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REVIEW ARTICLE

Carbon Nanotubes: Pharmaceutical Applications

Pravina N Gurjar[1], Sujay Chouksey[1], Ghanshyam Patil[1], Nivedita Naik[1], Surendra Agrawal[2]

[1] Sharadchandra Pawar College of Pharmacy, Otur, Tal: Junnar, Dist: Pune, India 410504

[2] Shobhaben Pratapbhai Patel School of Pharmacy & Technology Management, SVKMs NMIMS, Mumbai, India 400056

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ABSTRACT

The distinct structural properties of carbon nanoparticles, in particular their high aspect ratio and propensity to functional modification and subsequent use as carrier vectors, as well as their potential biocompatibility, make them useful for pharmaceutical nanodelivery. It is believed that the steady development and applications of CNTs can serve as a versatile tool for drug delivery. Therefore, the present review described about application of carbon nanotubes in drug delivery system.

Keywords: Carbon Nanotube, CNTs, Nano in Drug Delivery.

1. INTRODUCTION:

Nanoparticulate drug delivery system offer certain advantages over conventional dosage form, which include improved efficiency, reduced toxicity, enhanced biodistribution with improved patient compliance[1]. Typically the nanotubes are about 20-150 A^0 in diameter and about 1000-2000A^0 in length.. Carbon Nanotubes (CNTs) have been found to show good carrier properties by serving as a transporter of biomolecules to the target site of diverse array of compounds, including drugs, vaccines, small peptides, proteins, nucleic acid, vitamins and sugars [2,3].

Functionalize carbon nanotubes (f-CNTs) are emerging as new tool in the field of nanobiotechnology and nanomedicine. CNTs can be easily manipulated and modified by encapsulation with biopolymers or by covalent linking of solubilizing groups to the external walls and tips[4,5,6]. Properly f-CNTs are highly water soluble and serum stable and have been shown to enter mammalian cancer cells and help transport biological molecules without affecting their activity. Functionalized carbon nanotubes exhibited relatively long blood circulation time and low uptake in the reticuloendothelial system without obvious side effects, which make them as suitable nanovectors for drug delivery purposes.

This review focuses on the use of CNTs as pharmaceutical excipients, includes a brief description of the synthesis, purification, characterization, and quality control of CNTs, and provides a “mini-monograph” of CNTs that catalogues their chemical and physicochemical properties relevant to pharmaceutical applications. Carbon nanotubes are basically classified on the basis of atomic layer of arrangements into Single walled carbon nanotubes (SWCNTs) which are perfect graphene sheets in which graphene being the same poly aromatic mono- atomic layer made of hexagonal display of Sp^2 hybridized carbon atoms, rolled up into a cylinder, with the hexagonal rings put in contact to join seamlessly[7,8]. Another type is multi-walled carbon nanotubes (MWCNTs) consisting of multi walled graphene sheets rolled up in concentric CNTs, filling each other’s inner cavities to end up with Nanotubes filled within Nanotubes. SWCNTs with

*Corresponding author: Pravina Gurjar | Sharadchandra Pawar College of Pharmacy, Khamunde, Otur | Tal: Junnar Dist: Pune, India 410504 | Email: gurjar_pravina@rediffmail.com | Cell No: +919011499662

additional graphene tubes around the core of SWCNTs are called MWCNTs.

DISPERSION OF CNTS

CNTS require dispersion, dissolution or debundling of nanotubes to individual fibres for their Pharmaceutical application.

Generally four approaches have been used to obtain CNTs dispersion[9,10]. First by functionalization of CNT sidewalls by treatment with different oxidizing agents like HNO_3, H_2SO_4, Potassium permanganate; H_2O_2 for introduction of different functional groups on the CNT surface. In surfactants-assisted dispersion higher surfactant concentration and less sonication energy is required to achieve maximum dispersion. The surfactants molecules are adsorbed on the surface of the MWCNTs and prevent re-aggregation so that the colloidal stability of MWCNT dispersions could be maintained for several months. The other methods include solvent dispersion and biomolecular dispersion (example; single-stranded DNA wrapping around CNTs). CNTs solubility varies depending on the source of nanotubes (i.e. method of production), the solvent and the dispersion procedure.

MODE OF ACTION AND CELLULAR UPTAKE OF CNTs

The cellular uptake of CNTs has been confirmed in a range of studies but the mechanism of CNTs penetration into cells is still not well understood[11,12]. Because of their needle like shapes, CNTs might be able to perforate cellular membrane and pass into the cellular components without causing apparent cell damage. An *in vitro* CNTs nanoinjector system has been developed by chen and coworkers. The nanoinjector was designed using an atomic force microscope (AFM) tip and functionalized MWNT's attach to a model carbon compound via a disulfide linker. The MWNT's nanoinjector successfully transported into the cell where the disulfide bond was broken, resulting in the release of the carbon compound within the cytosol.

