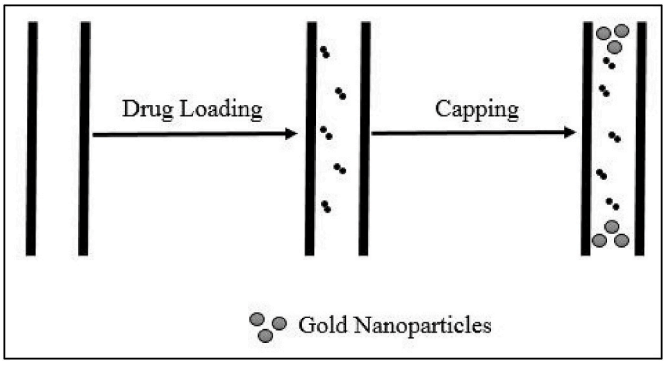

Fig. 1. Synthesis of carbon nanobottles, where the encapsulated carbon nanotubes are fabricated with nanoparticles of gold at the ends (Reprinted with permission from Ref. [32]. © 2013, American Chemical Society.).

urine, (2) to enhance the physical stability of APIs, (3) to improve the bioavailability of APIs, and lastly (4) to improve the APIs solubility [6, 7].

2. Drug loading onto CNTs

Drug loading involves the process of combining the active drug with the carriers, which to be delivered to the targeted cells or tissues. For this purpose, CNTs are widely used due to their high surface area to volume ratio and spherical shape, which have tremendous potential to carry the drugs at large scale [8]. Furthermore, the loading capacity of CNT can be enhanced by altering amphiphilic or hydrophilic polymers on their surface [9]. Also, the biocompatibility of CNTs could be increased via chemical functionalization of nanotubes surface [10]. The modification of CNTs can be employed through covalent anchoring of PEG layers [11], amphiphilic deblock copolymers [12], or PAMAM dendrimers [13] on their surface or modify it by dispersing in a matrix of hyaluronic acid [14]. CNTs, such as SWCNTs have the potential to improve the other carrier's properties, including polymeric and non-polymeric composites due to their mechanical strength [14]. Another advantage of using these nanomaterials is that they can carry pharmaceutical agents through multiple ways, for instance, encapsulation inside the hollow cavity [15], adsorption among the walls of CNTs and binding on the surface upon functionalization [16]. The drug delivery by encapsulation has more advantages compared to others as drug molecules are released within the targeted cells in a specific condition and also prevent the degradation of drug [17]. Certain examples of therapeutic drugs attached to different types of CNTs are discussed in Table 1. The release of drug from CNTs may be chemically and electrically controlled. In order to avoid the unwanted drug release, polypyrrole (PPy) film was used to seal the open ends of CNTs [18]. The selectivity of drug delivery system was improved by attached homing devices, such as epidermal growth factor [19], and folic acid [20]. In overall, CNTs have the potential to be applied in a wide range of biomedical applications as a drug delivery carrier.

The main role of these CNTs is to maintain the drugs structural integrity, where encapsulation or "endohedral modification" often diminishes the degradation of pharmaceutical agents in order to maximize the release of drugs under controlled circumstances [17]. This approach is mainly applicable to the drugs with reduced surface tension because the encapsulation of drug is driven by hydrophobic forces and capillary forces. For example, the oxidized carbon nanobottles are fabricated with nanoparticles of gold to prevent the uncontrolled release of the encapsulated drug (cisplatin), as shown in Fig. 1 [31].

However, surface derivatization (such as exohedral modification) leaves the drugs exposed as compared to encapsulation method [33]. There are various bio-conjugation methods; one of them is named tethering process (i.e., covalent interactions to the noncovalent attachment of drugs). It is worth mentioning that the tethering process requires an additional step of oxidation to produce functional groups for the conjugation. Also, a covalent bond could alter the molecular structure of the drugs, which could affect their bioactivity and specificity [33]. While the noncovalent method ultimately causes the unwanted dissociation of therapeutic agents in the biological fluids, this tethering approach is leading due to strong covalent bonds that produce a stable platform between nanocarriers and drugs [34]. In general, the process of drug delivery using CNTs to the target cells is as follows. The molecules of drug attached on the surface of modified CNTs, where chemical receptors are present. These chemical receptors are facilitated to carry the drug molecules inside nanotubes. Then the received conjugate is injected into the body through different routes, such as injection, oral, or directly introduced to the target cell. The chemical receptors internalize the CNTs capsule loaded with drug via the endocytosis pathway and finally escape the drug within the cell [35]. The schematic representation of drug delivery system is explained in Fig. 2.

3. Cellular uptake capacity of CNTs

A key factor in understanding the drug pharmacokinetics and pharmacodynamics is to comprehend how drugs are taken up by the projected cells effectively. The biochemical pathway and the permeation ability of the drugs across cellular cells are the main research questions that ought to be answered. For the drugs with high solubility, diffusion through lipid bilayer is thought to be the principal mechanism of drug intake. However, such mechanism is impaired for drugs with high molecular weight, which exhibits low lipophilicity to pass through bilayer structure [36]. In that case, the permeation of therapeutic agents could be salvaged or restored only through nanocarriers, which efficiently facilitates the whole process in many ways.

In 2007, Lacerda and coworkers had investigated CNTs with cell-penetrating ability in general context [37]. In view of their results, there were four parameters seem to affect the interactions of CNTs with cellular membranes: (1) the mode of manufacture and post-process procedures, (2) their structural aspects (i.e., whether the materials are functionalized), (3) the surface properties (i.e., whether the materials are charged), and lastly (4) the effect of functional groups on the surface (i.e., carboxylic acids or other oxygen-containing groups). Besides that, their work revealed an intriguing and unexpected finding that the uptake capacity of CNTs seems to be independent of the cell type.

