Review Article

Carbon Nanotubes: An Optimistic Nanomaterial with Superfluity Characteristics in Drug Delivery for the Treatment of Arthritis

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ABSTRACT

Arthritis is chronic disease that affects the joint system and induces pain and inflammation in human body. Nanotechnology based drug delivery has progressed to be viable and more attractive for the treatment of arthritis. A carbon nanotube is one of the foremost prominent nanomaterials with high surface area utilized to exhibit stable release of drugs. Nonetheless, researchers have done investigations using either single-walled carbon nanotubes (SWCNT) or multi-walled carbon nanotubes (MWCNT) to gain optimistic results in targeted delivery for arthritis disorder. In this view, functionalized carbon nanotubes are employed to deliver drugs with higher accuracy and controlled release of drugs with less toxic effects. Unfortunately, very limited investigations are reported the prospective utilization of functionalized carbon nanotubes as eminent drug carriers for arthritis treatment. Moreover, the amounts of toxicity of carbon nanotubes, as well as their aggregation in cells and tissues are the key limits that must be considered evidently. The biosafety exposure of carbon nanotubes to humans are still a source of concern. As a result, more research is needed to solve the obstacles associated with carbon nanotubes in conjugation with drugs such as agglomeration, lack of solubility and interaction mechanism with drugs. In this review, we discussed the significant characteristics and outcomes of carbon nanotubes in drug delivery for the treatment of arthritis disease. The toxic level of carbon nanotubes is projected and why the incorporation of CNTs in drug delivery is still limited in various phases is highlighted. The biosafety aspects, cellular uptake mechanism and the importance of functionalization carbon nanotubes in drug delivery are reviewed.

Keywords: Arthritis, Drug delivery system, Single-walled carbon nanotube, Toxicity, Multi- walled carbon nanotube, Nanoparticles.

INTRODUCTION

Carbon nanotubes (CNTs) progressed as a unique type of nanomaterial, exploring different possibilities in biomolecular identification and drug delivery. Their organised form, lightweight, excellent mechanical strength, good thermal conductivity, and large surface area make them as a promising material for biomedical activities.[1] Electric arc discharge, laser ablation, and chemical vapor deposition are the three primary methods for developing carbon nanotubes. High pressure, elevated temperature, and catalytic activities are employed in each process.[2] Moreover, carbon nanotubes are inaccessible in organic and aqueous solutions, and its surfaces should be amended for any kind of biological usage. For example, a chemically functionalized carbon nanotube has proved to operate as distinct delivery methods for transference of nucleic acid.[3] Carbon nanotubes are not soluble in their purest form. However, carbon nanotubes can be effectively used in biological activities by following the invention of techniques to functionalize these molecules with organic compounds and make them soluble. They can adhere or conjugate with a wide range of pharmaceutical compounds due to their large surface area.[4] Indeed, carbon nanotubes can be covalently or non-

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covalently conjugated with drugs and biomolecules to create remarkable features in targeted drug delivery. Even while tremendous progress has been made in recent decades, there are number of obstacles to address such as synthesis of carbon nanotubes with high pure rate, interactivity mechanism of drugs with carbon nanotubes as well as toxicity level.[5] Carbon nanotubes are often used as a carrier for transmission of biomolecules including proteins, DNA, and RNA. However, Kang *et al.* discovered that multi-walled carbon nanotubes were more hazardous, when they were debundled, and distributed in the solution.[6] Figure 1 shows the types of arthritis disease.

According to Magrez *et al.* and Tian *et al.* carbon-based nanomaterials, such as carbon nanoparticles, carbon nanofibers were reported to induce harmful effects to cells than multi-walled carbon nanotubes (MWCNTs).[7] On the other hand, covalently loaded single-walled carbon nanotubes (SWCNTs) had being found to exhibit significant optical or chemical characteristics that are intriguing for biomedical applications. Similarly, SWCNTs specific interactions with biomolecules may harm cell and organ functions.[8] Unfortunately, no scientific study on functionalized CNTs (f-CNTs) mediated drug delivery to the arthritic location has been published so far. Noticeably, the percentage suppression of arthritis by f-MWCNTs was observed to be considerably higher ($p<0.05$) than that of Methotrexate (MTX) loaded pristine multi-walled carbon nanotubes (MWCNTs). The pharmacokinetic and pharmacodynamic results clearly indicated that folate conjugated multi-walled carbon nanotubes (f-MWCNTs) could enhance the anti-arthritic drug's biodistribution characteristics and to target the arthritic location.[9] Dexamethasone-polyethylene-glycol (DEX-PEG) coated CNTs effectively suppressed human fibroblast-like synoviocytes (FLS) induced inflammation in rheumatoid arthritis (RA) by attaining increased drug absorption and effective intracellular drug discharged from the endosomes, thus indicating a mechanism for successful low-dose glucocorticoid (GC) treatment to alleviate inflammatory disorders such as rheumatoid arthritis and osteoarthritis.[10] Figure 2 shows the different treatment methods for arthritis.

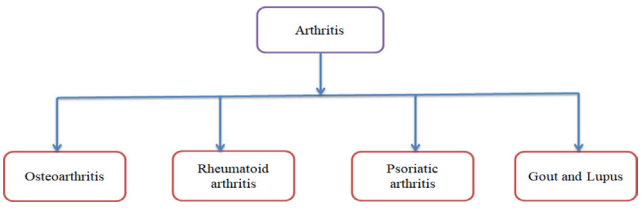

Figure 1: Types of Arthritis Disorder.

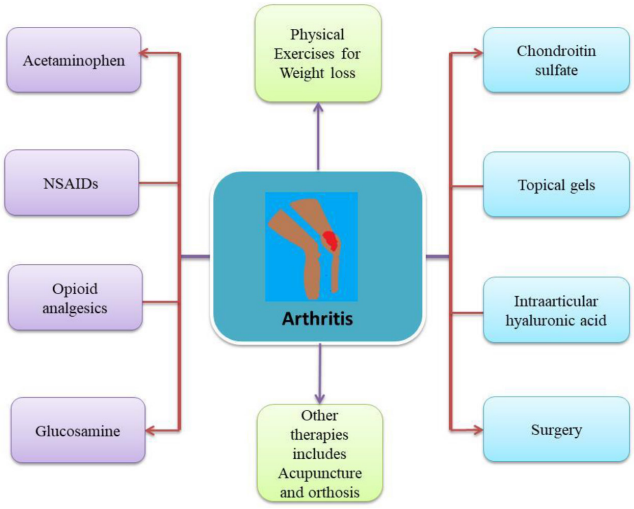

Figure 2: Treatment options for Arthritis disorder.

Carbon nanotubes can enhance osteocyte calcification while suppressing osteoclast development in bone tissues, implying that the material could significantly speed up osteogenesis. Although, when MWCNTs were injected into mice's bones and carried into synovial macrophages, a granular tissue was generated and swelling was reduced after four weeks.[11] Notable evidence on CNTs toxicity has been reported; however the outcomes are contradictory, which makes it impossible to create a consistent knowledge of CNTs toxicity. Muller *et al.* investigated the reaction of multi-walled carbon nanotubes (MWCNTs) in rat lungs. The author reported that there is a considerable development of tumor necrosis factor alpha (TNF-α) by macrophages, and demonstrated that multi-walled carbon nanotubes (MWCNTs) develop negative impact to human health.[12] Despite there are great possibilities for using CNTs as drug delivery carriers in therapeutics, one of the major barriers of utilizing single-walled carbon nanotubes (SWCNTs) as nanocarriers is their biosafety aspects. Numerous researches have concluded that SWCNTs is harmless, but previous studies have documented the impacts of SWCNTs on cells *in vitro* and tissues *in vivo*. Nevertheless, previous studies have indicated that the toxicity of SWCNTs *in vivo* is the effect of accumulation instead of high aspect ratio of carbon nanotubes. Fortunately, major impediment to effective employment of carbon nanotubes has being resolved.[13] In this review, we discussed about the significant characteristics, effective utilization and outcomes of carbon nanotubes in drug delivery for arthritis treatment. Furthermore, the biosafety aspects, cellular uptake mechanism, toxicity of CNTs and importance of functionalized carbon nanotubes are highlighted in the article.

DEVELOPMENT OF CARBON NANOTUBES AND THEIR VERSATILE PROPERTIES FOR DELIVERING DRUGS

Synthesis

Especially in comparison to other synthesis procedures, arc discharge method utilizes elevated temperatures (above 1700°C) for the development of carbon nanotubes (CNTs), which generally results in the formation of CNTs with very few structural flaws. In this view, Zhao *et al.* employed a hydrogen gas environment to create ultrafine multi-walled carbon nanotubes (MWCNTs). The hydrogen (H_2) gas produced a small amount of carbon fumes; however the evaporation of methane (CH_4) and helium (He) gases produced a significant amount of carbon fumes. It has been found that less carbon fumes were seen in the evaporation of H_2 gas, while substantially higher carbon fumes is identified in the vaporization of CH_4 and He gases.[14] Plasma rotating arc discharge method is being utilized to manufacture admirable grade of carbon nanotubes in large quantities. The plasma rotating electrode technique is a constant sustained evacuation method to produce standard nanotubes in large quantities. The modified arc discharge method for consistent CNTs production was proposed by Ishigami *et al.* The authors reported that the process could be executed continuously and ramped up for commercial purposes with CNTs yield similar to those of an optimised traditional arc technique.[15] Gamaly and Ebbesen reported that the development of vapor phase multi-walled carbon nanotubes (MWCNTs) is formed when carbon vapors condensed and nucleated. Wang *et al.* utilized arc discharge method to synthesize MWCNTs in a hydrogen atmosphere. Subsequently, single-walled carbon nanotubes (SWCNTs) are developed on a massive level in a helium atmosphere. The pulsed arc technique has more benefits over various power supply sources because it does not need a pressure chamber and may be executed in normal working conditions.[16] Figure 3 shows the schematic diagram of arc discharge method.