AFM-controlled MWNT's-based nanoinjector was able to penetrate into a cell and release the attached carbon compound after the breakage of the disulfide bond[13,14]. This was followed by successful retraction of the nanoinjector with no apparent cell damage being produced.

The perpendicular positioning of the nanotubes to the cell membranes suggests that uptake of CNTs are similar to that of nanoneedles which diffuse through cell membrane without causing cell death. Some studies suggested that uptake of the nanotubes occurred via endocytosis.

METABOLISM AND TRANSFORMATION OF CNTS

The skeleton of CNTs is relatively more stable than their functional groups[15]. In *in-vivo* the CNTs even stayed as long as 3 months. During the purification and shortening processes, CNTs would go through strong acid (HNO_3, HCl and H_2SO_4) treatment, sometimes assisted by ultrasonication. Under such harsh conditions, the carbon skeleton only breaks at the injured defects. The stability of CNTs is also reflected by the long-term accumulation *in vivo* without being metabolized. For the studies of biocompatibility and applications, the bio-degradation of CNTs is an important factor to be regarded. The stability of carbon skeleton also implies that CNTs are hard to be metabolized to small molecules, which may easily be excreted via urine and feces. More attention should be paid to design proper surface property of CNTs to accelerate the beneficial excretion of CNTs.

In contrast to the stability of carbon skeleton, the functional groups on CNTs are much easier to fall off from CNTs[15, 16]. Current results suggest that different functional groups could be detached from CNTs *in vivo* and this makes functionalized CNTs transformed into less functionalized or pristine CNTs. Comparing the stability of non-covalently and covalently functionalized CNTs *in vivo*, the covalently functionalized CNTs seem more stable than non-covalently suspended ones. This phenomenon indicates that covalently modified CNTs are more suitable for biomedical use *in vivo* from the stability view. A more stable suspending reagents, such as PEG-PL is preferred for the non-covalently suspended CNTs. The toxicity of SWCNTs was closely related to the oxidative stress.

APPLICATIONS OF CNTs:

A.SOLID PHASE EXTRACTION OF THE DRUGS

Drugs such as antibiotics, anxiolytics, anti-inflammatories or antidepressants have also been extracted using CNTs as SPE sorbents[17]. From the study of the literature, it is clear that small quantities of CNTs (lower than those of conventional SPE cartridges) can be used as SPE materials and thus, they may play an important role in miniaturization of extraction procedures. In some cases, these materials are more expensive than conventional SPE cartridges, however, several works have also demonstrated that highly economic CNTs (with adequate SPE performance) are also available and thus they may also represent a good economic alternative. It is very likely that commercial CNTs- SPE cartridges will soon be available, but for this purpose CNTs should be fabricated at a larger scale.

B.PREPARATION OF BIOCATALYSTS, BIOSENSORS AND BIOFUEL CELLS

Enzyme immobilizations on carbon nanotubes for fabrication of biosensors and biofuel cells and for preparation of biocatalysts are rapidly emerging as new research areas[18]. To improve enzyme stability, enzymes have generally been studied with the enzymes immobilized on a solid support. Nanomaterials serve as excellent supporting materials for enzyme immobilization, because they offer the ideal properties

for balancing the key factors that determine the efficiency of biocatalysts, including surface area, mass transfer resistance, and effective enzyme loading. Using non covalent approaches, enzymes can be less denatured upon immobilization and the intrinsic electronic structure and properties of CNTs are retained. Recently, more attention has been paid to the controlled immobilization of enzymes on CNTs. To that end, specific groups are introduced onto CNTs like organic, polymeric, and biological molecules. Through the functional groups, enzymes can be specifically and precisely bound onto CNTs. It is also necessary to study how the linking molecules interact with enzymes and affect the enzyme structure and the arrangement of enzymes on CNTs.

C.DETECTION OF TOXIC ORGANOPHOSPHORIC COMPOUNDS.

Organophosphorus compounds adversely affect CNS by inhibiting acetylcholinesterase which acts on acetylcholine neurotransmitters[19]. Carbon Nanotubes are the electrode materials and has the ability of promoting electron transfer reaction at enzymes immobilization. Acetylcholine esterase is immobilized on Nanotubes surface and then this immobilized Acetylcholine catalyses hydrolysis of thiocholine ester, forming thiocholine. This hydrolysis of thiocholine can be detected by electrochemical techniques. There is reduction in acetylcholinesterase catalytic property when it interacts with organophosphoric compounds and simultaneously the oxidation of thiocholine inhibited and this can be detected by amperometric analysis using CNTs electrodes.