On the other hand, Rafa et al. (2008) reported that MWCNTs with size smaller than 1000 nm could be transported across cellular membranes via energy-independent pathway [38]. In the same study, the researchers have also shown that submicron-sized MWCNTs, which are

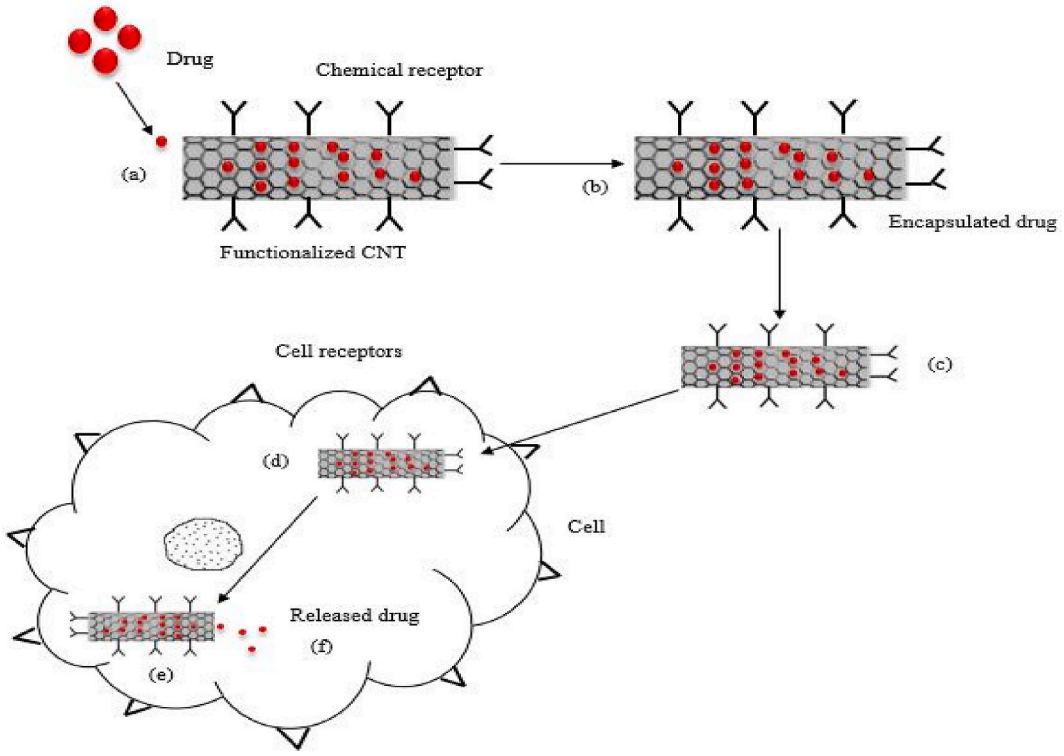

Fig. 2. Schematic illustration of drug delivery system. (a) The chemical receptors are attached on the surface of CNT (Y) and drugs (●) are carried inside, (b) CNT is capped at the open end, (c) CNT-drug carrier reaches to the target cell because of chemical receptors present on the surface of CNT, (d) CNT internalizes intracellularly by the cell receptors (V) through endocytosis pathway as an example, (e) then finally drugs are escaped [35]. (Reprinted from H. He, L.A. Pham-Huy, P. Dramou, D. Xiao, P. Zuo, C. Pham-Huy, Carbon Nanotubes: Applications in Pharmacy and Medicine, BioMed Research International 2013 (2013), https://creativecommons.org/licenses/by/4.0/.).

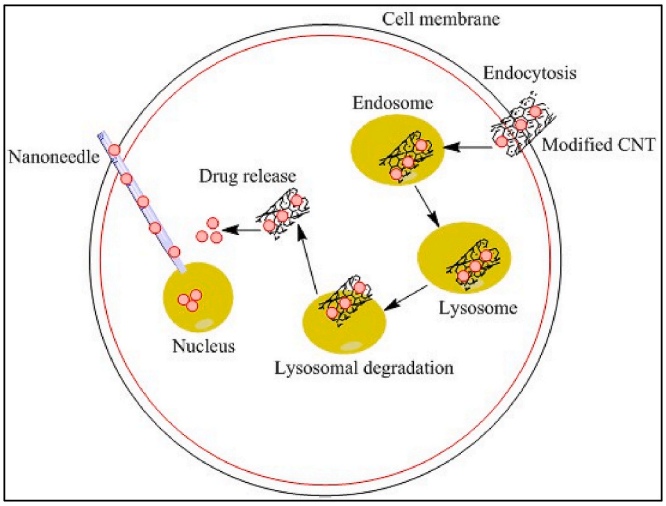

Fig. 3. Possible internalization pathway of CNTs. (Reprinted from C.M. Tilmaciu, M.C. Morris, Carbon nanotube biosensors, Frontier in Chemistry 3 (2015) 59, https://creativecommons.org/licenses/by/4.0/.).

commonly cited as "nanoneedles," are able to enter the cells more readily than the micron-sized MWCNTs, as shown in (Fig. 3). The correlation between the length of CNTs and the mode of transport is that SWCNTs with a size of up to 400 nm can be taken up by the cells via diffusion as a result of passive transport, while those with a size larger than 400 nm are internalized into the cell membranes through macrophages via endocytosis. Given that the diffusion was the predominant mechanism of the internalization, these findings are providing new insights on the biochemistry facts of CNTs, as well as the notion of drug delivery.