Smalley's group invented the laser vaporization process to develop CNTs and utilized to produce cluster and extremely fine particles. The laser ablation is an excellent vaporization method for processing materials with elevated boiling temperatures such as carbon. The technology has various benefits, including standard SWCNT fabrication, diameter controlling and the synthesis of novel materials.[17] The Pulsed laser vaporization (PLV) technique showed the development of single-walled carbon nanotubes (SWCNTs) with superior structural stability and good purity. A double-pulse laser system method exhibited a positive

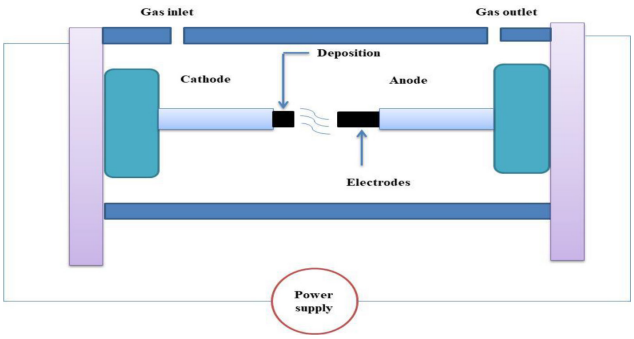

Figure 3: Arc Discharge Method.[16]

development of single-walled carbon nanotubes. To illustrate, Justyna Chrzanowska *et al.* reported that satisfactory grade single-walled carbon nanotubes (SWCNTs) were exclusively formed at fluence (F=3 $J.cm^{-2}$) for 355 nm laser wavelength, whereas for 1064 nm laser wavelength excellent outcomes were developed in the fluence range of ($1 \leq F \leq 6$ $J.cm^{-2}$).[18] Similarly, Eklund *et al.* demonstrated that the production of high quality SWCNTs are produced using a free electron laser (FEL) with 3-μm FEL radiation. Laser ablation's ability to produce SWCNTs is influenced by several factors, such as the laser's properties, flow characteristics, and target composition.[19] Certainly; the single-walled carbon nanotubes (SWCNTs) are produced under argon, nitrogen, and helium atmospheres at pressure ranging from 50 to 500 Torr by utilizing a continuous wave 10.6-μm CO_2 laser. Importantly, below 200 Torr, the quantity of SWCNTs in the soot is substantially reduced, and amorphous carbon occupies the material. The use of helium as an ambient gas resulted in the formation of insignificant quantities of SWCNTs.[20] The widespread utilization of laser ablation in high-temperature flow reactors (laser oven) is to achieve high quality SWCNTs with fewer defects. Increased input energy and a limited laser irradiating portion for evaporating intended materials are disadvantages of laser ablation.[21] The fundamentals principles of the laser ablation technique and arc discharge method are identical; nevertheless, the input source of utility is dissimilar. The diameter of CNTs can be regulated through laser power technique as reported in previous studies. Additionally, when the laser power is escalated, the carbon nanotube's diameter becomes skinny. Moreover, the ultrafast laser pluses have a lot of capability to develop huge quantities of single-walled carbon nanotubes (SWCNT).[22] Figure 4 shows the development of CNT through laser ablation method.

Particularly, the advancement of catalytic chemical vapor deposition (CCVD) for evolving carbon nanotubes can be ascribed to the primary factors such as lower

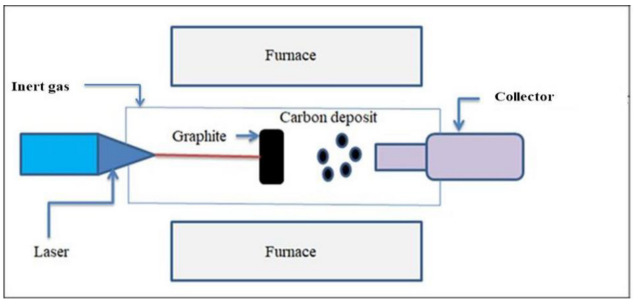

Figure 4: Laser Ablation Method.[22]

reaction temperatures resulting in lower costs, purity, ability to produce aligned carbon nanotubes, and mass production. Qingwen *et al.* looked into the effects of carrier gas on the cyclohexane CVD technique. Multi-walled carbon nanotubes (MWCNT) were created when argon was employed as a carrier gas, although when hydrogen was utilized to develop single-walled carbon nanotubes (SWCNTs).[23] Indeed, today's approved processes for CNTs development are VLS (vapor–liquid–solid) and VSS (vapor–solid–solid). The identity of the precipitated carbon is determined by several factors, such as catalyst particle size and precipitation rate. Cassell *et al.* have described scientific proof for root and tip growth mechanisms. Methane, acetylene, ethane, benzene, ethylene, xylene, carbon monoxide, isobutane, and ethanol are among the greatest prevalent carbon sources utilized by scientists around the world for CNT development by catalytic chemical vapor deposition (CCVD). Although, numerous impurities such as nitrogen dioxide (NO_2), sulphur dioxide (SO_2), and ammonia (NH_3) are incorporated to CNTs during the development method by CCVD, a thorough investigation into the incorporation of these impurities is required.[24] Nevertheless, carbon precipitates in an amorphous state and forms graphitic layers all over the metal particles when copper (Cu) is used. Normal tubes with a diameter of 20–30 nm and a length of around 10 μm were observed utilising zeolite as an assist and cobalt (Co) as a catalyst to develop tubular filaments with fine-tuned graphite layers with high quality.[25] Plasma CVD is used to generate vertically and independently aligned multi-walled carbon nanotubes (MWCNTs). As a result, certain plasma impacts may increase catalyst particle agglomeration, representing the fundamental cause of inability to develop SWCNTs using plasma CVD. According to Dai *et al.* plasma CVD was used to generate semiconducting SWCNTs exclusively. Despite, there have been other identical studies using plasma CVD and thermal CVD, the explication of this preferential growth remains unknown, and more research is required.[26] According to Hata *et al.* the "super growth CVD process," which involves the initiation of sign of water is one of the greatest effective expansions, ultimately results in significantly increased carbon nanotube development. However, carbon nanotube development is indeed a complicated process.[27] Especially, carbon nanotubes might also be developed at temperatures between 650°C and 800°C. Few studies demonstrated that carbon nanotubes are constructed over carbon nanofibers by carbon vapor deposition of xylene, toluene, and xylene. The emergence of multi-walled carbon nanotubes (MWCNTs) was noted by various researchers, and the carbon fiber's mechanical characteristics such as tensile strength and tensile modulus were significantly enhanced. Synthesis of carbon nanotubes at low temperature produced short MWCNTs with large diameters, and yet whenever the temperature has been raised from 700°C to 900°C, MWCNTs with smaller diameters were emerged.[28] M. Ghoranneviss *et al.* stated that the extent of crystallinity of developed CNTs rises when the significant temperature is raised, and agglomeration of nano-catalysts diminishes their catalytic properties that enhances graphite sheet deficiencies.[29] The schematic diagram of CVD method is shown in Figure 5.

However, obtaining lengthy carbon nanotubes structure development is challenging issue that remains a crucial constraint for applications (> mm scale) and expansion on conductive or adaptable substrates that are difficult to achieve. For graphene, it is also critical to create flawless, ecologically amiable, and consistent transmission methods. To overcome these concerns and perceive several of the envisaged graphene applications, it would be crucial to continue to establish on the advancement made so far in graphene CVD.[30] Carbon nanotubes are distinctive and their properties are extremely sensitive to structural specifications. This one-of-a-kindness causes a great number of physical processes in nanotube structures, as well as posing a substantial obstacle to

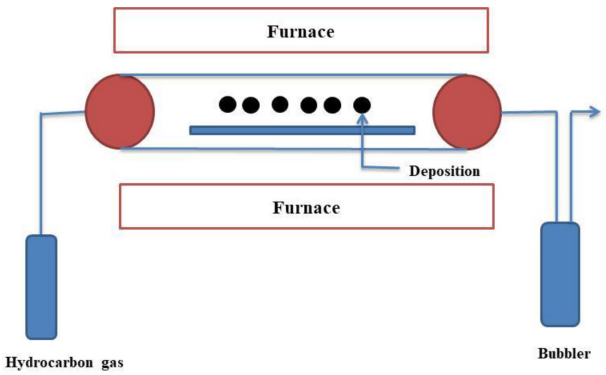

Figure 5: Chemical Vapor Deposition Method.[29]

chemical synthesis in aspects of nanotube diameter and chirality regulation. At this juncture, there is no effective development method for flawless carbon nanotubes at significant level.[31] Moreover, studies have been trying to reduce the diameter dispersion of single-walled carbon nanotubes (SWCNTs) to a certain level. Nevertheless, production of SWCNTs of a specific diameter is still in progress level. Controlling chirality is perhaps quite difficult. Regeneration from organised arrays of accessible SWCNTs could certainly assist up to a certain level. Another significant challenge is controlling the number of walls in multi-walled carbon nanotubes (MWCNTs). Scientists succeeded in developing CNTs from nearly any metal. Moreover, it is not clearly described on how various materials impact the physical, chemical, electronic, optical, and magnetic properties of CNTs in their unprocessed state.[32]

Structure and Properties

Carbon could indeed connect in a variety of forms to create structures with a wide range of characteristics. The inner diameter of multi-walled carbon nanotubes (MWCNTs) varies based on the number of layers, ranging from 0.4 nm to very few nanometers and the outer diameter typically ranges from 2 nm and 20 to 30 nm.[33] The chiral vector is characterized by two integers, n and m, which correlate to the amount of unit vectors beside particular direction in the honeycomb's lattice. When m = 0, the nanotube is referred to as "zigzag," when n = m, it is referred to as "armchair," and other forms are referred to as "chiral".[34] The flexural and compressive experiments on cement composites incorporating functionalized carbon nanotubes revealed a substantial drop in effectiveness in comparison to pristine. However, functionalized CNTs (f-CNTs) are extremely hydrophilic that they absorbed the majority of the water in the cement paste; preventing appropriate hydration of the cement mixture.[35] A simple π-only model captures the band structure of single-walled carbon nanotubes (SWCNTs). Despite variations imply that more study is needed to completely identify how the action takes place between tube-tube interactivity that can cause shattered symmetry and curved factors disrupt the structure of SWCNTs.[36] Carbon nanotubes primary applications comprise of biomolecule, drug delivery to specified organs and biosensor diagnosis and evaluation. Multi-walled carbon nanotubes have greater promise in biosensors because of their ease in enabling protein adsorption while retaining protein intrinsic functionality.[6] Unfortunately, it is widely acknowledged that carbon nanotubes (CNTs) are a diverse material with specific physicochemical features that might cause harmful biological reactions. As a result, the use of CNTs in drug delivery necessitates the development of materials with improved biocompatibility qualities in order to assure the secure adaptation of this technology into therapeutic application. Carbon nanotubes toxicity has largely been investigated by evaluating cell viability, inflammation, and the formation of reactive oxygen species (ROS).[37] Carbon nanotubes typically possess discrete inner and outer surfaces, which can be selectively altered for functionalization. As a result, biocompatible materials can be fixed on the exterior surface of CNTs, whereas the interior part can be loaded with the necessary biochemical content. Carbon nanotubes have Van der Waals and hydrophobic forces that are very essential in the encapsulation process.[38] Also, carbon nanotubes agglomeration tendency exhibit higher negative impacts than fine dispersed carbon nanotubes and promote lung interstitial disease. Furthermore, it has been discovered that as the quantity of nanoparticles increases, the toxic effects reduces at greater concentrations.[39] Nevertheless, investigations found that when single-walled carbon nanotubes (SWCNTs) were exposed to acids, their physicochemical properties changed, and ensuing O-derived surface functionalization. In particular, it could have a significant negative impact on nanotube interactions with cellular membranes. Reem Eldawud *et al.* reported that the increased length and greater agglomerate dimensions of pristine SWCNTs may deliver a higher surface area for implication and activity with different cellular proteins and organs, potentially causing increased amounts of stress in cells and decreased cell viability.[40] Single-walled carbon nanotubes (SWCNTs) possess excellent capabilities to enhance the qualities of various carriers, notably polymeric and non-polymeric composites owing to their higher mechanical strength. Moreover, one of the most significant obstacles in using CNTs is their hydrophobicity and pharmacological process after drug release in cells is unknown. Additionally, SWCNTs have a perfect surface shape, which means that each SWCNTs molecule may effectively contact and allowing interactions with surrounding molecules.[41] Carbon nanotubes pH-dependent effectiveness and magnetic characteristics enable targeted drug delivery for fruitful outcomes. Nonetheless, the main issue with CNTs in therapies is their biocompatibility *in vivo*. However, various scientific studies have carried out to solve this major obstacle in CNTs based drug delivery.[42]