D. DETECTION OF CHEMICAL SUBSTANCES

CNTs exhibit very good adsorption properties because of their high specific surface area and nanoscale structures which provide large number of sites where the chemical in gaseous form can react [20,21,22]. This adsorption of chemicals on CNTs surface after the CNTs electrical properties enable the CNTs to act as a gas sensor. Researchers developed a gas sensor based on SWCNTs whose electrical conductance, on exposure to gaseous molecules, changes quickly (e.g. NO_2, NH_3). They achieved ultrahigh sensitivity detection of NO_2 gas using composite film of SWCNTs mash doped with alkane thiol monolayer protected gold cluster (MPC).

E.CARBON NANOTUBES AS A NANOCOMPOSITE MATERIAL

CNTs can create nanocomposite materials for medical device development[23,24]. Pristine carbon nanotubes combined with nylon-12, form a nanocomposite material that can be utilized to form microcatheters for arterial cannulation. The biocompatibility of such CNT-based microcatheter is greater compared to nylononyl microcatheter and less cellular infilteration and no inflammatory reaction observed.

F. CARBON NANOTUBES IN TISSUE ENGINEERING

The carbon nanotubes can be used for tissue engineering by visualizing and enhancing cellular performance and by tracking and labeling of cells[25,26]. As tissue engineering advances, new tools for better examining and evaluating engineered tissues along with new biomaterials to direct tissue growth are needed. Carbon nanotubes may be an important tissue engineering material for improved tracking of cells, sensing of microenvironments, delivery of transfection agents, and scaffolding. Carbon nanotubes can also be incorporated into scaffolds providing structural reinforcement as well as imparting novel properties such as electrical conductivity into the scaffolds may aid in directing cell growth. Potential cytotoxic effects associated with carbon nanotubes may be mitigated by chemically functionalizing the surface.

G.DETECTION OF TOXIC PROTEINS, MICRO ORGANISMS AND ALKYLATING AGENT CONTAINING SULPHUR AND NITROGEN

By change in electrical signals, the CNTs can be used as a measuring platform for various toxic proteins which will immobilized on the CNTs[27]. Scanning electron microscope (SEM) and electrochemical chemiluminescence (ECL) can be used to test the bonds of proteins with antibodies on CNTs platform. Finally the detection can be done by integrating these sensor tips to a single conditioning and processing circuits and measurements analysis of conductance and electrical signals obtained in presence of toxic proteins.

Alkylating agents (nitrogen mustards; ethylenimes; alkylsulphonates; triazenes; piprazenes; nitrosureas.) can be detected by DNA sensing as the biological recognition element.

H.CNTs AS A CARRIERS FOR DRUGS, GENES AND ROTEINS

The acquisition of multidrug resistance poses a serious problem in chemotherapy, and new types of transporters have been actively sought to overcome it[28]. Recently, poly(ethylene glycol)-conjugated (PEGylated) multi-walled carbon nanotubes (MWCNTs) are explored as drug carrier to overcome multidrug resistance.

It is well known that cancer cells overexpress folic acid (FA) receptors, and several research groups have designed nanocarriers with engineered surfaces to which FA derivatives can be attached. Moreover, nonspherical nanocarriers (e.g., CNTs) have been reported to be retained in the lymph nodes for longer periods of time compared to spherical nanocarriers (e.g., liposomes). Thus, CNTs might be used for targeting lymph node

cancers as shown by various investigators. In some studies, magnetic nanoparticles containing the anticancer cisplatin has been trapped into folic-acid-functionalized MWCNTs. An external magnet was employed to drag the nanotubes to the lymph nodes where the drug showed release over several days and the tumor growth inhibited.

The ability of macromolecules (e.g., genes) to cross the biological barriers and be expressed within a target cell is particularly challenging, owing to their hydrophilicity and large molecular size and therefore use of viral or nonviral vectors to carry the gene and internalize it into the cell is necessary. Nonviral vectors are less competent than viral vectors and short lived; however, they are far safer. Confocal microscopy and flow cytometry have shown much greater fluorescent activity of protein and DNA when conjugated to SWCNTs as compared to the naked macromolecules indicating that CNTs are promising vectors for gene and protein. Cai and coworkers have introduced an approach to gene delivery named "carbon nanotube spearing". Plasmid DNA with a fluorescent protein was immobilized onto nickel-embedded CNTs. The formulation was "speared" into Bal 17 B lymphoma cells using a magnetic field, which produced high transfection in the target cells.