Unfortunately, the cellular uptake profile of these biomaterials is far more perplexing than what we came to know. The nanotube tends to locate into the cytosolic compartment of the cell when it diffuses across the cellular, whereas endocytotic vesicles are the main entry region for the CNTs after endocytosis [39]. In other words, the intracellular location of materials upon entry predetermines the mechanism of cellular uptake. It was elaborated by the researchers in analyzing the transportation pathways of various MWCNTs into the human embryonic kidney epithelial cells (HEK293) [40]. In their work, it became perspicuous that single-typed MWCNTs penetrate the cytoplasm via diffusion mechanism, while bundle-typed MWCNTs cross the cellular membrane through endocytosis, regardless of their surface charge. The basic understanding of the interaction behavior of these biomaterials across the cellular membrane is reported in Ref. [41].

The development of robust analytical techniques is still under heavy research in order to fully explicate the biochemistry of CNTs. In year 2011, Draper and his coworkers developed an electrophoretic method to investigate the cellular penetration of CNTs. In their work, the cells that were exposed to nanocarriers had been first isolated, lysed and separated through gel electrophoresis [42]. Upon processing the gel images, this method enables one to quantify the behavior of nanoparticles in a specific region of cells. Likewise, Lin et al. (2011) developed a mass spectrometric technique to measure the uptake of CNTs by mammalian cells via endocytosis. The cellular uptake rate will be reflected by a proportional shift in mass or charge values of cells through the mentioned mass spectroscopy [43]. Besides, it has been reported that carbon nanotubes may perform similarly to cellular penetrating peptide, which enables translocation via the cellular plasma membrane because of the presence of a specific polycationic region. Moreover, cationic modified carbon nanotubes are alike in terms of morphology and charge

Table 2
Recent literature survey on applications of CNTs in drug delivery systems.

Study	Type of CNTs	API	Administration Route	Indication
[57]	CNT-(Fe)/hydroxyapatite composite	Doxorubicin (DOX)	NR	Magnetic targeted drug delivery carrier
[58]	Ph- responsive polyethylenimine-betaine functionalized CNT	siRNA and doxorubicin	Intravenous injection	The nanocomposite shows effective antitumor effects both in vivo and *in vitro* study
[59]	Thermosensitive and injectable Chitosan–CNT hybrid hydrogel	Methotrexate	NR	MCF-7 breast cancer cells
[25]	Covalently functionalized carbon nanotubes	Doxorubicin	NR	Increased efficiency of drug release
[60]	Oxidized MWCNTs	Metformin	NR	Reduced CNTs cellular uptake
[61]	MWCNTs	Gemcitabine/Lentinan	Subcutaneous injection	Enhanced the antitumor efficacy
Study	**Type of CNTs**	**API**	**Administration Route**	**Indication**
[27]	Folic acid (FA)-modified MWCNTs	Doxorubicin	Subcutaneous injection	Enhanced the suppression of tumor growth
[62]	Transferrin-conjugated MWCNTs	Docetaxel (DTX)	Intravenous injection	A549 human lung cancer cell line
[63]	Carboxylated-CNTs	Griseofulvin (GF) and Sulfamethoxazole (SMZ)	NR	Enhanced the dissolution of drugs
[64]	Pristine (NT) and COOH (FNT) functionalized carbon nanotube	Cladribine	NR	Mechanistic understanding of the surface functionalization of CNTs
[65]	Chitosan-multiwalled carbon nanotubes	Doxorubicin (DOX) and rhodamine B (RB)	Subcutaneous injection	Observed programme release of RB and DOX from dual drug delivery system
[66]	TiO2–Au embedded on MWCNTs	Doxorubicin (DOX)	NR	A549 and MCF7 cancer cell lines
Study	**Type of CNTs**	**API**	**Administration Route**	**Indication**
[67]	Boron nitride nanotubes and CNTs	Efavirenz	NR	Anti-HIV drug delivery system
[61]	MWCNTs	Gemcitabine	Subcutaneous injection	Enhanced the antitumor efficacy
[28]	PEG-functionalized CNTs	Ciprofloxacin	NR	Improved the dissolution and antibacterial activity
[68]	Cyclodextrin-modified SWCNTs	Formononetin	NR	Hela and MCF-7 cell lines
[69]	Hyperbranched polyglycerol modified CNTs	Doxorubicin	NR	A549 human lung cancer cell line
[70]	MWCNTs modified with cyclodextrins and polyethyleneimine	Cidofovir	NR	Improved the antiviral drug delivery system
Study	**Type of CNTs**	**API**	**Administration Route**	**Indication**
[71]	Carboxylated-SWCNTs	Silibinin	NR	Improved the biocompatibility of nanocomposites
[72]	MWCNTs	Ruthenium polypridyl complex	Intravenous injection	Enhanced the cellular uptake of RuPOP in liver and cancer cells
[73]	f-SWCNTs	Ribavirin	NR	Improved the antiviral effect on grass carp and could be applicable to control fish viral diseases in aquaculture
[74]	MWCNTs	Irinotecan	Oral delivery	HT-29 human colon cancer cell line
[75]	MWCNTs	Diltiazem hydrochloride	Transdermal delivery	Angina pectoris and hypertension
[76]	MWCNTs	Oxaliplatin	Intravenous injection	HT-29 human colon cancer cell line
Study	**Type of CNTs**	**API**	**Administration Route**	**Indication**
[77]	MWCNTs	Indomethacin	NR	Inflammation
[78]	SWCNTs	Pirarubicin	Intravesical injection	Human bladder cancer cell line BIU-87 xenograft rat bladder cancer
[79]	SWCNTs	Prednisolone	Local injection	Collagen-induced arthritis
[6]	MWCNTs	Captopril	Oral delivery	Hypertension
[7]	MWCNTs	Carvedilol-A	Oral delivery	Heart failure and hypertension

to cellular penetrating peptides and can more likely to penetrate that plasma membrane than undergoing endocytosis and release cargo through the cytoplasm [44] (Fig. 3).