Crucial role of carbon nanotubes as drug delivery carriers

Notably, carbon nanotubes (CNTs) can aggregate in tissues such as the heart, brain, spleen and also cause

oxidative stress as well as exhibiting harmful effects to good cells. The length and diameter of CNTs influence whether effectively they permeate macrophage membranes or absorbed in cells. Shortened multi-walled carbon nanotubes (MWCNTs) (length varying from 100 to 600 nm) demonstrated lesser cytotoxicity to human umbilical vein endothelial cells (HUVECs) than longer MWCNTs (lengths varying from 200 to 2000 nm).[43] It has previously being documented that organic compounds can be successfully encapsulated inside single-walled carbon nanotubes (SWCNTs). The benefit of this technology derived from carbon nanotubes capacity to give security and manage the discharge of loaded molecules, thereby extending the action of potential drugs. Functionalized CNTs enable the concurrent incorporation of many drugs, targeting compounds, and perhaps even metals capable of inducing hyperthermia and therefore improving treatment actions. Previous studies demonstrated that the impacts of various water dispersible single-walled carbon nanotubes on human fibroblasts (HDF) are found to be effective.[44] Certainly, one of the key reasons for this is carbon nanotubes capability to transport macromolecules that would otherwise be impossible to penetrate across the cellular membrane. Functionalized carbon nanotubes (f-CNTs) could be employed as transporters for gene delivery, because they can be coupled to a broad range of active molecules, such as peptides, proteins, nucleic acids, as well as other pharmacological agents. According to Kostarelos *et al.* several forms of f-CNTs can be absorbed by a broad variety of cells, including both prokaryotic and mammalian cells, and can cross cellular boundaries. Lacerda *et al.* studied the usage of functionalized CNTs and showed initial *in vivo* findings for the transfer of DNA and small interfering RNA (siRNA) employing non-covalent functionalization for both single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs).[45] According to specific concentration distribution of the drug mapped to the diameter and length of the SWCNTs, Gemcitabine were found to concurrently transference from one side of the SWCNT to another. However, the dislocation is at a distance of from the gemcitabine centre of gravity 4.7 Å from the exterior of the tube, where the cytosine band of gemcitabine is positioned at a 19° angle to the interior region of the SWCNT. This suggests that the drug particle is constantly within the tube and in the π-π stacking configuration with its cytosine and also the drug molecules tends to be enclosed within the SWCNT.[46] Carbon nanotubes (CNTs) could not only transfer a vast amount of DNA/siRNA into cells, but they could effectively deliver it to diseased locations in a regulated manner.[47] Functionalized carbon nanotubes (f-CNT) promote the formation of osteoblastic cells, which are necessary for bone formation. Optimal bone-tissue suitability and efficient periosteal tissue rejuvenation were found in the *in-vivo* testing of f-CNT. Also, lower molecular weight drugs and antibodies with enhanced cellular permeability could be entrapped by functionalized SWCNTs. This technique enables for increased drug loading and biological molecular attachment without eliciting an immune reaction.[48] Moreover, pH-dependent charging and releasing could be accomplished by allowing the device to deliver site-specific drug delivery, improving effectiveness and lowering toxicity. Carbon nanotubes are widely recognized for their ability to traverse the cell membrane due to their structure, which may restrict their use in specific targeting. Hence, there is a necessity for more investigation into the significance of CNTs in targeted drug delivery.[49]

WHY FUNCTIONALIZED CARBON NANOTUBES ARE AUSPICIOUS IN DRUG DELIVERY

Functionalized carbon nanotubes can be developed through various methods such as exohedral, covalent, non-covalent and endohedral. Regardless, due to their excellent drug loading effectiveness and exceptionally remarkable surface area, functionalized carbon nanotubes has evolved as a unique and adaptable drug carrier. S. Sharma *et al.* investigated the influence of functionalization carbon nanotubes in drug delivery, and observed that drug-loaded surface modified multi-walled carbon nanotubes have a longer resistant duration and more consistent release pattern. Poly (ethylene glycol) (PEG) is the more extensively used functionalization compound because it improves the biocompatibility and dispersibility of carbon nanotubes (CNTs) in aqueous phase.[50] Covalently functionalized carbon nanotubes can bypass the endosome region, transmit rapidly into the cytoplasm of many cells, and allow for a greater payload to be delivered into the nanotubes. Functionalized CNTs (f-CNTs) showed superior loading efficiency, enhanced biocompatibility characteristic, and higher pharmacokinetic (PK) variables when compared to pristine CNTs. The toxicity of pristine CNTs is well recognized, making them unsuitable for drug administration and targeting; however, their toxicity can be lowered via functionalization by removing the intrinsic dirt contaminants.[51] Surface-engineered multi-walled carbon nanotubes (MWCNTs) outperformed other nanocarriers in terms of *in vivo* and *ex vivo*

performance, with increased drug loading and a longer release pattern, particularly in an acidic condition.[52] In an acidic media, the multi-walled carbon nanotubes (MWCNTs) conjugated methotrexate (MTX)-methoxy polyethylene glycol (mPEG) has a capability to release the drug quicker than in a neutral pH. Nevertheless, the release of drug remained constant throughout a 48 hr period in both neutral and acidic environments.[53] Certainly, it has been discovered that functionalized carbon nanotubes (fCNTs) permeate the lipid layer by passive diffusion, analogous to a "nanoneedle" that can damage the cell membranes. While carbon nanotubes are utilized to distribute proteins by extracting them into their exterior surface, endocytosis appears to be the mechanism of absorption.[54] Additionally, single-walled carbon nanotubes (SWCNTs) functionalized with polyethylene glycol (PEG) grafted to poly (g-glutamic acid) and poly (maleicanhydride-alt-octadecene) had a lengthy blood circulation time of 22.1 hr.[55] Carbon nanotubes functionalized with fluorescein (FITC) have proven to pass the cell membrane. Unlike the carbon nanotubes with FITC, which mostly diffused in the cytoplasm before eventually moving into the nucleus, the carbon nanotubes with fluorescent peptide quickly infiltrated the nucleus. Accordingly, carbon nanotubes are employed in an identical way to carry streptavidin inside the cell.[56] Carbon nanotubes are oxidized similarly those raw CNTs are purified, which is often done by returning the CNTs in an acidic environment solution such as nitric acid-sulfuric acid (HNO_3/H_2SO_4). Carbon nanotubes can be extensively modified by esterification or amidation processes because of their carboxylic content. Zeng *et al*. identified sp^3 carbon atoms on SWCNTs following oxidation and subsequent covalent conjugation with amino acids. The 1,3-dipolar cycloaddition of azomethineylides could quickly bind a huge number of pyrrolidine rings to the wall surface of carbon nanotubes.[57] One of the most extensively utilized conjugated polymers such as polyethylene glycol could be covalently attached on CNTs or non-covalently covered on CNTs sidewalls to enhance CNTs distribution and solubility. Subsequently, previous investigations suggested that endocytic routes are the highest possible mechanism indicating an essential concept for defining the therapeutic target when evaluating the drug's eventually endpoint. Nonetheless, a significant portion of drug delivery was accumulated in tissue whenever the nanostructures were functionalized with target molecules coupled with polymer chains.[58] Current research has revealed that functionalizing multi-walled carbon nanotubes (MWCNTs) with chitosan in the existence of sodium tripolyphosphate resulted in cross-linking of chitosan on carbon nanotube walls, resulting in nanohybrids for efficient distribution of bovine serum albumin into cells. Furthermore, noncovalent functionalization of single-walled carbon nanotubes (SWCNTs) using an amphiphilic diblock copolymer (polyoxyethylene-polycaprolactone) resulted in increased carbon nanotubes solubility in aqueous conditions. Functionalization of siRNA molecules on PEG-SWCNTs enables for quicker cellular penetration of the siRNA-PEG-SWCNTs combination, because of increased affinity and interaction with cells via hydrophobic contacts with the cell membrane.[59] Pantoratto *et al*. used transmission electron microscope (TEM) to investigate the cellular and nuclear absorption of CNTs, and revealed that CNTs with specific activity improved after functionalization owing to the binding of surface functional groups on cell membranes. Likewise, Zhang *et al*. created nanohybrid hydrogels for sustained drug delivery. The hydrogels were developed through hydrogen bond self-assembly of poly (methacrylic acid) and carboxyl-functionalized multi-walled carbon nanotubes (MWNT-COOH). The hydrogels exhibited lower micropore densities and high mesh dimensions with increasing MWNT-COOH content. Dexamethasone drug loaded in oxidized single-walled nanohorn *in-vitro* investigation revealed a controlled release pattern in mouse bone marrow stromal ST2 cells owing to the elevation of alkaline phosphatase levels in mouse osteoblastic MC3T3-E1 cells[60] It is worthwhile noting that functionalized SWCNTs employed in scientific research have lengths ranging from 50 to 300 nm and diameters ranging from 1 to 2 nm, which differs significantly from the size and shape of MWCNTs. Notably, PEGylated SWCNTs were administered into mice and monitored for four months. The blood chemistry was normal during the observation for four months. Hence, functionalized biocompatible SWCNTs could be more suitable for *in vivo* biological activities.[61] Figure 6 shows the schematic diagram of carbon nanotubes loaded drug release pattern.

