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Nanotube Platforms For Drug Delivery Applications

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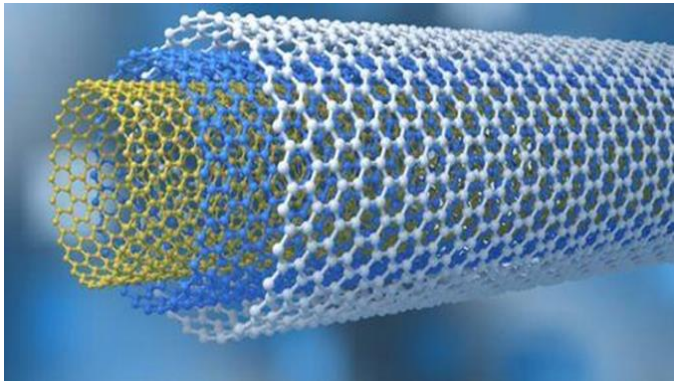
Introduction

- Nanotubes have an important role in drug delivery technology because of their unique and favorable properties such as (Losic & Simovic, 2009).
  - Low cost.
  - High loading capacity.
  - High surface area.
  - Controllable structure.
  - Chemical resistivity and mechanical rigidity.



- Carbone nanotubes (CNTs) are considered as an ideal material for different types of applications(Hilder & Hill, 2008).

- CNTs firstly discovered by Japanese physicist Sumia lijima in 1991 (Sharma et al., 2016).
- Carbon nanotubes (CNTs) have been employed as efficient delivery system of many drugs for example antineoplastic agents, cardiovascular drugs, anti-infective anti-inflammatory drugs and genes.
- There are many other nanotubes such as boron nitride, silicone and boron carbide and others that can be used for drug devilry applications (Hilder & Hill, 2008).

Aim of the review

- To understand the CNTs applications in drug delivery, what the kinds of drug molecules have been used and the effect of CNTs on the drug properties (solubility, stability, therapeutic efficacy and toxicity).

Types of Carbon nanotubes (CNTs)

- Regarding of CNTs diameter, lengths and presence of the number of graphite sheets, CNTs are categorized mainly into four types (fig. (1))

