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Standpoint on the priority of TNTs and CNTs as targeted drug delivery systems

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Conventional drug delivery systems have limitations according to their toxicity and poor solubility, bioavailability, stability, and pharmacokinetics (PK). Here, we highlight the importance of functionalized titanate nanotubes (TNTs) as targeted drug delivery systems. We discuss the differences in the physicochemical properties of TNTs and carbon nanotubes (CNTs) and focus on the use of functionalization to improve their characteristics. TNTs are promising materials for drug delivery systems because of their superb properties compared with CNTs, such as their processability, wettability, and biocompatibility. Functionalization improves nanoparticles (NPs) via their surface modification and enables them to achieve the targeted therapy.

Introduction

Conventional drugs often have poor solubility, PK, biopharmaceutical properties, and stability or cause toxicity [1]. By contrast, nanotechnology-based drug delivery systems can improve the solubility, absorption, permeation, retention time, and bioavailability of drug molecules in target tissues, as well as improving their stability and, therefore, enhancing the shelf-life and acceptability of drugs by increasing either their uptake efficacy or patient compliance [2].

Nanosized delivery systems can be internalized by cells more effectively compared with micro-sized particles. In addition, NPs can be formulated in various shapes, sizes, and compositions, and can be modified physicochemically and functionally to obtain specific properties depending on the requirements of both the drug molecule and the targeted organ [1]. Nanotubes have an ideal inner diameter of 5–6 nm for loading with large biological molecules, with a surface area five times higher than that of other NPs. Furthermore, cell internalization is higher in the case of tubular NPs compared with their spherical counterparts (H.P. Kulkarni, PhD thesis, University of North Carolina at Chapel Hill, 2008).

The first nanotubes to be discovered were CNTs. The first synthesis method was described by Lijima in 1991, whereas TNTs were first synthesized by Hoyer via template-assisted synthesis in 1996 (reviewed in Ref. [3]). Nevertheless, over the past decades, numerous synthesis routes with various advantages and disadvantages have been developed (Tables 1 and 2).

Structure and classification

Although both CNTs and TNTs have a tubular structure, there are general differences in their structure. CNTs are allotropes of carbon made from graphene/graphite and are rolled up into concentric cylinders with various wall numbers, on which their classification is based.

Single-walled CNTs (SWNTs) have a diameter of 1 nm and length up to centimeters, prepared by rolling a single graphene sheet to form a cylinder. The conducting properties of SWNTs depend on the wrapping nature [10], which is represented by chiral vectors (n, m). A zigzag structure is obtained when $m = 0$, an armchair is obtained when $n=m$, and a chiral structure is obtained when m lies between the zigzag and the armchair structure values.

Although double-walled CNTs (DWNTs) generally have the same morphology and properties as SWNTs [11], they also exhibit several advantages, such as significantly improved resistance to chemicals, the same thermal and electrical stability as multiwalled CNTs (MWNTs), but the same flexibility as SWNTs [12].

MWNTs have a diameter from 2 nm to 100 nm and a length of tens of microns. They have two

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TABLE 1

Comparison of CNT preparation methods

Method	Product	Advantages	Disadvantages	Refs
Arc discharge	SWNTs 0.6–1.4 nm in diameter or; MWNTs with 1–3 nm inner and 10 nm outer diameter	Upscalable for volume production; nanotube diameter distribution can vary; yield up to 90%	Solid graphite source required; requires high temperature; SWNTs only obtained with use of metal	[4]
Laser ablation	SWNTs 1–2 nm in diameter and 5–20 μm long, or fullerenes	High-quality nanotubes; yield up to 70%	Solid graphite source required; not suitable for manufacture of MWNTs because of short length	[5]
Chemical vapor deposition (CVD)	SWNTs 0.6–4 nm in diameter or MWNTs 10–240 nm in diameter	Distinguished configuration and positional control	Two-step method; typical yield is 30%; often riddled with defects	[6]
Plasma-enhanced CVD	SWNTs or MWNTs	No solid graphite source required	Complicated process	[6]
Alcohol catalytic CVD	SWNTs 1 nm in diameter	SWNTs produced on large scale and at low cost	Obstacles in creating high-purity SWNTs	[6]
Hydrothermal Methods	MWNTs with 10–100 nm inner and 50–150 nm outer diameter nanorods, nanowires, nanobelts and nano-onions	Starting materials stable at ambient temperature; low temperature (150–180 °C) required; no hydrocarbon or carrier gas required		[7]