4. Carbon nanotubes as a drug delivery carrier

In the last decades, researches have paid significant attention to use CNTs for various purposes in the biomedical field. This is only because of the high aspect ratio, high electrical, mechanical, and physicochemical properties of CNTs. In this frame, these nanotubes have been used broadly as nanocarriers to deliver several peptides [45], proteins [46], plasmid DNAs [47], siRNAs [48,49], and API [5,9,50]. Many biomedical applications of CNTs are summarized in Table 2 to demonstrate that functionalized CNTs are very stable and versatile systems with several routes of administration.

4.1. Antineoplastic APIs

Cancer is the second leading cause of death after cardiovascular diseases in the world. Diverse side effects associated with APIs therapy, such as systemic or cardiac toxicity have been induced to the surrounding healthy tissues [51]. In replacing the conventional chemotherapy to treat cancers, drug delivery to the targeted cancerous cells region remains the latest challenge in therapeutic research [52]. This is

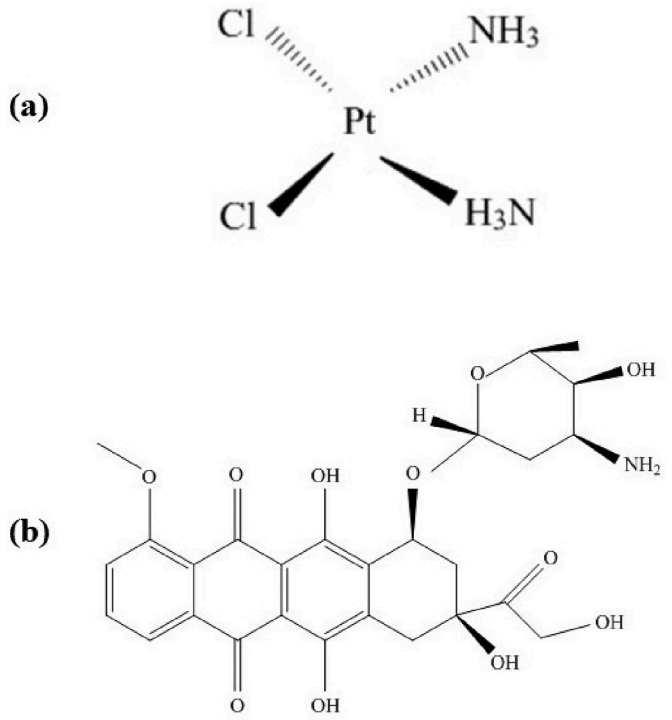

Fig. 4. The structure of cisplatin (a) and doxorubicin (b).

due to the expression of P-glycoprotein (P-gp) by tumor cells, which tends to block the therapeutic agents from entering into the tissue. Thus, most of the antineoplastic agents are obliterated unexpectedly before effecting a massive killing of targeted tumor cells [52]. Therefore, innovative technologies of delivering therapeutic agents are required to handle these concerns for the treatment of cancer [53].

Various nanomaterials have been previously used as a drug delivery carrier for many therapeutic agents. Among them, CNTs are widely used as a nanocarrier for antineoplastic agents, namely cisplatin, methotrexate, doxorubicin, and camptothecin. For instance, cisplatin has been used as a therapeutic agent for several disorders associated with cancer. The mode of action of cisplatin is to inhibit the replication of DNA and, thereafter stimulates cellular death due to cross-link among different DNA strands. However, this anticancer drug initiates many side effects, such as ototoxicity, nephrotoxicity, and neurotoxicity, etc. The structure of cisplatin has been given in (Fig. 4a).

In most cases, the interaction of chloride ions with water in the plasma obliterates the therapeutic effect of drug. Therefore, CNTs are used as drug carriers to prevent deactivation of the carried therapeutic agent in the process, which ultimately reduces the side effects to a large extent. Authors in Ref. [54] synthesized functionalized-SWCNTs loaded with cisplatin to target on PC3 and DU145 prostate cancerous cell lines. The cellular uptake findings of cisplatin had demonstrated that this therapeutic drug was effectively penetrating the cellular membrane and selectively found within the cytoplasm membrane of cancerous prostate cells. To this point, the encapsulation of drug is very important to stabilize the drug delivery system of cisplatin.

Doxorubicin is another anticancer therapeutic agent that has been extensively utilized in cancer treatment. The chemical structure of doxorubicin has been shown in (Fig. 4b). Previous studies conducted by Hwang showed that copolymer MWCNTs and functionalized-SWCNTs with polyethylene glycol (PEG) were forming complexes (non-covalently) with doxorubicin [55]. Surprisingly, the MWCNTs–doxorubicin complex was observed to be more active against cancerous cells compared to doxorubicin alone. In recent years, researchers have synthesized SWCNTs with two different types of polysaccharides, such as chitosan and sodium alginate, and further conjugated it with doxorubicin and folic acid [56]. On the other hand, it has been reported that therapeutic agent binds to the nanocarrier can be released at physiological pH less than 7.4 [56]. Thus, the surface modification of CNTs by functionalization is implemented in order to control the rate of drug release and manipulate the loading efficiency. According to Ref. [52], it is demanding to establish a novel method to improve the synthesis method and characterization of modified CNTs to boost its therapeutic application.