EFFECTIVE UTILIZATION AND OUTCOMES OF CARBON NANOTUBES IN DRUG DELIVERY FOR ARTHRITIS DISORDER

Carbon nanotubes (CNTs) have evolved as intriguing nanomaterial for a multifunctional drug delivery system in recent years. Certainly, they have a number of significant benefits over other nano-sized delivery carriers, such as a higher drug loading capability owing to their large surface area.[62] Polyethylene glycol chain - single-walled carbon nanotubes (PEG-SWCNTs) are

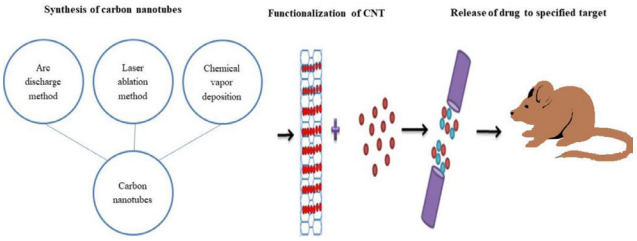

Figure 6: Schematic diagram of carbon nanotubes loaded drug release pattern.

capable of permeating into the cartilage extracellular matrix (ECM), transfer into chondrocyte cytoplasm, and release gene inhibitors without disrupting cartilage homeostasis. However, primary chondrocytes developed, aligned, and produce high amounts of extracellular matrix (ECM) proteins when enlightened on 3D pristine CNT sheets. Functionalized single-walled carbon nanotubes (SWCNTs) can improve agarose hydrogels' mechanical characteristics and offer the optimum structure for cellular survival and cartilage development.[63] Tumor necrosis factor (TNF-α) is a major inflammatory cytokine generated mostly through stimulated macrophages. The suppression of TNF-α could be done by antibodies or receptor fusion proteins and this method has shown to be quite effective in rheumatoid arthritis patients.[64] According to the statement of previous investigation, multi-walled carbon nanotubes accompanied with collagen and recombinant human bone morphogenic protein-2 (rhBMP-2) enhanced bone growth following implant in a mouse muscle. This study is significant in creating new drug delivery systems for bone rejuvenation by utilizing multi-walled carbon nanotubes because it showed no toxic effects.[65] Similarly, multi-walled carbon nanotubes (MWCNTs), carbon black (CB) was administered into the front knees of rats as investigation done by Hiroki *et al.* Multi-walled carbon nanotube penetrated into the synovial membrane and moderately thickened it in 1 week of treatment of 0.003mg MWCNTs. Multi-walled carbon nanotubes were further absorbed by macrophages, resulting in a modest inflammatory response (lymphocytes). The inflammatory reaction enhanced after four weeks; MWCNTs stayed integrated, and normal synovial fibroblasts filled the topmost layer after twelve weeks.[66] However, adding functionalized MWCNTs to a polymeric membrane increases the system's controlled releasing capability. Similarly, acid oxidized MWCNTs enhanced hydrophilicity, resulting changes in membrane structure and permeability. Single walled nanohorns (SWNH) are promising carrier for efficacious prednisolone administration. The technique

Table 1: Diffusion coefficients and burst release from the samples.

Sl. No	Materials	Radius (nm)	D X 10^{14} (Cm^2/s)	Burst (%)	R^2	Reference
1	SWCNT-MIP	476	-0.28	8.5	0.975	68
2	SWCNT-NIP	735	-1.12	12.6	0.922	
3	MIP	523	-0.64	13.4	0.927	
4	NIP	620	-2.78	6.9	0.978	
5	SWCNT	2000*	-70.32	7.2	0.987	

* Length of carbon nanotube is 2000 nm
MIP = Molecularly imprinted polymer
NIP = Non-molecularly imprinted polymer
SWCNT = Single-walled carbon nanotube.

demonstrated efficient drug release in a cultured channel, and rats with considerably lower arthritic scores (reduced osteoclastic cells) were observed.[67] Nonetheless, Fenbufen (FB) is a nonsteroidal anti-inflammatory drug used to manage rheumatoid arthritis, rachitis, gout, and osteoarthritis disorders. Xin-Lu Liu *et al.* reported that a molecularly imprinted polymer (MIP) nanocomposite doped with SWCNTs could be an effective stabilised release mechanism for Fenbufen (FB). Table 1 shows the burst release from the samples.[68] Jun-Young Park *et al.* investigated the structure of methotrexate (MTX) surrounding carbon nanotubes through covalent and non-covalent (PEGylation) methods. In particular, covalent MTX bonds surrounding carbon nanotubes caused more structural distortion than non-covalent bonds (PEGylated CNT). Modifications in the structural variants of MTX enhanced the anti-inflammatory drug effectiveness of human fibroblast like synovial cells (FLS) through sustained extracellular drug release and burst drug release beneath intracellular state.[69] Moreover, methotrexate (MTX) has adverse side effects such as gastrointestinal complications and hepatotoxicity leading to MTX discontinuation. Subsequently, a high-pressure carbon monoxide synthesized single-walled carbon nanotubes (HiPco-SWCNTs) and carboxyl-SWCNTs combined with a small interfering RNA (siRNA) targeting NOTCH1gene are examined as drug carrier for methotrexate. *In vivo* investigations revealed that HiPco-SWCNTs retained in arthritic mice joint. In particular, HiPco-SWCNTs showed a greater absorption efficacy, aided by siRNA's existence. Single-walled carbon nanotubes targeting consistency to immune cells and B cells was decreased after loading with MTX, while the target accuracy was improved by loading siRNA. When cultured with human blood, SWCNTs interacted

with monocytes, neutrophils, and minimum extent with B cells. Hence, HiPco-SWCNTs are effective drug delivery carriers with the prospective to be employed in the management of rheumatoid arthritis.[70] Consistently, polyethylene glycol-single-walled carbon nanotubes (PEG-SWCNTs) are efficient to remain in the joint space for a considerable period, penetrate the cartilage matrix, and transmit gene blockers to the chondrocytes of osteoarthritis (OA) mice. When observing the joint retention duration of intra-articular IA-PEG-SWCNTs, the researchers discovered that intra-articular injected free fluorochromes left the joints in less than 8 hr; greater than 25% of the effective dosage level of IA-PEG-SWCNTs was maintained in healthy joints for 14 days after treatment.[71] In another report, *in vivo* multi-walled carbon nanotubes (MWCNTs) caused the development of granulation tissues within adipose tissues at elevated doses. With RAW 264.7 cells, MWCNTs enhanced the tumor necrosis factor alpha (TNF-α), monocyte chemoattractant protein 1 (MCP-1), and regulated activation on normal T cell expressed and secreted (RANTES) induced inflammatory responses in a dose-dependent pattern. However, with human fibroblast-like synoviocytes (HFLS), they reduced the emission of interleukin-6 (IL-6) and MCP-1.[72] Zhipo Du *et al.* compared the osteogenic ability of multiwalled carbon nanotubes (MWCNTs) to the inorganic mineral element of natural bone, nano-hydroxyapatite (nHA). *In vitro*, growth of human adipose derived mesenchymal stem cells (HASCs) on the MWCNTs and nHA revealed that, while there is no substantial change in the quantity of cell adhesion between the MWCNTs and nHA, the MWCNTs had greater cell adhesion intensity and development. Moreover, *in vivo* findings showed that MWCNTs could promote ectopic bone growth, whereas nHA was unable to, which can be due to MWCNTs ability to enhance inducible cells in tissues to frame inferential bone by focusing enough proteins, and that include specific bone inducing proteins secretory by M2 macrophages. Table 2 shows the quantitative outcomes of *in vivo* studies.[73]

Juan Ma *et al.* stated that MWCNTs might cause inflammatory reactions, which altered the primed condition of synoviocytes and chondrocytes as demonstrated by increased synthesis and function of joint deterioration molecules such as matrix metalloproteinase MMP-1, MMP-2, and MMP-3, as well as cyclooxygenase COX-1 and COX-2. *In vivo* study revealed that MWCNTs induced substantial arthritic symptoms in mice involving synovial inflammation and articular degradation in mice knees.[74] Furthermore, multi-walled carbon nanotube (MWCNT) can attract

Table 2: Quantitative outcomes of *in vivo* studies.

Group	Bone mineral content (mg/cm²)	HE staining revealed the area of new generated bone tissue in the total tissue region. %	Bone volume ratio (BV/TV) %	Reference
nHA	0	0	0	[73]
MWCNTs	2.8 ± 1.6	2.3 ± 1.1	2.5 ± 1.3	

nHA - nano-hydroxyapatite
MWCNTs – Multi-walled carbon nanotube.

and concentrate proteins like recombinant human bone morphogenetic protein-2 (rhBMP-2), activated the manifestation of alkaline phosphatase (ALP) and the genes cbfa1 and COL1A1, as well as enhanced the osteogenic differentiation of human adipose-derived mesenchymal stem cells (MSCs) *in vitro*. Nevertheless, previous study demonstrated that carbon nanotubes with high surface areas may adsorb substantial quantities of dexamethasone (DEX) by connecting with aromatic moieties, and DEX-loaded CNTs displayed prolonged release of DEX in phosphate-buered saline at 37°C, giving a good foundation and viability for drug delivery.[75] Habibizadeh *et al.* also attempted to PEGylated MWCNTs in order to functionalize them. The drug used was ibuprofen, which was substantially and covalently coupled with PEGylated carbon nanotubes. The findings revealed that PEGylated nanotubes had no notable negative impacts on the reliability of L929 cells. Chemically loaded MWCNTs released considerably more consistently than physically loaded MWCNTs, notably at pH 5.3 and the percentage ibuprofen loading of chemically and physically was found to be 52.5% and 38% respectively.[76] The delivery of genes to chondrocytes has previously being accomplished using carbon nanotubes (CNT) modified with polyethylene glycol (PEG) and coated with polyethylene imine (PEI). Carbon nanotube modified with PEG penetrates the cartilage's extracellular matrix (ECM) layer and aggregates inside the chondrocytes.[77] Kagan *et al.* showed a peroxynitrite activated oxidative destruction route of SWCNTs in active THP.1 macrophages. Elgrabli *et al.* used the similar cell type to show that MWCNTs are degraded both inside and outside the cell. To illustrate, polyethylene glycol modified single-walled carbon nanotubes (PNTs) were utilized as a nano-carrier and delivered into chondrocytes in arthritic mice and *in-situ* degenerated within 3 days. Although PNTs was found in the synovial membrane, polyethylene glycol modified single-walled carbon nanotubes (PNTs) were oxidatively