TABLE 2

Comparison of TNT preparation methods

Method	Advantages	Disadvantages	Refs
Electrochemical treatment	Self-organized TNT layers with large (100 nm) diameter; suitable for surface modification of Ti implants	Length varies (2–101 μm); not suitable for many biomedical applications because of size and potential clearance by reticuloendothelial system	[8]
Template-assisted synthesis	Variable (50–400 nm) diameter based on template pore size		[9]
Hydrothermal treatment	Small (5–10 nm) diameter and 100–1000 nm length; variable dimensions, porosity and specific surface depending on temperature, NaOH concentration, sonication and acidic post-treatment	Strongly agglomerated TNTs, which need to be dispersed before bioapplication; nanosheets result as byproducts (10% of batch)	[8]

structural models: the 'Russian Doll' model, when graphite sheets are ordered in concentric cylinders (Fig. 1), and the 'Parchment' model [11], when a single sheet of graphite is rolled in around itself. The layers have different chiralities with inconsiderable interlayer electronic coupling, and can shift randomly between metallic and semiconducting varieties. The main advantage of MWNTs is that their stiffness is higher than that of SWNTs, especially during compression [12]. The length-to-diameter ratio of MWNTs is >1 000 000 given that they are nanometers in diameter and several millimeters in length [3].

By contrast, TNTs are rolled up into a spiral (Fig. 1). with an inner cavity of ~4 nm and have an amorphous or crystalline structure depending on the specific electrochemical parameters [8]. The TNTs obtained after anodization are amorphous and not photoactive, whereas high temperature annealing converts amorphous TNTs into a crystalline form (anatase or rutile) and, hence, broadens their application range. TNTs are classified according to the synthesis parameters used to prepare TNTs, such as with template-assisted synthesis, hydrothermal treatments, or electrochemical treatments (H.P. Kulkarni, PhD thesis, University of North Carolina at Chapel Hill, 2008), which cause variations in their physical features (e.g., length, and inner diameter and outer diameter distributions).

Comparison of the physicochemical properties

CNTs have highly hydrophobic surfaces because they preserve the apolar characteristics of native graphene/graphite nanosheets and are insoluble in aqueous solutions [13], where the surface charge of CNTs is a function of the pH of the solution [14]. However, their solubility can be enhanced by functionalization [12], which can also facilitate their movement in the body and reduce both the blockage of body organ pathways and toxicity, partially by hindering the accumulation of highly apolar molecules in tissue. Nevertheless, the grade of toxicity (*in vivo* and *in vitro*) is determined by diverse factors, such as size, shape, purity, surface chemistry, and the existence of transition metal catalysts. Furthermore, it appears that the effect of CNTs on organs is related to the administration route used [15]. Intravenous, oral, and dermal administration of CNTs can cause only mild symptoms, whereas inhalation can result in severe inflammation and toxicity to the respiratory system. By contrast, another study reported that no significant lung inflammation or tissue damage was observed following direct inhalation of CNTs.

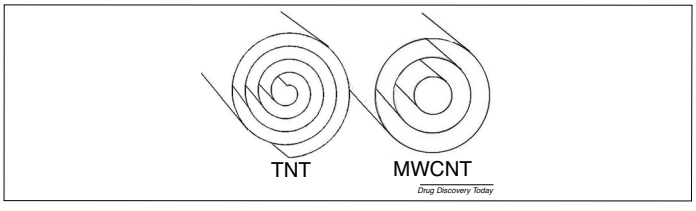

FIGURE 1

Schematic representation of the structural differences between titanate nanotubes (TNTs) and multiwalled carbon nanotubes (MWCNTs).