4.2. Anti-inflammatory APIs

Over the years, plenty of research work has been carried out in order to enhance the properties of cellular uptake, to reduce the side effects, and to improve the molecules release profile [80]. On the other hand, the application of CNTs in the therapeutic delivery of anti-inflammatory APIs has also got attention among researchers. Zanella et al. (2007) have investigated the interaction of well-known anti-inflammatory drug, namely nimesulide, onto both Si-doped capped and pristine SWCNTs by first-principle estimations. Nimesulide is used in reducing the fever and acts as pain relief medicine, but the selection of this therapeutic agent for the calculations of Density Functional Theory (DFT) is a debatable point. In their work, CNTs have been reported as the potential carrier of this therapeutic agent in transporting aromatic residues, and the physisorption effect has been improved with Si-doped SWCNTs due to its electronic properties [81].

To overcome the ineffectiveness of the conventional administration method in controlling the drug release rate onto the targeted area, the current anti-inflammatory delivery system has been integrated to extend the drug release over a longer duration in order to provide stable plasma concentration of therapeutic agent in the process. In such circumstances, the membrane around the therapeutic agent tends to absorb the drugs through osmotic pressure out of the carrier. For instance, Madaenia et al. (2012) have synthesized and functionalized MWCNT with cellulose acetate, which subsequently changed the porosity of membrane and increased the hydrophilicity for the release of indomethacin [77].

The other alternative drug release method called “stimulated drug release” tends to release therapeutic agents from its vehicle triggered by specific stimulants such as temperature, pH, and other physiological conditions. As the potential of electrical signal unravels to electronics and incorporation of microsystems, synthesis of much sophisticated and intelligent systems is within the option [82]. For example, SWCNTs-chitosan hydrogel films developed by Arti Vashist and co-workers, have stimulated the release of dexamethasone through electrical signals. Therein, they investigated that functionalized SWCNTs would encompass the indomethacin by electrostatic interactions. Once activated, the charge of CNTs can be fully reversible, and as a result, the release of indomethacin occurs due to electrostatic repulsion. This study has pointed out that SWCNTs are able to produce electrical signals to control the release of therapeutic agents and hence improve the bioavailability of active molecules [83].

4.3. Cardiovascular APIs

The diseases associated with cardiovascular are often stated as a set of disorders related to heart blood vessels. Based on the data from WHO, these disorders are the leading cause of death worldwide [84]. In recent, the preferred remedy of cardiovascular disease is the provision of drugs by conventional routes. Though, the medication for atherosclerosis and other cardiovascular disorders, including rheumatic heart diseases and cardiomyopathy, and thus is confined through the failure to proficiently deliver anti-cardiovascular medications across the layers of the endothelium [85]. For example, rosiglitazone drug acts as an agonist of peroxisome proliferator-activated receptor, is used to treat atheroma through macrophage infiltration into atherosclerotic wounds. However, the pharmaceutical effect of this therapeutic agent is observed through its toxicity to normal healthy cardiovascular tissues, which comes with

other unwanted side effects such as fluid retention and heart failure [86, 87].

Therefore, there are some other methods been implemented to deliver the anti-cardiovascular drugs, such as macromolecular-assisted and thiomer-mediated strategies [88] and by using silica particles in the delivery system [89]. For example, the study on the use of silica-based nanoparticles is crucial in the transportation of annexin V that subsequently facilitates the invention and application of the nanomaterials in cardiovascular disorders treatment [89]. The authors in Ref. [75] have reported that CNTs have progressive impacts on the treatment of cardiovascular diseases. Besides, Liu et al. (2009) studied the feasible interactive mechanism of SWCNTs with nifedipine to further investigate that: (1) encapsulation behavior of the nifedipine with CNTs, (2) absorption by the internal cavity of CNTs, and (3) energies translocation of the therapeutic agent. As an antagonist for calcium channel, this pharmaceutical drug is widely used in the various treatment of cardiovascular disorders, such as angina pectoris and hypertension. The authors have also stated that nifedipine was spontaneously encapsulated by the CNTs and easily adsorbed by the internal cavity of CNTs due to van der Waals forces [90].

Nevertheless, as compared to pristine MWCNTs, modified nanotubes are suitably tailored for the encapsulation of therapeutic agents due to better hydrophilicity [7]. Meanwhile in the same study, the authors have investigated the loading mechanism of a therapeutic agent named carvedilol using both pristine and oxidized CNTs. As an adrenoceptor/vasodilator antagonist, this drug is generally used for hypertension treatment as well as some other biological functions such as myocardial protection and neuroprotection. Three different approaches have been adopted in the mentioned study, which includes solvent method, fusion method, and incipient wetness impregnation method for the loading of carvedilol in the internal cavity of CNTs. Different approaches contribute to the distinct physical state and loading capacity of the carvedilol.