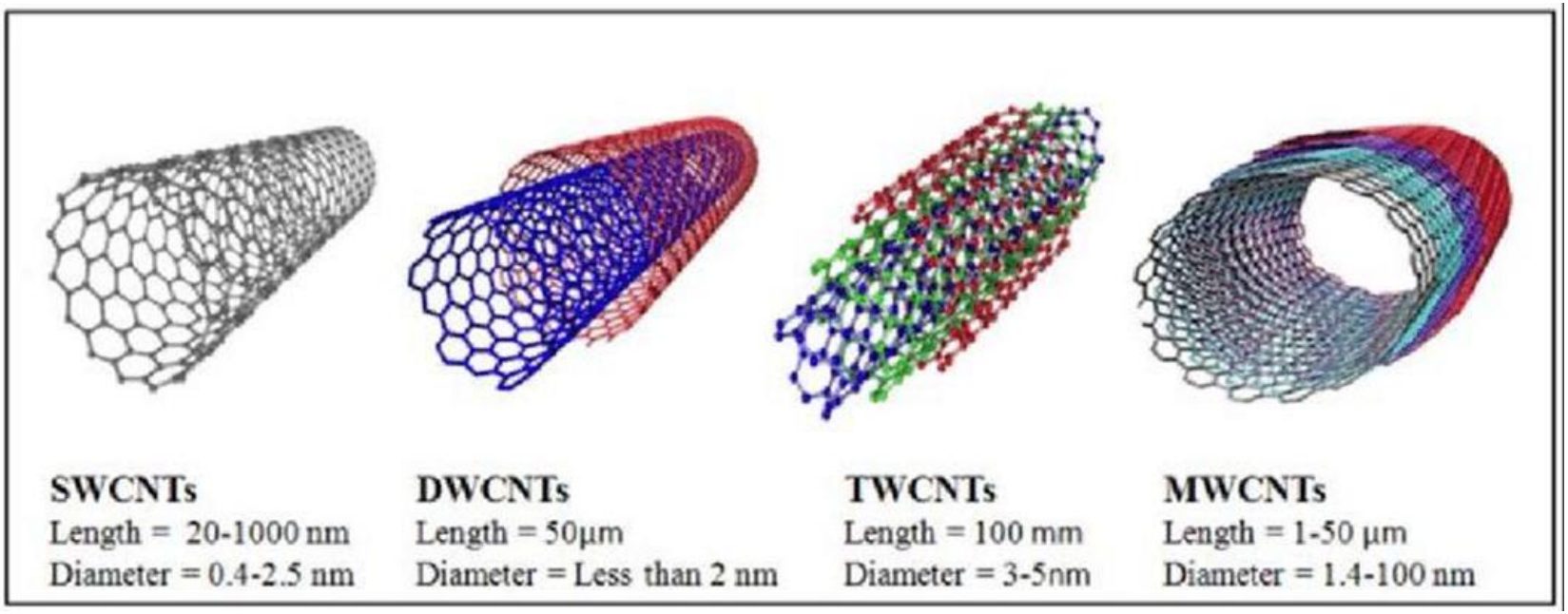


Fig. (1).Types of Carbon nanotubes (Sharma et al., 2016).

Functionalization of CNTs

- CNTs are insoluble in most types of solvents or media due to (Alpturk et al., 2018).
  - Strong van der Waals interactions between the CNTs.
  - Their hydrophobic feature.
- Functionalization of CNTs is important to improve biocompatibility, dispersibility and reducing the aggregation behavior of nanotube.
- Functionalization can also provide functional sites for drugs and targeting agents attachment (Alpturk et al., 2018).