By contrast, TNTs display strong hydrophilicity because of their partially hydroxylated surface, which causes a negative ζ-potential (after washing until pH = 6) that, when combined with hydrogen bonds, causes superior wettability [16] but often leads to the agglomeration of the particles, especially in dry forms [8]. Their hydrophilicity is also supported by the capillary effect, resulting in the quick penetration of water droplets into the tube pores, and by their crystallinity, given that the amorphous, mixed crystalline phase shows high polarity because of the O–Ti–O bonds and to the extensive presence of hydroxyl groups on the TNT surface. Furthermore, the structure of TNTs also influences the contact angle, which decreases with increases in both tube and pore diameters and with increasing anodization voltage or thermal treatment up to 450 °C; however, beyond 450 °C, their hydrophilicity decreases because of the detachment of hydroxyl groups from the surface [17]. The high surface energy and polarity causes good wettability and, hence, improved cell adhesion. Therefore, TNTs showed extremely good biocompatibility. Bone cell adhesion and differentiation were improved by the use of TNT-covered implants and were proven to be better than those with a pure Ti surface. TNTs were also nontoxic when internalized by cells [18–20]; thus, they appear to have good applicability for therapeutic use in the clinic [21].

Despite their different surface characteristics, CNTs and TNTs exhibit considerable similarities regarding their impressive mechanical, electrical, and optical properties. Nanotubular structures usually have good mechanical properties. In CNTs, the covalent bonds between carbon atoms lead to high tensile strength (up to 63 GPa) and Young's modulus of elasticity (1–1.8 TPa depending on the diameter and the chirality of the tube) [3]. Therefore, SWNTs are stronger than steel by 10 to 100 times per unit weight. By contrast, MWNTs have lower Young's modulus values than SWNTs because stress is only supported by the outer graphite shelf on account of weak intertube cohesion. Similarly, TNTs exhibit high, but one grade lower Young's modulus (230 GPa) and tensile strength (680 MPa) compared with SWNTs. Nevertheless, these values still reflect impressive mechanical properties, supported by the results of Sipos *et al.*, who reported that TNTs and their composites formed with various drugs showed supreme flowability, compressibility, and compactibility compared with crystalline APIs, thus proving their superior processability [22–24]. In terms of their electrical behavior, CNTs display semiconducting or metallic resistance, capacitance, and inductance properties because of their electronic structure and symmetry of graphene [12]. SWNTs can be either semiconducting or metallic, whereas MWNTs are semiconducting. The electrical conductivity of self-organized TNTs is based on their crystalline structure and is tunable with the annealing temperature, because when the amorphous material converts into anatase at 300 °C, it results in significantly higher conductivity, whereas the conversion of anatase into the more resistive rutile above 500 °C reduces the conductivity [25]. In terms of their optical properties, both CNTs and TNTs show optical absorbance: the absorbance of CNTs is in near-infrared (NIR) zone [12], whereas TNTs display wider photo absorption properties, although not as good as TiO_2 NPs. However, when rare earth ions (Pr^{31}, Er^{31}, Nd^{31}, and Yb^{31}) were intercalated into TNTs, higher photoluminescence emission was observed compared with pristine Na-TNTs [26]. Overall, these remarkable properties make CNTs and TNTs an ideal target for a range of diagnostic, biomedical, or pharmaceutical applications.