destroyed largely in the cartilage and meniscus zones, and PNTs may eventually be removed through the lymphatic system. Simultaneously, the cellular absorption and destruction of PNTs in macrophages was perceived, however destruction was slower than in interleukin -1 (IL-1) activated chondrocytes.[78] Bisphosphonate derived carbon nanotubes offer a mechanism to precisely localise medicinal compounds to regions of skeletal disorder, whereas insidiously reactive polymer single-walled carbon nanotube combinations provide enhanced distribution consistency. *In vitro* cytotoxicity experiments on C2C12 cells demonstrated that bisphosphonate carbon nanotube conjugates had minimal cytotoxicity and a high biocompatibility characteristic. A biodistribution investigation of G1(covalent functionalization) and G2 (reactive polymer-nanotubes) conjugates *in vivo* in a balb/c mouse model revealed that quick blood consent after 1 hr and improved bone localisation of G2 conjugates compared to G1 conjugates.[79] Ultimately, matrix metalloproteinase-3 (MMP-3) levels were reduced in rats' knee joints after intra-articular injections of hyaluronic acid reinforced with graphene oxide, and it is plausible to assume that this impact is due to macrophage regulation. Similarly, PEGylated single-walled carbon nanotubes (SWCNTs) loaded with antisense oligomers were remained in the knee joint of OA mice and for more than 14 days without inducing TNF-α or interleukin-1β (IL-1β) beta activation. Although graphene-based nanomaterials or carbon nanotubes have been studied extensively for osteoarthritis management, no investigations specifically targeting macrophages.[80] Tumor necrosis factor alpha (TNF-α) instigated inflammation in synovial fibroblasts was suppressed using carbon nanotubes. Carbon nanotubes had a greater absorption of dexamethasone by caveolin dependent endocytosis and effective intracellular distribution, inhibiting reactive oxygen species generation by targeting mitochondria.[81] Singh *et al.* also explored the impact of functionalization density on murine macrophage cell lines using surface engineered multi-walled carbon nanotubes. The level of cellular absorption was shown to be precisely related to the surface hydrophobicity of nanotubes, which was speculated to be owing to cell receptors drawing up carbon nanotubes in a charged manner. Also, carbon nanotubes were employed to cause considerable activation of pro-inflammatory genes IL-1β and IL-6, which are remarkably similar to asbestos induced inflammation mechanisms.[82] In a study, single-walled carbon nanotubes modified with PEG were charged with morpholino antisense oligomers (mASOs) and administered into knees of good health and arthritic green fluorescence protein (GFP) transgenic mice. Furthermore, they conducted *in vivo* investigations of activation of interleukin-1 and tumour necrosis factor in osteoarthritis mice and discovered that there was no protein up-regulation in PEG-SWCNT-650-treated knees particularly in comparison to normal knees.[83] Samori *et al.* used peptide and ester linkers to attach MTX to multi-walled carbon nanotubes, taking leverage of the ammonium functionality created by the 1,3-dipolar cycloaddition activity of azomethineylides to the carbon nanotubes. It was also discovered that the cytotoxic action is significantly stronger when the peptide linker serves as a protease substrate.[84]

BIO-SAFETY

Due to the apparent harmful impact of excessive cohesiveness, single-walled carbon nanotubes are highly toxic than C60 nanoparticles and multi-walled carbon nanotubes. Cui's investigation involved bringing human's HEK293 cells and single-walled carbon nanotubes into touch, and it has been discovered that when the dosage of single-walled carbon nanotubes and the activity period extended, the cell adhesion and proliferation were inhibited, and apoptosis was accelerated.[85] The primary issue of biomedical applications relying on carbon nanotubes (CNTs) biosafety had become extremely contested until to this point. Several researchers are confident that processes relying on functionalized carbon nanotubes are rather safe by considering the reality that some show harmful and hazardous effects on tissues and cells in both *in vivo* and *in vitro*. In a latest studies conducted on rats by various scientists discovered that nanotubes do not always interact with genetic materials, whereas secondary genotoxicity is caused by oxidative degradation to DNA, the techniques utilized to produce and deliver carbon nanotubes based systems have considerable prospects for genotoxicity. The destruction is caused by free radicals produced by the CNTs-induced inflammation.[86] *In vitro* experiments showed that CNTs may cause cytotoxicity by causing oxidative stress and genotoxicity by causing DNA degradation. According to *in vivo* investigations, CNTs enter the lungs of mice and possess the ability to cause a strong inflammation and fibrotic response. When nanoparticles exposed with biological materials, the interaction between the nanoparticle and the protein may have an impact on how cells engage with, which have crucial consequences for security. Carbon nanotubes could react with blood proteins after they entered the blood circulation system. It is critical to understand on how carbon nanotubes react with blood proteins, as this could reveal more

information on CNT biosafety aspects.[87] Nevertheless, the investigational data on CNTs' cytotoxicity so far is inconsistent, and there has been considerable debate about it. The first cytotoxicity investigation on CNTs looked at the effects of unprocessed single-walled carbon nanotubes (SWCNTs) on human epidermal keratinocytes. The cells were cultured in medium with unprocessed SWCNTs (0.06-0.24 mg/mL) for 18 hr. Access to SWCNTs caused rapid oxidative stress, cell survival reduction, and morphological changes in the cell structure. Purified multi-walled carbon nanotubes (MWCNTs) cultured with human epidermal keratinocyte (HEK) cells for up to 48 hr, indicated in the emission of pro-inflammatory cytokines and a reduction of cell stability.[88] Carbon nanotubes coupled bioactive peptides can enter through cell membranes, and therefore it may aggregate in the cytoplasm or penetrated in the nucleus. Whenever the quantity of peptide functionalized CNTs in the cell exceeds 10 μM, they may indeed be hazardous to the cells. Carbon nanotubes of 825 nm long generated more inflammation in the human acute monocytic leukemia cell line THP-1 than CNTs with 220 nm long. Single-walled carbon nanotubes (SWCNTs) prohibited HEK293 cells from growing by triggering apoptosis and lowering cell adherence.[89] On HL60 cells, functionalized SWCNTs demonstrated no toxicity. One of the processes contributing to CNT cell toxicity is oxidative stress, however differing chemical surfaces qualities of CNTs can impact a varied mechanism on cell survival, so the mechanism has to be studied extensively as well as production techniques.[90] According to the majority of investigations, CNT delivery causes long-term inflammation and oxidative stress, which causes unfavourable health outcomes such as gene damage and cancer. Also previous findings showed that CNTs administered intravenously can cause platelet accumulation.[91]

LIMITATIONS

To begin with, pristine CNTs are insoluble due to their metallic composition and typically create enormous bundles in a variety of solvents, notably water and preventing them from getting utilized effectively in medical purposes. Furthermore, the CNTs were never uniform in both diameters and length, making it difficult to provide repeatable findings and assess the biological functionality of certain structures. Carbon nanotubes penetrate the body and quickly spread throughout the central and peripheral nerve systems, lymphatic and blood circulation, and may induce harmful impacts to tissues and organs, including the heart, kidney, bone and liver.[92] Indefensibly; carbon nanotubes may offer negative effects to both patients and exposing individuals. Indeed the size, length, diameter, purity, manufacturing methods, and functionalization are all parameters that have been shown to influence CNT toxicity in investigations. Unfortunately, most of these investigations had being done *in vitro* or on animals, and it is impossible to apply the findings from animal experiments to humans, since the dosage supplements induced in the experiments are usually larger than that of normal living conditions.[93] Dispersibility, toxicity, and interaction with DNA substances are all influenced by parameters like as length, stiffness, and surface hydrophobicity. To illustrate, hard CNTs have a good degree of dispersion and cell viability; nevertheless, functionalized carbon nanotubes (f-CNTs) agglomerate and lose consistency independent of their functionalization and increasing their cytotoxicity.[94] Yet, constraints remains in a way such as producing structurally and chemically repeatable volumes of carbon nanotubes with equal features, quality control, and minimum defects remains a problem for pharmacological and clinical applications of these nanomaterials.[95]

CELLULAR UPTAKE MECHANISM OF CARBON NANOTUBES

Passive diffusion over the cells and energy dependent endocytosis are two key mechanisms that could be implicated in the cellular uptake of single-walled carbon nanotubes. Acridine orange functionalized SWCNTs (AO-SWCNTs) rapidly penetrate the cytoplasm at 37°C, and while at 4°C, the absorption is minimum. Therefore, the SWCNTs cellular uptake method appears to be dependent on surface functionalization, length, and aggregation condition. Long-term observation of internalised AO-SWNTs revealed that these species stayed inside cells' lysosomes for more than a week before progressively disappearing over time.[96] Obviously, most of SWCNTs were found within phagosomes and lysosomes of healthy cells after 4 days of contact to human monocyte derived macrophages, indicating that the cell uptake is governed by phagocytosis. Short nanotubes can serve as small linear 'nano-needles,' piercing the cell membrane better effectively than longer nanotubes that are commonly bundled in a 'ball' shape. In a study, single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs) in a length ranging from 300 to 1000 nm were covalently functionalized with a variety of smaller molecules such as ammonia functionalized CNTs, acetamido functionalized CNTs, fluorescein

isothiocyanate (FITC) functionalized CNTS, CNTs bifunctionalized with ammonium and FITC, CNTs bifunctionalized with methotrexate and FITC, CNTs bifunctionalized with amphotericin B and FITC, and CNTs bifunctionalized with ammonium and FITC. The findings of these functionalized CNT suggested that cellular internalization of CNTs occurs in a broad variety of cell types; including of which have inadequate phagocytosis (fibroblasts) and particularly the energy-dependent systems such as endocytosis are unable to take up extracellular substances.[97] Kostarelos *et al.* demonstrated that single-walled carbon nanotubes-$COOC_{18}H_{37}$ compounds coated with phosphatidylethanolamine (PE) or phosphatidylserine (PS) phospholipids showed micelle-like structures and cellular uptake of these structures by phagocytic cells is discovered through endocytotic mechanism for size greater than 400 nm and through diffusion across the cell membrane for size up to 400 nm. Macrophages efficiently absorb material that penetrates the cell via phagocytosis and stores it in endocytotic vesicle. Various cell groups can effectively absorb the unique biomimetic constructions based on alkylated SWCNTs covered with phospholipids if their size is less than 400 nm.[98] Bottini *et al.* discovered that pristine multi-walled carbon nanotube exhibits minimum harmful effects and purified MWCNT shows significantly higher negative impacts, when the quantity of nanotubes for cell exposure was 400 μg mL^{-1}. In contrast to these findings, Sayes *et al.* reported that the amount of functionalization of single-walled carbon nanotubes influenced the cytotoxic reaction of cells in growth. In serum-containing cell culture medium, the cell uptake ratios of high temperature annealing carbon nanotubes (CNTan), acid oxidation carbon nanotubes (CNTox), and gamma irradiation carbon nanotubes (CNTir) are 6.53%, 10.67%, and 12.74% respectively; implying that cell uptake of MWCNTs is surface hydrophilicity dependant.[99] Pantorotto *et al.* identified micro level single-walled carbon nanotubes concentrations uptake pathways at 37°C and 4°C; however, the actual uptake mechanism is still unknown. It has already being demonstrated that materials larger than 1 mm have trouble performing endocytotic cellular uptake, especially at 37°C. Larger SWCNT collection are obviously undesirable for biological carrier purposes due to their poorer water persistence, increased potential for indiscriminate cell surface attachment, and reduced capacity to cross different biological membrane obstacles.[100]