4.4. Anti-infective APIs

In this modern age, various infectious diseases remain challenging to be cured due to the emergence of strong microorganisms, which are resistant to a variety of broad-spectrum antibiotics. On the other hand, most of the anti-infective APIs have low physisorption by the cells due to their deficient penetration ability and solubility [91]. The demand for the development of new effective antibiotics remains great. Despite that, the invention of new therapeutic agents involves complicated laboratory experiments and clinical trials, which are time-consuming at a high cost. Therefore, the existing carbon-based nanomaterials, such as CNTs are applied to administer the therapeutic agents in the infected regions, to overcome the bacterial resistibility [92,93], and to enhance the solubility of therapeutic drugs [93]. For instance, therapeutic agents named amphotericin B is less soluble in water and commonly used for the treatment of fungal infection. Parenteral administration of this drug is prohibited due to the possible formation of aggregation in the bloodstream. To resolve this, formulation of amphotericin B with MWCNT has been proposed: (1) to enhance the cellular uptake, (2) to enhance the therapeutic effect against different pathogens, (3) to improve their solubility in water, and lastly (4) to reduce the formation of aggregation in the bloodstream after parenteral administration [94]. It has been reported that amphotericin B conjugated with MWCNT shows a significant reaction against different fungal strains, such as *Candida albicans*, *Candida parapsilosis* ATCC 90118, and *Cryptococcus neoformans* ATCC 90112 [94].

In addition to the study, API-modified with MWCNTs was absorbed rapidly by the mammalian cells and showed no toxicity effect. The integration of antibacterial agents, such as dapsone with MWCNTs was revealed to protect the therapeutic agent from being metabolized. Hence, the anti-mycobacterium activity is increased, and the systemic cytotoxicity to the liver can be reduced significantly [93].

4.5. Gene therapy

Gene therapy was first implemented in 1980 and played its role in altering the genetic defects through the therapeutic delivery of nucleic acids inside cells. The transportation of nucleic acid into the targeted cells requires a reliable and robust delivery system for viral and non-viral genetic systems [44]. In this respect, the intracellular gene transportation by nano-sized carriers, such as CNTs, liposomes, and polymeric-based nanoparticles are intensively studied in recent days. The main factors of choosing these nanoarchitectures are due to their flexibility with respect to immunogenicity, the diameter of nucleic acids, and the suitability of scaling-up process [95].

In general, cationic polyelectrolytes, such as dendrimers, protamine sulfate, and polylysine make decent tools to develop non-viral therapeutic delivery systems for DNA [96]. After noncovalent binding with the nucleic acid, these systems improve the cellular uptake capacity of DNA by endocytosis and safely transport them to the nucleus. To achieve the same result with polycationic carbon nanotubes, many polycationic functionalized-CNTs have been established to transport plasmid DNA to the human cells. The findings show that the transported plasmid DNA is compressed around carbon nanotubes and the therapeutic system is reported successful to induce marker gene upregulation. The results have convincingly validated the approach for gene therapy [44].

4.6. CNT-liposomes conjugate based drug delivery system

CNTs are extensively explored as vehicles for therapeutic agent delivery applications due to their ability to facile transportation by cellular membranes. The covalent of CNTs binds with the drug-loaded liposomes and form conjugates between liposomes-CNT [97]. This approach can be reliable in delivering a large amount of therapeutic agents across cellular cells via covalently attached liposomes. A large number of drug molecules can be loaded inside the cavity of each CNT and could be utilized for target-specific treatment. Modification of CNTs made new prospects in the investigation of their biological applications. Lately, there are reported accomplishments of functionalized-CNTs in the drug delivery systems, with manifested stable biological application, e.g., higher cellular uptake, types of drug, and nucleic acid delivery [28,44, 53,68,70].

4.7. CNTs-nanocomposites for targeted drug delivery

CNTs are the most studied allotropic form of carbon. CNTs are among a highly competent vehicle, which has attracted growing attention for transporting several therapeutic molecules into the cells. Their natural morphology makes it easier to penetrate across the biological membrane without causing any damage [98–101]. As discussed earlier, the molecules of drug are adhered to CNT sidewalls by their surface modification (covalent or non-covalent) bonding present between functionalized CNT and molecules of drug. But these modification methods have also certain advantages and limitations. For this, to resolve the inequity of drug molecules discharge in the microenvironment of tumor cells, researchers have been tested some external stimuli via an electric field, light, pH, temperature, and a combination of all these parameters. To determine the thermo-responsive delivery of biomolecules, Kang et al. (2017) developed chitosan-modified carbon nanotube (CNT) with thermo-sensitive polymers, such as 1-butyl-3-vinyl imidazolium bromide (NIPAAm-co-BVIm) and poly-N-Isopropyl acrylamide (NIPAAm), followed by bovine serum albumin (BSA) protein encapsulation at temperature (37°C). The authors found that the discharge of protein (BSA) happened only above the lower critical solution temperature (LCST) of poly-VBIm at 38-40°C [102]. In contrary, the Shi group applied an electric field in order to discharge the ibuprofen from a prepared hybrid hydrogel comprised of bacterial cellulose, sodium alginate, and MWCNTs [103]. Besides, Estrada and colleagues reported the near-infrared (NIR) light and temperature-responsive discharge of

Table 3
An updated summary of CNT's patents[a].