Types of functionalization

- Covalent Functionalization
- Non-Covalent Functionalization

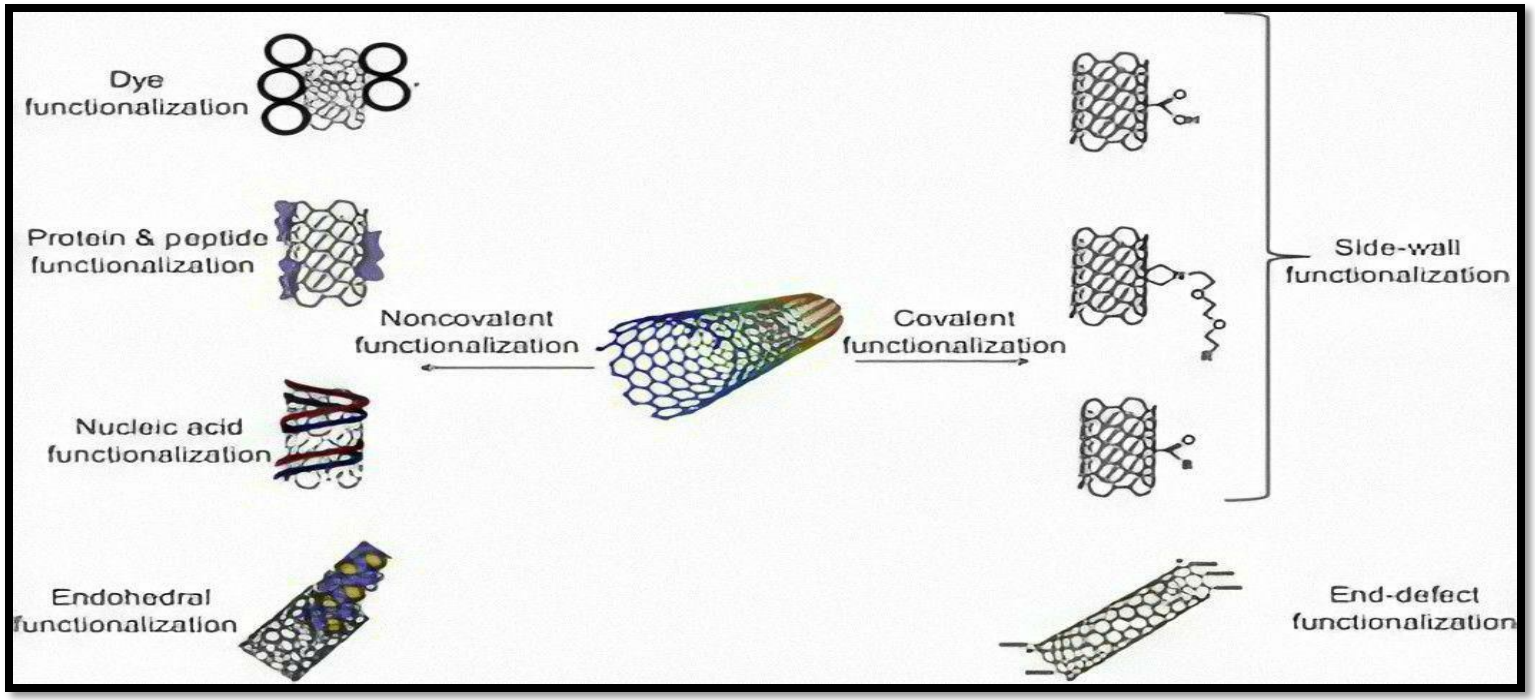


Fig. (2). Common strategies for CNTs surface functionalization (Grumezescu, 2016).

Pharmacokinetics and Distribution of CNTs

- Functionalized SWCNT&MWCNT accumulate in the muscle, skin and kidney and excrete in the urine (Riviere, 2009).
- Simply dispersed CNTs are easily distinguished by macrophages and cleared from blood very fast (Yang et al., 2012).
- There are different factors that may affect the distribution of CNTs within the body(Sharma et al., 2016):

➢ Types and density of functionalization,

➢ Length and Shape of CNTs

➢ Degree of aqueous dispersibility of CNTs

Metabolism of CNTs

- The metabolism of CNTs affects their biomedical applications and also might produce undesirable toxicity.
- Biodegradation of SWCNTs was observed in vitro through enzymatic catalysis.
- Neutrophil myeloperoxidase degradation considerably reduced the pulmonary toxicity of CNTs.
- The functional groups on CNTs are much easier to fall off from CNTs upon metabolism (Sharma et al., 2016; Yang et al., 2012).

Cellular uptake of CNTs

- The mechanisms that could control cellular uptake and release of CNTs till now under the research.
- Essentially there are several uptake mechanisms have been reported:-
  - Phagocytosis.
  - Endocytosis (Energy Dependent Pathway).
    - Clathrin Mediated Endocytosis (CME).
    - Caveolae mediated endocytosis.
    - Receptor Mediated Endocytosis.
  - Transcytosis.

Drug loading onto CNTs

- CNTs have high loading capacity because of their high surface area to volume ratio and hollow core.

- The loading capacity of CNTs could be enhanced by decorating hydrophilic or amphiphilic polymers on their surface → provide extra space for drug loading.

- Incorporation of the drug into CNTs either by (Alpturk et al., 2018):
  - Encapsulation inside the cavity.
  - Binding on the surface upon functionalization.

Application of CNTs in drug delivery

- Anti-cancer therapy
- Anti-infective drug delivery
- Anti-inflammatory drugs delivery
- Cardiovascular drug delivery
- Neurodegenerative diseases and Alzheimer drug delivery
- Vitamins delivery
- Peptide and protein delivery
- Genes delivery

Application of CNTs in drug delivery

➢ Anti-cancer therapy:

- The current treatments of cancer by surgery, radiation, and chemotherapy lack of selectivity towards cancerous cells, kill healthy cells and cause systemic toxicity.
- CNTs can be used for delivery such drugs to increase the selectivity, decrease the toxicity and so increase the therapeutic activity of anticancer drug (Alpturk et al., 2018).

○ Doxorubicin when loaded onto SWCNTs ⟶ higher cytotoxicity obtained by 2-4 folds against leukemia cells (He et al., 2013).