TOXICITY OF CARBON NANOTUBES

Although the toxicity of carbon nanotubes was first identified, there has been considerable dispute on whether single-walled carbon nanotubes (SWCNTs) or multi-walled carbon nanotubes (MWCNTs) produce higher toxicity. According to previous studies, SWCNTs trigger greater toxic level than MWCNTs. Several research data indicate that CNTs cause varying degrees of toxicity in various organs. Many theories propose that carbon nanotubes physical properties are the main cause for animal pulmonary toxicity. According to Warheit *et al.* intratracheal accumulation of SWCNTs in the lungs of rats caused temporary inflammation and toxic consequences that lasted up to one month. Multi-walled carbon nanotubes (MWCNTs) were ingested to albino mice in an *in vivo* investigation, and toxicology tests were conducted subsequently. Impaired macrophage cells, blood clotting, inflammation were discovered during a histological study of the liver.[101] In an investigation, the intracellular dispersion of functionalized SWCNTs was investigated in human 3T6 fibroblasts and murine 3T3 cells. According to the findings, functionalized CNTs can penetrate through the cell membranes and congregate in the cytoplasm. The functionalized SWCNTs were proven to be extremely non-toxic to the cells at doses of up to 10 μM. *In vitro* cytotoxicity studies in human dermal fibroblasts with functionalized SWCNTs have previously shown that they have reduced harmful impacts than unfunctionalized SWCNTs.[102] Several researchers did cell culture investigations *in vivo* trials and found no evident toxicity of functionalized carbon nanotubes. According to Sayes *et al.*, the toxic impact of CNTs is based on the density of functionalization and found that the toxic level was low for those strongly functionalized with phenyl-SO3X groups. Prato *et al.* found that carbon nanotubes covalently functionalized via 1,3-dipolar cycloaddition were harmless for the cell lines particularly immune cells. Yang *et al.* found that SWNTs suspended by Tween-80 showed little toxic effects in examined mice at a very higher dosage of 40 mg/kg after IV administration. This toxicity could be caused by the oxidative stress caused by the accumulation of SWCNTs in the liver and lungs.[103] L. Moore *et al.* demonstrated both hydrophobic and hydrophilic polymer coatings on the surface of CNTs for reducing toxicity and increasing treatment effectiveness. It has been observed that carbon nanotubes (CNTs) coated with a co-polymer consisting of poly (lactide)-poly (ethylene glycol) (PLA-PEG) diminishes the level of toxicity. However, in comparison to pristine CNTs, the carbon nanotubes coated with (PLA-PEG) was

considerably less toxic in both *in vitro* and *in vivo*, with a highest tolerable dose of roughly 50 mg kg^{-1} and 25 mg kg^{-1} respectively.[104] Shaoxian Tanga *et al.* studied the toxic effect of functionalized multi-walled carbon nanotubes with polyethylene glycol (PEG) and normal multi-walled carbon nanotubes on cells in mouse model. *In vivo*, there was no changes between the control group and experimental group in terms of inflammatory reactions, coagulation system, haemograms, and organ functioning. Furthermore, the nanotubes had no toxic effect on the development of male mouse sperm. In addition, no presence of CNT particles accumulated in the tissues. There was also no indication of neutrophil, lymphocyte, inflammatory cell, as well as haemorrhage.[105] Dumortier *et al.* discovered that fluorescein-labeled solubilized SWCNTs were nontoxic to mouse B and T-lymphocytes and macrophages and preserving their functionality. The enhanced oxidative stress caused by MWCNTs triggered cytotoxicity in C6 rat glioma cells. However, pristine carbon nanotubes have proven to be extremely toxic *in vitro* to various cell types, notably human keratinocytes, rat brain neuronal cells, human embryonic kidney cells, and human lung cancer cells. Folkmann *et al.* on the other hand, discovered that SWCNTs can cause oxidative DNA destruction in mice when orally administered, while Fraczek *et al.* discovered that embedded SWCNTs and MWCNTs caused inflammation. However, there is considerable debate over the possible risks of access to immaculate CNTs and their persistent metal impurity.[106] Nevertheless; the utilization of multi-walled carbon nanotubes (20 mg/kg) revealed no abrupt toxicity. However, when SWCNTs are given intravenously, they stimulated the platelets. Toxicological investigations are essential for each individual species of CNTs, as well as consideration of the material's desired usage. Only a few researches have looked at the impact of CNTs on humans and there is a need for in-depth investigations.[107] Monteiro-Riviere *et al.* found that the interface of MWCNTs with human epidermal keratinocytes resulted in nanotube internalisation in the cytoplasm of the cells and indicated both a cytotoxic activity as well as an elevation in IL-8 secretion. Carbon nanotubes may cause cell death when they come into touch with cellular membrane or when they are internalised. The precise mechanisms that cause cell apoptosis are currently unknown.[108] Indications of oxidative stress, apoptosis, toxicity owing to metal residues from carbon nanotube production, mitochondrial dysfunction, variations in cell structure, and platelet aggregation are all potential inhibitors to carbon nanotubes utilization in humans. Despite the uncertainty of carbon nanotube toxicity and the vast range of toxicological reactions, the contradicting evidence on carbon nanotube toxicity clearly indicates that more investigation is needed for effective application of carbon nanotubes in drug delivery.[109] Table 3 shows the carbon nanotubes characteristics and outcomes for the treatment of arthritis disease.[110-114]

REPRODUCIBILITY OF CARBON NANOTUBES

Carbon nanotubes (CNT) are one-dimensional structures that have a high aspect ratio and may or may not possess metallic conductivity. Carbon nanotubes are not soluble carbon, but they can be converted into large macromolecules with at least some solubility and other fascinating features through a certain chemical treatment.[115] Utkarsh kumar *et al.* utilized direct liquid injection chemical vapor deposition (DLICVD) in order to develop the multi-walled carbon nanotubes (MWCNT). This approach required the use of ethanol as a precursor and a furnace temperature of 750°C. The responsiveness of the sensor was determined to be 2.1 at 5000 ppm, and 98% reproducible. The synthesized cobalt (Co) nanoparticle was reliable and had a structure that was free of impurities, which demonstrates an efficient catalytic activity for the production of CNT.[116] Figure 7 shows the Synthesis of carbon nanotubes using DLICVD method.

Songyun Xu *et al.* developed carbon nanotubes derived from coal and using an arc discharge process as matrix for the matrix assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOFMS) for analysis of tiny molecules. It has been observed that carbon nanotubes, when subjected to laser irradiation, are capable of transferring energy to the analytes. This results in analytes that are well desorbed and ionized, and the disturbance caused by intrinsic matrix ions can be minimized. A high level of sensitivity as well as an outstanding repeatability of the spectrum signals is obtained.[117] The influence of ageing on the field emission (FE) reproducibility of multiwalled carbon nanotubes (MWCNTs) developed through plasma enhanced chemical vapor deposition as reported by Zou *et al.* The FE repeatability improved with ageing due to the increased number and better equally distributed shorter MWCNTs in order to become dominant emitters, which will ultimately result in an improvement in FE repeatability.[118] C. Cantalini *et al.* conducted an investigation and developed carbon nanotubes (CNTs) thin films produced by plasma accelerated chemical vapor deposition on silicon/silicon nitride (Si/Si_3N_4) substrates supplied with platinum interdigital electrodes have been explored as resistive gas sensors for nitrogen

Table 3: Carbon nanotubes inherent characteristics and there outcomes for the treatment of arthritis disease.

Sl. No	Type of CNT	Drug used	Synthesis/Preparation	Toxicity	Findings	Reference
1	MWCNT	Corticosteroid	Corticosteroid (triamcinolone) on Polyethyleneglycol (PEG) fabricated multi-walled carbon nanotubes.	PEG–MWCNTs showed no cytotoxicity at dosages varying from 0.125 to 1.0 μg ml^{-1}.	A minimum dosage of TA–PEG–MWCNTs dramatically reduced nuclear localization of NF-κB by suppressing phosphorylation of mitogen activated protein kinases (MAPKs) and Akt in pro-inflammatory cytokine cells.	[110]
2	MWCNT	Methotrexate	Folic acid (FA) and methotrexate (MTX), an anti-inflammatory drug, were utilized to functionalize MWCNTs noncovalently.	Functionalized CNTs deposited at a reduced level in liver, kidney, and lung.	When compared to the intervention with pristine CNTs, the conjugated treatment resulted in a larger proportion of arthritis suppression. Furthermore, higher drug rate was discovered in the rat's arthritic joints after treated with CNT-FA-MTX.	[111]
3	MWCNT	Dexamethasone	The drug solution is loaded into pre-treated CNTs. The free ends of the drug-filled CNTs are subsequently covered with polypyrrole (PPy) films to avoid undesired drug release.	No indication of cell injury or damage.	The utilization of CNT drug can greatly enhance the quantity of loaded and freely distributable drug, as well as create a better linear and long-lasting drug release pattern.	[112]
4	MWCNT	Diclofenac	Emulsion polymerization was used to create spherical hybrid hydrogels made of gelatin and multi-walled carbon nanotubes.	No indication of toxicity	Controlled release of Diclofenac with good thermal stability and biocompatibility.	[113]
5	MWCNT	Diclofenac	Hybrid nanocomposite hydrogel was synthesised at ambient temperature utilising carboxymethyl cellulose (CMC-MWCNT) and acid functionalized multi-walled carbon nanotube.	Non-cytotoxic	The hybrid nanocomposite is biocompatible with rat fibroblasts. The diclofenac sodium was released in a controlled manner by the CMC-MWCNT nanocomposite, which could be a good option for a transdermal tool as well as the drug stabilised for up to three months.	[114]

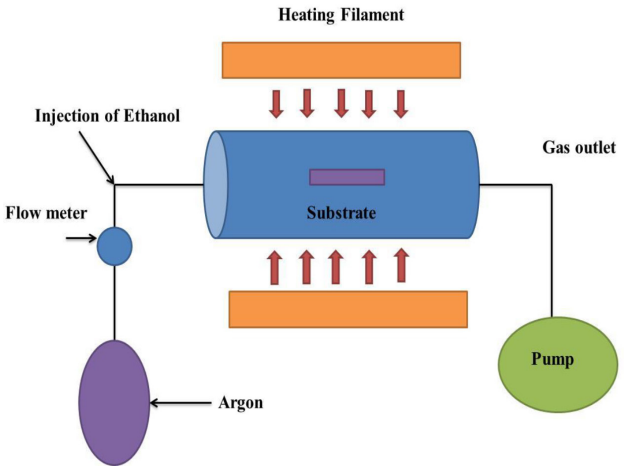

Figure 7: Synthesis of carbon nanotubes using DLICVD method.[117]

dioxide (NO_2) oxidizing gas. The developed films demonstrate a high level of repeatability. The response of the CNTs reaches its sensitivity maximum when exposed to NO_2 at an operating temperature of 165°C.[119]