Reference	Title	Patent number	Date of publication
[120]	Drug delivery and substance transfer facilitated by a nano-enhanced device having aligned carbon nanotubes protruding from device surface	US20150238742A1	August 27, 2015
[121]	Targeted self-assembly of functionalized carbon nanotubes on tumors	EP2797605A4	July 8, 2015
[122]	Sharp tip carbon nanotube microneedle devices and their fabrication	US8764681B2	July 1, 2014
[123]	Use of carbon nanotubes for preventing or treating brain diseases	EP2594289A2	May 22, 2013
[124]	Hydrophobic nanotubes and nanoparticles as transporters for the delivery of drugs into cells	US20130034610A1	February 7, 2013
[125]	Carbon nanotube-polymer composite coating film which suppresses toxicity and inflammation and has improved biocompatibility and adjusted surface strength	WO2012060592A3	August 16, 2012
[126]	Method for preparing a highly dispersive carbon nanotube for reducing in vivo immunotoxicity	WO2012057511A2	May 3, 2012
[127]	Drug delivery by carbon nanotube arrays	US20120058170A1	March 8, 2012
[128]	Noncovalent sidewall functionalization of carbon nanotubes	US8029734B2	October 4, 2011
[129]	Poly (citric acid) functionalized carbon nanotubes drug delivery system	US20100324315A1	December 23, 2010
[130]	Chitosan/carbon nanotube composite scaffolds for drug delivery	US20100266694A1	October 21, 2010
[131]	Compositions and methods for cancer treatment using targeted carbon nanotubes	US20100184669A1	July 22, 2010
[132]	Functionalization of carbon nanotubes with metallic moieties	US20100173376A1	July 8, 2010
[133]	Carbon nanotube-based drug delivery systems and methods	US20100021471A1	January 28, 2010

[a] Adapted from Ref. [145].

methylene blue from hydrogel carrageenan-k-MWCNTs [104].

Up to date, several drug molecules have been used to load onto the carbon nanotubes, such as paclitaxel [105], oxaliplatin [106], doxorubicin [107], and docetaxel [108], etc., to show the efficacy for *in-vivo* and *in-vitro* cancer treatment. In addition, Dai and colleagues have widely studied the modified CNTs for the *in-vivo* and *in-vitro* delivery of drugs [20,50,109,110]. They discovered a novel approach to develop a highly water-soluble CNT for trapping drug molecules [9]. Jain et al. (2015) determined and compared the *in-vivo* and *in-vitro* study of cancer-targeting propensity of PEG-modified MWCNTs anchored with estrone (ES) and doxorubicin (DOX) loaded folic acid on MCF-7 tumor-bearing Balb/c mice [111]. They observed that DOX/ES-PEG-MWCNTs treated mice exhibited a longer period of survival after 43 days compared to other groups of mice treated with PBS for 12 days and DOX for 18 days. Another group, Khandare and colleagues reported that calcium phosphate-crowned MWCNT loaded with drug (CNT-GSH-G4-CaP) could be used for the intracellular release of anticancer therapeutic drugs [112]. However, Risi et al. (2014) gradually noticed the loading efficiency and a new anticancer therapeutic drug release on CNTs [113]. The Xu group developed a nanosystem, comprised of amine-terminated PEG-modified polydopamine (shell)-CNT (core) for targeted drug delivery to improve the biocompatibility of CNT [114]. Mejri et al. (2015) reported on the theoretically releasing and loading of cisplatin from/onto CNT [115]. Moreover, CNTs have the capacity to absorb strong NIR light, which makes them an efficient photothermal agent. Su and colleagues developed a nanosystem, composed of iRGD-polyethyleneimine (PEI) modified multi-walled carbon nanotube (MWCNT) followed by candesartan (CD) conjugation. The iRGDPEI-modified MWCNT-CD nanosystem was placed with plasmid AT-2 (pAT-2). The candesartan (CD) and iRGD were applied to target the ATIR, avb3-integrin of endothelium and lung tumor cells, respectively. As a chemotherapeutic, CD demonstrated synergistic downregulation of VEGF when incorporating with the pAT-2 and effectively inhabited angiogenesis [116].

Currently, Dong group has developed another nanosystem, comprised of TAT-chitosan modified MWCNT loaded with DOX in order to combine chemo and photothermal therapy [117]. Kim et al. (2017) prepared the nanodrug of CNT-ABT737 coated with PEG to enhance apoptosis in cancerous cells, which targeted the mitochondria [118]. The mitochondrial membrane disruption, which led to cytosol discharge of nanodrug resulted in apoptosis of lung cancer cells. Also, they found that the material showed a significant therapeutic efficacy *in-vivo* study. Song et al. (2016) prepared a CNT ring coated with gold nanoparticles (CNTR) that had superior optical and Raman signal properties. They reported the improved signaling of photoacoustic (PA) and photothermal changing behavior of CNTR-Au [119] and this material plays a significant role in the image-guided treatment of cancer.

5. Recent CNT's patents as a drug delivery system

CNTs are the most widely studied drug delivery carriers in recent years. Encouraged by spectacular progress, the scientific community pays much attention to improve the structural properties of these materials to be used as an effective drug delivery carrier with low cytotoxicity. From this standpoint, there are various patents related to CNTs on the fabrication, purification methods, functionalization, toxicology profiles, and encapsulation strategies, as summarized in Table 3.

6. Toxicology/biosafety profile of CNTs

In the modern age of medicine, carbon nanotubes offer another possible platform whereupon many difficulties associated with conventional methods of therapeutic are addressed simultaneously [51,134]. Considering all the challenges which were comprehensively observed in this study, the toxicological profile of these nanomaterials is one of the main challenges that needs further investigation. For this purpose, researchers initially harped about the safety profile of these materials and insisted that no apparent toxicity caused by CNTs [134,135]. On the other hand, some researchers claimed that CNTs produced toxic effects, particularly during intravenous and pulmonary administration of nanomaterials [136,137]. There was inconsistency reported in different studies, which has deprived its wide application in the biomedical field. It came utterly clear that a novel procedure should be developed for the synthesis method of CNTs and the characterization needs to be done by using reliable models and approaches.