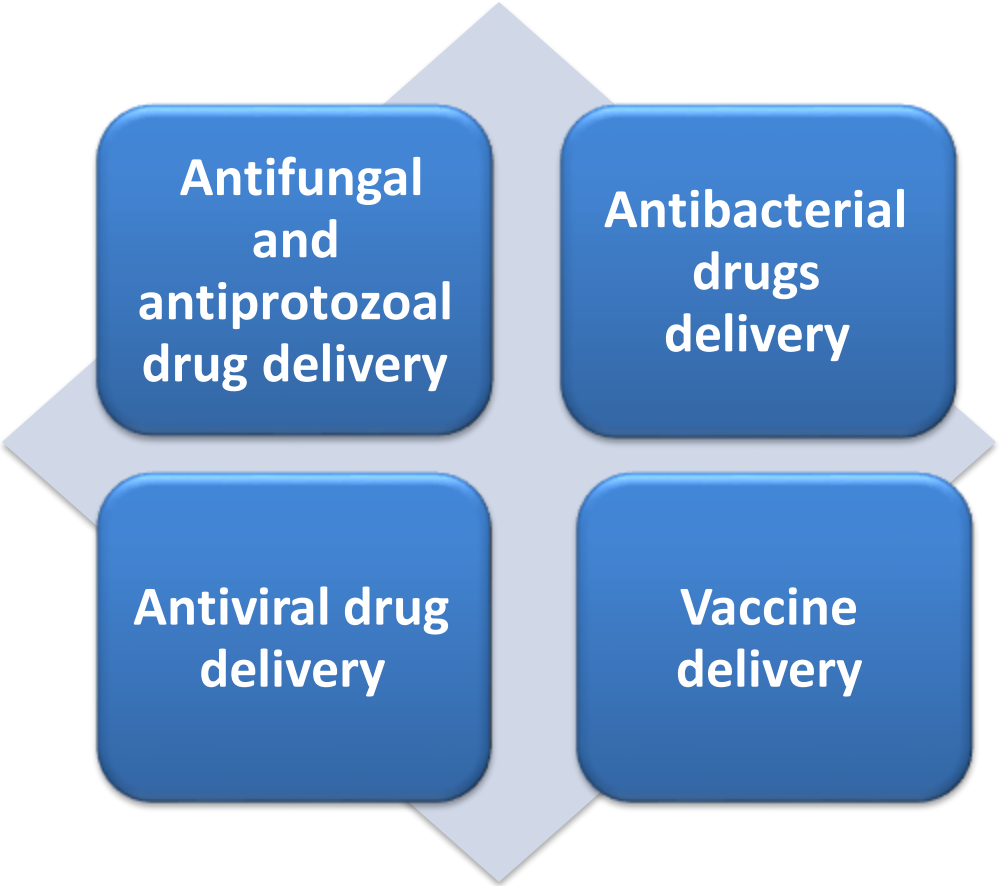
- Epirubicin (EPI) - CNTs ⟶ changes the distribution and elevates effective concentration at the tumorous site (Vashist et al., 2011).

- Containment cisplatin within the CNT ⟶ decrease the side effects of this drug (nephrotoxicity, neurotoxicity, ototoxicity and others) and increase the cellular permeability and selectivity to the prostate cancer cells (Alpturk et al., 2018).

- SWCNT- paclitaxel conjugate ⟶ has higher effectiveness in suppressing tumor growth and less toxic effect on normal organs a murine breast cancer model (He et al., 2013).
- CNT have a valuable role in the enhancement the efficacy of antitumor immunotherapy(but the mechanism remains unknown) (He et al., 2013).
- When embryonic stem cells (ESC) conjugated with MWCNTs ⟶ the therapeutic effect was found to be improved in a colon cancer induced C57Bl/6 mouse (Sharma et al., 2016).

➢ Anti-infective drug delivery

- CNTs are promising alternatives to concentrate drugs in pathogenic cell, and then overcome the bacterial resistance (Alpturk et al., 2018).



➢ Antifungal and antiprotozoal drug delivery

- Amphotericin B - MWCNT conjugation ⟶ ↑ water solubility, ↑the cellular uptake, and better antifungal activity obtained (Alpturk et al., 2018).
- Dapsone – MWCNTs conjugation ⟶ protect the drug from unwanted metabolism, ↑the activity and ↓liver toxicity (Alpturk et al., 2018).