Functionalized SWCNTs have been designed as carrier for siRNA for internalization into K562 cells and subsequent inhibition of the production of cyclinA (2) and treatment of chronic myelogenous leukemia[29]. It has been found that suppression of cyclinA(2) expression using siRNA-CNTs can promote apoptosis in the targeted tumor. Streptavidin is a protein that has anticancer activity but due to its very large molecular weight (approximately 60,000 KDa), it does not penetrate through cells. A conjugate of streptavidin with SWNTs-biotin has been produced, which resulted in internalization of the protein into model cancer cells by adsorption-mediated endocytosis.

I. PHOTOTHERMAL THERAPY OF CANCER USING CNTS

CNTs are able to absorb light in the near infrared (NIR) region, resulting in heating of the nanotubes[30]. This unique property of CNTs has been exploited as a method to kill cancer cells via thermal effects.

CNTs demonstrate strong optical absorption in the near infrared (NIR) regions (NIR I: 700-900 nm, NIR II: 1–1.4 μm). NIR optical radiation has a dissemination depth of 1.6 mm into biological tissue. CNTs produce heat by light absorption and provoke the thermal destruction of those cancer cells containing sufficient CNT concentrations. To avoid damage to normal tissues, targeted CNTs have been prepared by the covalent affection of tumor-specific ligands to the CNTs. The conjugated CNTs showed good stability under physiological conditions and produce a highly specific photo-thermal killing of the targeted cells.

Antenna theory suggested that optical coupling of light with CNTs is highest when the length of the nanotubes is more than half the wave length of the incident light beam[31]. Engineering the structure of MWNTs by creating intentional surface defects might enhance the antenna properties of the nanotubes. Such engineered "defects" or dopants will cause scattering in the travelling currents and also increase the heating of the nanotube.

J. ADSORPTION AND PHOTO-CATALYTIC PERFORMANCE

CNTs can be widely utilized in photo-catalysis, catalysis and adsorption process[32,33, 34, 35,36]. These properties have been extrapolated in removal of pollutants from aqueous solutions and environment. This led in the fabrication of Nanosensors, which have number of application in Pharmaceuticals and Development processes. Nanocomposites offer chemically inert surfaces with high specific surface areas for physical adsorption and provide more adsorption sites. Presence of small amount of CNTs can enhance the photocatalytic activity of TiO_2. Carbon coated TiO_2 have been accepted for their high activity in decomposition of Poly vinyl alcohol, rhodamine B and methyl orange in water under UV irradiation.

TOXICITY OF CNTs

Despite the widely demonstrated potential of CNTs in drug delivery, research indicates these particles can potentially cause adverse effects because of their small size and extreme aspect ratio [37,38,39, 40]. The toxicity is related to properties of the CNT material, such as their structure (SWCNT vs. MWCNT), length and aspect ratio, surface area, degree of aggregation, extent of oxidation, surface topology, bound functional group(s), and method of manufacturing (which can leave catalyst residues and produce impurities). The general approach has been to consider and treat CNTs as toxic, because nanosized particles are markedly more toxic than larger sized particles. However, controversy surrounds the interpretation ascribed to CNT toxicity data. Toxicity of CNTs is also related to their concentration and the dose to which cells or organisms are exposed. Adequate modulation and care in the above mentioned parameters leads to more efficacious and low toxic CNTs.

5. CONCLUSION

CNTs are nanostructured vectors possessing some unique features which can be utilized in delivering a variety of drug ranging from low to high molecular weight. CNTs can easily be modified or functionalized due to their structural properties & can be internalized in the cells with great ease. The pharmacokinetics, metabolism and toxicity of CNTs are dependent on the physicochemical parameters of CNTs and regulated by the surface chemistry. Adequate modulation and care in the above mentioned parameters

leads to more efficacious and low toxic CNTs. Well functionalized CNTs by both non-covalent and covalent methods are promising for the biomedical applications. In doing so, PEGylation is a most efficient method to improve the *in vivo* behaviors of CNTs.

There are many interesting and promising pharmaceutical applications for CNTs but basic pharmaceutical studies on the effective dispersion of CNTs in commonly used pharmaceutical solvents (with and without surfactants), particle size characterization, purity, and stability of such dispersions will be necessary as the next steps in the use of CNTs in pharmaceutical formulations. Another possibility lies in the use of CNTs as devices for the controlled release of therapeutic agents, using the inner cavities of CNTs for nanochannel fluidic delivery. Future developments on all these aspects will surely contribute to the increased use of CNTs.

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