TOXICITY OF NANO SIZED PARTICLES IN DRUG DELIVERY

Nanoparticles based technology developments have achieved prominence due to their outstanding physical and chemical characteristics.[120] Moreover, inadequate specificity, low bioavailability, and significant toxicity are the issue arises with traditional drugs. The employment of nanoparticles based drug delivery methods can significantly alleviate these issues.[121] A nanoparticle can be utilized in treatments in one of two aspects such as a drug or as a carrier for another therapeutic material.[122-123] Although these nanoparticles penetrate the biological process, they engage and activate with various biological mechanisms and biomolecules. Several studies over the years have backed up the idea that nanoparticles can create both positive and negative aspects. Nevertheless, the tremendous benefits of nanoparticles utilization in drug delivery are proved, but there is a lack of knowing about their toxicity, non-specific protein interactions, redistribution to secondary target organs, and so on.[124] The important factors such as particle size, surface area, structure, surface coatings are the characteristics of nanoparticles that may raise their level of toxicity. *In vivo* investigations of different studies have shown that administration of nanoparticles (NPs) leads to respiratory disease. Nanoparticles (NPs) have been found to have a widespread dispersion into the bloodstream and lymphatic routes.[125]

Carbon Nanotubes

In this view, carbon nanotubes (CNTs) have become one of the most studied nanocarriers due to their widespread used in cancer therapy.[126] According to previous investigations, CNTs have been associated to neurotoxicity, lung toxicity, immune toxicity, embryotoxicity, genotoxicity, and cardiovascular toxicity.[127-133] Fujita *et al.* undertook research to better evaluate the pulmonary toxicity of single-walled carbon nanotubes (SWCNTs) *in vitro* and *in vivo*. Single-walled carbon nanotubes (SWCNTs) increased the activation of genes that control cell proliferation, inflammation, and reactive oxygen species formation, as well as caused inflammation and delayed healing.[134] Similarly, CNTs were examined in conjunction with tau protein and PC12 cells by Zeinabad *et al.* According to the findings multi-walled carbon nanotubes (MWCNT) and single-walled carbon nanotubes (SWCNT) both produced various mechanisms of cell death.[135] *In vitro* stimulation of keratinocytes and bronchial epithelial cells with high concentrations of SWCNTs leads to the production of reactive oxygen species (ROS), oxidative stress, and morphological changes in cells.[136] Moreover, Cao *et al.* discussed the toxicological effects of CNT on the vascular system, stating that they cause atherosclerotic plaque development and low heart rates in animal models.[137] In addition, MWCNTs causes pro-inflammatory actions in keratinocytes.[138] According to Magrez *et al.* the cytotoxicity of carbon based nanomaterials depends upon their sizes. These researchers used the MTT assay to evaluate several kinds of carbon NPs on lung cancer cells in order to determine cell viability. Long-term aggregation of single-walled carbon nanotubes in the liver has resulted in changes in biochemical risk factors such as aspartate transaminases, alanine transaminases, and glutathione as well as changes in organ index in animal models.[139] According to Muller *et al.* agglomerates of pure CNTs stayed entangled in respiratory pathway, although ground nanotubes were well diffused in lung tissue. Carbon nanotubes (CNTs) induce pulmonary inflammation, pulmonary fibrosis, and increased cytotoxicity in the lungs once they entered the respiratory system. Carbon nanotubes (CNTs) and ground CNTs significantly increased type I collagen contents in lungs when compared with the control rats.[140] The overexpression of inflammatory cytokines like tumor necrosis factor-alpha (TNF-α) is hypothesized to play a role in cytotoxicity.[141] However, Mutlu *et al.* reported that toxicity after SWCNT intra-tracheal instillation in mice is caused by nanotubes accumulation instead of the single nanotubes high aspect ratio.[142] An animal exposed to MWCNTs provides

different outcomes with a few researchers reporting that the toxicities is similar to asbestos poisoning, while other studies showed MWCNTs are biocompatible and non-cytotoxic.[143-144] It was also discovered that a nanoparticle's form or crystallinity can determine its toxicity. At this point, while developing nanoparticles it is essential to examine the harmful consequences of nanoparticles.[145]

Liposomes

Liposomes have been investigated extensively because of their biocompatibility and biodegradability.[146] Liposomes, like every other foreign particle that enters the body are met with a variety of defense systems aimed at recognizing, neutralizing, and eliminating invading substances. To illustrate, RES, opsonization, and immunogenicity are three of these defense mechanisms. While these barriers must be overcome in order for liposomes to work optimally, additional variables such as the increased permeability and retention (EPR) effect can be used for improved drug delivery.[147] Liposomes have been employed as optimistic carriers for pharmacological with distinct benefits such as shielding the drugs or siRNA-based treatments from deterioration and low toxicity or adverse consequences. Liposome structure and particle shape are the factors that might cause toxicity. For example, cationic liposomes can associate with serum proteins, lipoproteins, and extracellular matrix causing accumulation or discharge of loaded drugs before they meet the target cells, resulting in toxicities.[148] In this view, cationic liposomes can cause macrophage-mediated toxicity when exposed for more than 3 hr.[149] Similarly, when compared to carbonate apatite, cationic liposomes exhibited substantial cytotoxicity *in vitro* for siRNA delivery.[150] At present, only a few investigations have looked into the possibility of ocular toxicity after intravitreal injection (IVT) of liposomes. The liposome formulations diffused within the vitreous cavity and obstructing the patient's vision and the ophthalmologist's capability to inspect the fundus until the composition was completely reabsorbed 14–21 days after delivery.[151] Lajavardi *et al.* reported that vesicles coated with polyethylene glycol on the surface, known as PEGylated liposomes, do not elicit ocular inflammatory reaction in rats following IVT injection in 24 hr.[152] When compared to the injectability of the free drug, the integration of negatively charged lipids in liposome forms increased the distribution of cardiotoxic agents such as doxorubicin, which resulted in a reduction in the overall toxicity of the treatment.[153] In addition, in comparison to cationic liposomes, anionic liposomes showed significantly more vascular extravasation and significantly reduced aggregation in the vascular endothelium. Moreover, the utilization of liposomes in clinical applications, the off-target toxicity of a variety of drugs has been significantly decreased. Additionally, liposomes have permitted longer blood circulation and advantageous drug biodistribution.[154] There have been a lot of investigations carried out on liposomes, and the aim of those studies has been to either reduce the toxicity of drugs or target certain cells. Numerous pre-clinical and clinical investigations have made it abundantly evident that drug, such as anti -tumour treatments packed in liposomes demonstrated lower toxicities, while retaining greater efficacy. Liposome-encapsulated antivirals such as ribavirin, azidothymidine, and acyclovir have also been demonstrated to minimize toxicity, and additional extensive investigations about their efficacy are being conducted.[155] Encapsulating drugs in liposomes naturally prevents the drug from building up in these organs and drastically lowers its toxic potential.[156]

Solid lipid nanoparticles (SLN)

Nanoformulations are excellent tools for drug delivery applications, but they must be optimized to be secure, efficacious, and affordable before industrial production and clinical utilization. Lipid nanoparticles have acquired popularity since they are harmless, biocompatible, and easy to develop formulations. The nanotoxicological classification system (NCS) does not represent the impact of particle surface charge on toxicity. It was also reported that positively charged lipid nanoparticles could transport nucleic acids.[157] In spite of these benefits, positively charged nanoparticles (NPs) have been linked to a variety of toxic effects.[158] However, precaution should be exercised while working with cationic solid lipid nanoparticles/ nanostructured lipid carriers (SLN/NLC), as there are additional reports of *in vivo* toxicity. For example, Wu *et al.* showed that SLN with various surface charges and PEG densities was toxic to platelets and that the toxic impacts were based on the surface charge and PEG densities.[159] It is important to keep in account that the mode of delivery has a significant impact on the toxicological consequences. For example, bile salts and pancreatic lipase in the body can diminish and deteriorate SLN and NLC that was taken orally and cause them to lose their toxicological properties.[160] According to Evelyn Winter *et al.* nanoparticles that included the solid lipid glyceryl monostearate (GMS) and nanostructures lipid carriers (NLC) generated a significant amount of cytotoxicity *in vitro*, but exhibited only a modest amount of toxicity *in vivo*, as demonstrated by the body weight study. The

nanoemulsion (NE) did not cause any toxicity to be produced *in vitro* and did not cause any changes in body weight. On the other hand, there is some evidence that the SLN and NLC may contribute to the inflammatory process that occurs *in vivo*.[161] Despite toxicity can only be evaluated precisely *in vivo*, there are a number of *in vitro* toxicological experiments that offer initial evidence. Certainly, *in vitro* studies have demonstrated that SLNs are tolerable at concentrations of <1 mg/mL and particle diameters greater than 500 nm can be less endured that can be attributed towards the accumulation.[162] Consequently, De Souza *et al.* reported that the SLN offered a controlled release of praziquantel (PZQ) with higher schistosomicidal activity on the S. mansoni culture in contrast to PZQ suspension due to the interactivity between the parasite tegument and the lipid matrix. The encapsulation of PZQ into SLN can lead to an enhancement in oral delivery with low cytotoxicity.[163] Despite, the majority of polymeric microsphere and nanoparticle delivery systems, SLN production methods do not require the employment of potentially hazardous chemical solvents, which may also have a detrimental impact on protein drugs. Moreover, greater levels of the drug were also identified in the brain after intravenous administration, indicating the possible utility of SLN as a brain delivery method for drugs such as doxorubicin and tobramycin that are not susceptible of bridging the blood brain barrier.[164] Solid lipid nanoparticles with magnetite are a type of particles that can be effectively used in drug targeting. They are incorporation of SLNs and inorganic magnetite nanoparticles. Mussi *et al.* designed solid lipid nanoparticles (SLNs) loaded with doxorubicin to test the effect of docosahexaenoic acid. *In vitro* investigations on the human lung tumor cell line A549 revealed that doxorubicin–docosahexaenoic acid loaded SLN has a greater cytotoxicity.[165]