➢ Antibacterial drugs delivery

- Isoniazid – CNTs conjugation ⟶ enhances the solubility and maintains the stability of the drug molecule (Kumar et al., 2014).
- Doxycycline/SWCNTs complex ⟶ did not show any bacterial resistance and provides only minor increase in efficacy (Khazi-Syed et al., 2016).

- SWCNTs- methicillin complex ⟶ 40-fold efficacy enhancement compare to conventional antibiotics (Khazi-Syed et al., 2016).

- **CNTs for antiviral drug delivery**
  - Protoporphyrin IX (PPIX)- MWCNT conjugation ⟶ reduction of Protoporphyrin used dose (about 250 fold) also prevention of the drug resistant (Kumar et al., 2014)

➢ Vaccine delivery

- CNTs act as carrier system for delivering safe and effective synthetic vaccines (Sharma et al., 2016).
- The linkage of an antigenic peptides (bacterial or viral) with CNTs permits of keeping intact antigen conformation thereby, inducing antibody response with the right specificity (He et al., 2013).

➢ Anti-inflammatory drugs delivery

- Indomethacin (NSAID)- MWCNs ⟶ promote the hydrophilicity and altered the membrane porosity (Alpturk et al., 2018).
- Other drugs that combined with CNTs show good activity such as Ketorofen, Dexamethason and Nimesulide.

➢ Cardiovascular drug delivery

- Carvedilol (CAR) - MWCNTs ⟶ improve the CAR solubility and enhancement in drug bioavailability (Kumar et al., 2014).
- Nifedipine - SWCNTs ⟶ efficient transportation and translocation (Kumar et al., 2014).
- Captopril - MWCNTs ⟶ higher drug absorption (Kumar et al., 2014).
- Clonidine and Dilitiazim each one of them when conjugated with CNTs give a better properties to the drug itself.

➢ Neurodegenerative diseases and Alzheimer drug delivery

- Acetlycholine /SWCNTs ⟶ deliver and release of Ach into the brain with ↑ safety rang in Alzheimer's induced in mice (Sharma et al., 2016).

➢ Vitamins delivery

- vitamin B3 (Nicotinammide) and vit. C improved carrier delivery system obtained with CNTs and maintained the stability of these vitamin molecules which are unstable (Kumar et al., 2014).

➢ Peptide and protein delivery

- Erythropoietin (EPO) - CNTs conjugation ⟶ showed improved GI absorption and higher serum level (Vashist et al., 2011).
- Streptavidin/ SWCNTs complex ⟶ exhibit improved stability and strong biotin recognition capability (Vashist et al., 2011).

➢ Genes delivery

- Plasmid DNA / CNTs ⟶ enhance the cell membrane transportation with an efficient delivery of pDNA and expression of b- galactosidase (marker gene) in Chinese hamster ovary (CHO) cells(Kumar et al., 2014).

Toxicity of CNTs

- Several cytotoxicity mechanisms have been showed with CNTs include(Rastogi et al., 2014):
  - Oxidative stress.
  - Malignant transformation.
  - DNA damage and mutation.
  - Formation of granulomas, and interstitial fibrosis.
- Functionalized CNTs could also cause toxicities i.e. anionic func.→ ↓production of profibrogenic cytokines and growth factors (Rastogi et al., 2014).
- CNTs can mechanically block the large air ways in rat lungs and induce dose-dependent interstitial granulomas and pulmonary injuries in mice (Kumar et al., 2011).

Conclusion

- Carbon nanotube CNT has been considered as the most commonly used nanotube for drug delivery .
- CNTs have unique and favorable properties (high surface area, biocompatible , non immunogenic and high drug load ability etc.).
- Anticancer, antibiotic, anti-inflammatory , proteins, peptide and many therapeutic agents have been combined with CNTs.
- Better drug properties obtained with CNTs (↑solubility, ↑stability , ↑targeting delivery, efficient activity, ↑cellular permeability, ↓ toxicity …).
- Aggregation phenomenon of CNTs, presences of metal catalysts, length and types of CNTs and other factor can induce some types of toxicity.
- oxidative stress, inflammatory responses and malignant transformation are some mechanism by which CNTs induce toxicity.

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