Despite the challenges faced, the functionalization of CNTs with polyethylene glycol (PEG) [28], surface modification with diethylentriaminepentaacetic dianhydride [55], surface coating with immunoglobulins [138], manipulation with genetic materials [139], adhering to blood proteins [140], conjugation with RGD and PEG peptides [55], and surface coating with vitamin E [141] are the few strategies among many others that brought accomplishment. To summarize, the pure form of CNTs is very hard to atomize in organic solvents and aqueous solutions. Therefore, the toxicity of pure CNTs is high than functionalized ones, which influence the biological responses. An appropriate

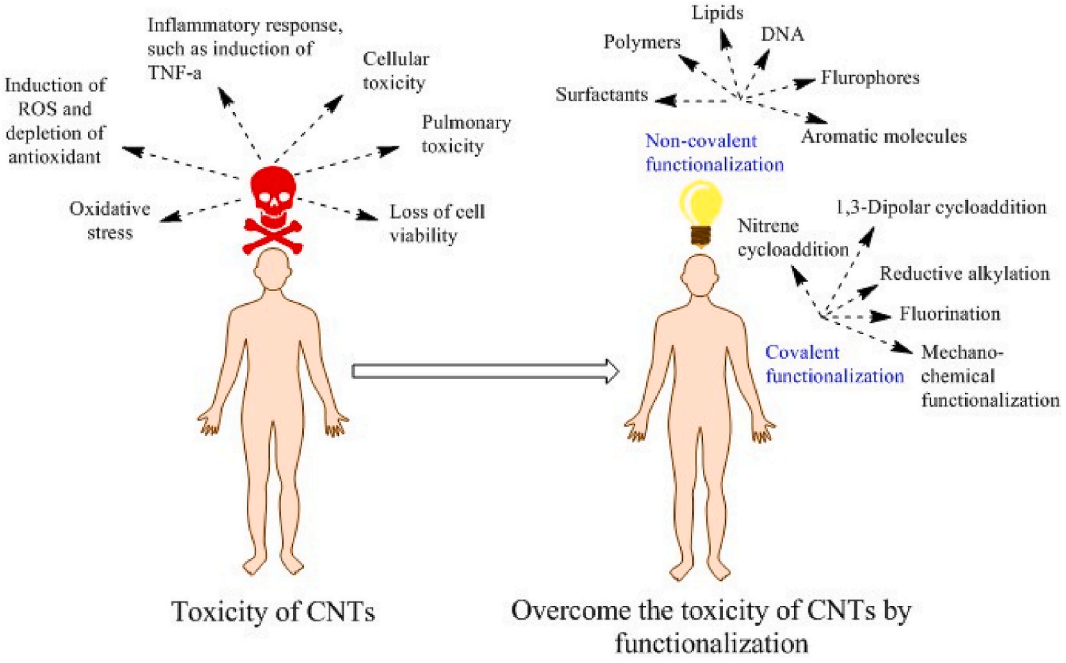

Fig. 5. Toxicity of CNTs and their possible resolution. (Reprinted from Critical Reviews™ in Therapeutic Drug Carrier Systems, 35(4), V. Mishra, P. Kesharwani, Biomedical Applications and Toxicological Aspects of Functionalized Carbon Nanotubes, 293–330., © 2018, with permission from Begell House, Inc.).

functionalization approach is needed to make the dispersion of CNTs in solvents by attaching other molecules to the surface of nanotubes [142]. The covalent or noncovalent functionalization of CNTs may also reduce toxicity associated with non-functionalized nanotubes (Fig. 5).

7. Conclusion and future perspective

CNTs have been widely used in recent days to deliver therapeutic agents to the targeted tissues and cells due to their physicochemical properties, high aspect ratio, good electrical and mechanical properties, and the physisorption to the cell membrane. The good compatibility of CNTs with all notions of manifold functionalization helps to reduce systemic toxicity and improves the efficacy of therapeutic agent delivery. CNTs can also be coated with different compounds, which play a respective distinct role in different areas: as diagnostic agents to examine the path of drug delivery system, stealth agents to evade the immune system, targeting agents to minimize side effects, and drugs carriers to provide therapeutic effects. In this context, the application of CNTs is producing positive therapeutic result particularly in treating various cancer cells as compared to the conventional method, such as spraying the therapeutic agents to the infected tissues.

However, one of the main challenges in the application of CNTs is its hydrophobicity. Unlike other materials such as liposomes, CNTs are non-biodegradable and non-disposable that their biological cycle after drug releasing in the cells remains unclear. Some verified studies showed that CNTs could play an important role as delivery systems for genes, antigens, and drugs across cell lines with a little cellular toxicity [143]. However, the potential toxicity and cellular uptake of CNTs in the biological systems remain uncertain [137]. Several *in-vivo* and *in-vitro* studies conducted by researchers are inconclusive due to different evidence established to the cell lines. In these various reports, there are problems associated with the sizes of CNTs, multiple attached ligands, accumulation in the biological system after delivery, diverse surface and physiological properties of CNTs, and the possible occurrence of hypersensitivity reactions during the administration of these nanomaterials. Moreover, certain metal catalysts (*i.e.*, free iron, nickel, and transition metals) are used for the synthesis of CNTs that could be hazardous to human health [144]. For this reason, current research on the noncovalent or covalent functionalization of CNTs has been extensively carried out. The amphiphilic molecules such as PEGylated polymers or phospholipids are used for the chemical functionalization of CNTs in order to exploit their biomedical applications [28]. Consequently, extensive research on toxicological studies is required to further investigate the synthesis method in minimizing the toxicity of CNTs in the biological media.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

This project was supported by the Research Collaboration between Faculty of Health and Medical Sciences, and Faculty of Innovation and Technology, Taylor's University Lakeside Campus, Malaysia under the Flagship Grant with project code: TUFR/2017/001/05.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jddst.2020.101855.

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