Dendrimers

Dendrimers are new types of polymeric design that are becoming popular due to their well-defined patterns, adaptability in drug delivery, and high efficiency. Dendrimers also have features that are similar to those of biomolecules. Dendrimers with cationic surface patterns usually bind with lipid bilayer that increases the membrane penetrability and stability.[166] Jevprasesphant *et al.* conducted an investigation in cytotoxicity of PAMAM dendrimers utilizing Caco-2 cells culture and concluded that anionic dendrimers showed substantially lower toxicity in comparison to cationic group.[167] Furthermore, the *in vitro* cytotoxicity of cationic melamine dendrimers with surface groups such as amine, guanidine, carboxylate, and sulfonate was studied and concluded that the cationic dendrimers were significantly more cytotoxic than anionic dendrimers.[168] Moreover, dendrimers toxicity in *in vivo* is only reported by a few scientists. According to the findings, a dose of 10 mg/kg of PAMAM dendrimers emerged to be non-toxic up to the fifth generation of the PAMAM dendrimers. When the G3, G5, and G7 generations were injected into mice, it was discovered that none of the generations under examination produced an immune response.[169-170] Furthermore, it has been demonstrated that the cytotoxicity of the dendrimer is influenced not only by the generation to which it originates but also by the structure of its surface, which is determined by the functional groups. According to the findings of certain investigations, there is apparently a connection between cytotoxicity and dendrimer development. For instance, the cytotoxicity of poly (amidoamine) (PAMAM) and poly (propylene imine) (PPI) dendrimers is sensitive to the quantity and generation. This is because primary amines terminal zones are present in both types of dendrimers.[171] Dendrimers are known to have the ability to interact with biological membranes, which can ultimately result in substantial disturbance and the cell apoptosis.[172] In terms of hematological and immunological toxicity, it was found that PPI dendrimers G4 and G5, both of which had terminal amine groups, caused a substantial amount of hemolysis. The galactose PPI dendrimers exhibited a reduced level of toxicity.[173] In addition to this; it was found that the number of leukocytes increased while the number of erythrocytes decreased while using the PLL G4 dendrimer.[174] After macrophages had been exposed to PAMAM G4 to G6 dendrimers, there was an evident cytokine response that was regulated by the formation of reactive oxygen species. The cell apoptosis may result from exposure to certain substances in high concentrations.[175] Certainly, mice were utilized to conduct *in vivo* toxicological studies to determine the effects on organs such as liver and kidney. The deposition of cationic G4 or higher generation dendrimers in the liver as a result of intravenous injection has the potential to cause hepatic toxicity.[176] Mukherjee and Byrne also demonstrated that later-stage HaCaT cell reactions to PAMAM G4–G6 were related with mitochondrial damage, whereas early-stage reactions were connected with endosomal entrapment. It was found that the toxicological reaction had a strong correlation with the production of dendrimers and, as a result, with the particle surface area; an elevation in the particle surface area resulted in a rise in the toxic effect. In general, the

inherent cytotoxicity of dendrimers can be neutralized through the use of specific chemical changes.[177]

Quantum dots

Quantum dots (QD) are nanoscale semiconductor that emits fluorescence. The size ranges from 2-10 nm and can be composed of either hard material or inorganic material. The utilization of biocompatible quantum dots in drug delivery systems, such as carbon quantum dots, graphene quantum dots, and zinc oxide quantum dots, contributes to the aqueous solubility of the drug. Cadmium selenide (CdSe) is by far the most typical type of quantum dot employed. The toxicity of cadmium is greater because it persists in the spleen and does not disintegrate. It has been observed that quantum dots based on cadmium triggered local neutrophill inflammation in the lungs.[178] Notably, the toxicity of QD depends on several parameters derived from both the physicochemical features of individual QDs and ambient conditions. This might be a potential cause of misunderstanding when attempting to evaluate QD toxicity. It has been established that the toxicity of QD can be determined by a number of different characteristics, including its size, charge, concentration, and oxidative, photolytic, and mechanical durability. To illustrate, researchers have discovered that certain QDs become cytotoxic only after the core coatings on them have been degraded by oxidation.[179] Specifically, in experiments conducted on small animals, the majority of QD collection occurred in the liver, spleen, and lymphatic system after intravenous administration of the drug. Moreover, little aggregation was detected in the heart, lungs, and kidneys**.** Modifications to the composition of the inorganic QD core may help reduce some of the issues regarding toxicity. Subsequently, **e**mploying QD formulations that are based upon indium phosphide (InP) or silicon is one way to get rid of the local cytotoxicity that is caused by the release of Cd ions.[180] Monika *et al.* reported that the Ag-ln-Zn-S quantum dots/ 11-mercaptoundecanoic/folic acid/ doxorubicin (QD–MUA–FA–DOX) nanoconjugates demonstrated the highest levels of cytotoxicity and genotoxicity, while also being able to considerably restrict the migratory capacity of A549 cells.[181] Derfus and co-workers showed that oxidized mercaptoacetic acid-stabilized cadmium selenide quantum dots (CdSe QDs) might release free Cd^{2+} ions into solution, which could contributed to the demise of liver cells**.** Moreover, Lovric and his colleagues found a correlation between the production of reactive oxygen species (ROS) and the consequent toxicity. They discovered that sustained cadmium telluride quantum dots (CdTe QDs) had the ability to cause cytotoxicity to MCF-7, the human breast cancer cell**.** Additionally, Pompa and his colleagues have found that CdSe/ZnS and InP/ZnS QDs are toxic when tested in an *in vivo*.[182] According to the findings of Roberts *et al.* cadmium containing QDs were responsible for causing lung injury through lung injury markers such as lactate dehydrogenase (LDH) and albumin. The injury was at its worst seven and fourteen days after the initial exposure, and there was a positive correlation between the dose of QD and the degree to which the lungs were damaged.[183] As most QDs contain cadmium, experts believe they are dangerous to humans. The toxicity of cadmium containing QDs is strongly connected to the disintegration of QDs structures and elimination of shells, producing cadmium ions**.** Aside from human pulmonary cells, cell activity was substantially affected even in Chinese hamster lung cells (CHL) when QD exposure dosage was as high as 20 mg/ml. Appropriately constructed QDs have the potential to be chosen for usage in the diagnostic and therapeutic applications of certain significant disorders affecting human beings in the future.[184]

CONCLUSION AND PERSPECTIVE

Indeed, a carbon nanotube has shown substantial attraction in pharmacology due to their unique characteristics and sustained release of drugs at targeted region. Despite of effective implementation, carbon nanotubes possess certain limitations such as it cannot be directly used in drug delivery due to their insolubility property in aqueous media. Nevertheless, functionalization of carbon nanotubes is required to reduce the toxic level and making them soluble. The functionalization can be done either through covalent or non-covalent methods, which induces certain challenges such as structural damage of carbon nanotubes. Hence, more research is needed in functionalization techniques to reduce the adverse impacts in structures of carbon nanotubes. Similarly, one of the important limitations of carbon nanotubes in drug delivery is their toxic nature. Previous research demonstrated that single-walled carbon nanotubes are more toxic when compared with multi-walled carbon nanotubes. Numerous studies have found that carbon nanotubes instigated variable proportions of toxicity in different organs such as heart, kidneys and lungs. Carbon nanotubes have been shown to produce cytotoxicity and genotoxicity *in vitro* by inducing oxidative stress and DNA destruction. Carbon nanotubes may interact with blood proteins after they penetrate the circulatory system. It is essential to know how carbon nanotubes

interact with blood proteins since this may give more evidence about CNTs biosafety. Hence, a proper care should be taken before the administration of carbon nanotubes in drug delivery. However, several researchers conducted cell culture studies as well as *in vivo* trials and found no evidence of toxicity of functionalized carbon nanotubes. Significant drug loading, targeted distribution and regulated discharge are only a few of the difficulties that have yet to be resolved. Nevertheless, severe limitations such as manufacturing structurally and chemically reproducible amounts of CNTs with similar characteristics, quality control, and minimum flaws continued to be a concern for pharmacological and therapeutic applications of these nanomaterials. Unfortunately, the quantity of inclusion of carbon nanotubes in drug formulation is limited and more investigations are required to determine if the quantity level of CNTs is increased. Carbon nanotubes cellular absorption has been confirmed in a number of studies, but even though the mechanism of carbon nanotubes cellular permeability is unclear. Previous investigations demonstrated that multi-walled carbon nanotubes combined with collagen and recombinant human bone morphogenic protein-2 (rhBMP-2) increased the positive rate of bone regeneration. Particularly, carbon nanotubes are widely used as eminent nanocarriers in drug delivery and analyzed effectively both *in vivo* and *in vitro*. Additionally, yet there is data available on clinical utilization of carbon nanotubes loaded drugs, and more investigation is required in future for exposure of carbon nanotubes in developing nano based drugs with null toxic effects and at the same time it is well known that there are inherently scientific and safety challenges to be resolved.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

CNT: Carbon nanotubes; **SWCNT:** Single-walled carbon nanotube; **DWCNT:** Double-walled carbon nanotube; **MWCNT:** Multi-walled carbon nanotube; **f-CNT:** Functionalized carbon nanotube; **CVD:** Chemical vapor deposition; **RA:** Rheumatoid arthritis; **OA:** Osteoarthritis; **MTX:** Methotrexate; **DEX:** Dexamethasone; **PEG:** Polyethylene-glycol; **TNF-α:** Tumor necrosis factor alpha; **NO_2:** Nitrogen dioxide; **SO_2:** Sulphur dioxide; **NH_3:** Ammonia; **siRNA:** Small interfering RNA; **IL-1β:** Interleukin-1beta; **HiPco:** SWCNTs- High pressure carbon monoxide synthesized single-walled carbon nanotubes; **FB:** Fenbufen; **MSCs:** Mesenchymal stem cells; **rhBMP:** Recombinant human bone morphogenetic protein-2; **MMP:** Matrix metalloproteinase; **HFLS:** Human fibroblast-like synoviocytes; **Ag:** Silver; **CdSe QDs:** Cadmium selenide quantum dots; **CdTe QDs:** Cadmium telluride quantum dots; **InP:** Indium phosphide; **ZnS:** Single phase Zinc Sulphide; **ROS:** Reactive oxygen species; **SLN:** Solid lipid nanoparticles.

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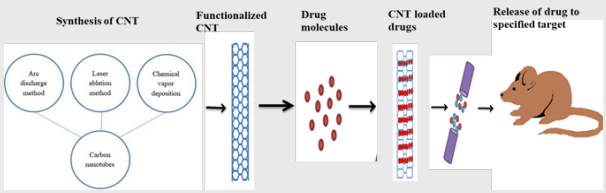
PICTORIAL ABSTRACT



SUMMARY

Arthritis is a degenerative disease of the joints that causes pain and inflammation. The viability and desirability of nanotechnology-based drug delivery has increased for the treatment of arthritis. Functionalized carbon nanotubes are utilized for more precise drug delivery and controlled drug release with less toxic effects. Carbon nanotubes are frequently employed as outstanding nanocarriers in drug delivery and are efficiently examined *in vivo* and *in vitro*. There are intrinsic scientific and safety issues to address. Future research is necessary to determine the exposure of carbon nanotubes in the development of nano-based drugs with less adverse consequences.

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