Applications

The high binding capacity and unique physicochemical, especially electrical properties of nanotubes can be well utilized in specific molecule recognition and other diagnostic applications. CNTs can be used as biosensors to diagnose diseases, record the pulse and temperature of a patient, and measure blood glucose, or other biomolecules, such as H_2O_2, organophosphate pesticides, or cancer markers, in diagnosis and treatment [12,27–29]. In addition, their good biocompatibility and mechanical properties also make nanotubular structures suitable for tissue-engineering applications. CNTs can improve the mechanical strength of implanted catheters and, hence, reduce thrombus formation in cardiovascular surgeries [12]. CNT-coated polyurethane has high interconnected porosity, bioactivity, and nanostructured surface topography. Thus, CNTs can be used as bioactive scaffolds in bone tissue engineering and provide new properties, such as electrical conductivity, to these scaffolds [30], or, when filled with calcium, they can be used directly as a bone substitute, with improved mechanical properties because of their high tensile strength [3]. Consequently, they can help in directing cell growth [12]. Correspondingly, TNT coatings on scaffolds reinforce cell growth on the biodegradable photopolymer scaffolds [31] and also promote bone formation by hastening osteoblast growth by 300–400% compared with non-anodized Ti surfaces [32]. This effect was further improved when TNTs were coated with biocompatible polymer films comprising chitosan and poly(lactic-co-glycolic acid), when superior osteoblast adhesion and cell proliferation were achieved, compared with uncoated TNTs [33].

Given their unique characteristics, such as their hollow monolithic structure, nanoneedle shape, considerable molecule-binding capacity and versatile binding mechanisms, nanotubes are also ideal carriers in other biomedical and pharmaceutical applications. Two different methods exist for binding: wrapping, when drugs and biological molecules are attached to the surface through functional groups; and filling, when drugs and biological molecules are loaded inside CNTs [34].

CNTs display immunogenicity and devised antibody responses linked to viral protein VP1 of foot-and-mouth disease virus (FMDV), which could be utilized for the stimulation of the immune system [3]. The high RNA binding and internalization capacity also make CNTs suitable for cytoplasm or cell core targeting and valuable as vectors to transfer genes and drugs into cells to cure cancer and various genetic disorders [35]. However, SWNTs are more useful compared with MWNTs because of their 1D structure, efficient drug-loading capacity, and large surface area [36]. CNTs conjugated to small interfering (si)RNA molecules were successful in silencing the expression of CD4 cell surface receptors and CXCR4 co-receptors, thus inhibiting the infection of T cells by HIV [37]. Drug-embedded CNTs can also be utilized to kill viruses in viral ulcers without antibody production against the drug, because viruses present no intrinsic immunogenicity for CNTs [38]. CNTs can carry streptavidin and cytochrome C into the cell cytoplasm via the endocytosis pathway [12] and showed high selectivity to kill cancer cells after internalization, achieved by hyperthermia because of their thermal conductivity [39]. However, MWCTs are more suitable than are SWCTs for thermal cancer treatment given that MWNTs absorb NIR radiation faster than do SWNTs [40].

Nevertheless, CNTs can be applied for drug delivery and targeting without external stimulation because the SWCNT-anticancer drug complex increases blood circulation time, enhancing permeability and the retention effect by tumor cells [41], as shown by the successful delivery of amphotericin B [42], the successful delivery and retention of polyphosphazene platinum to the brain [43], the successful oral administration of erythropoietin (EPO) [43] and the slow release of cisplatin in an aqueous

environment to terminate the growth of human lung cancer cells [44].

Based on their physicochemical properties, TNTs offer fewer opportunities to attach drugs or other molecules; however, based on their unique properties, such as biocompatibility, mechanical strength, and chemical resistivity, they are proposed to be ideal materials for the development of various medical implants and devices. Thus, TNTs have so far been applied mainly in dentistry, orthopedics, and cardiovascular surgery [45].

Functionalization of TNTs and CNTs

Functionalization is the attaching of appropriate molecules to the nanostructure surface to render them soluble in water, reduce toxicity, increase biocompatibility [46], achieve targeted drug delivery, obtain selective binding to the desired epitope, achieve controlled drug release, facilitate cellular internalization, enhance biodistribution, and improve biofluid circulation. Many types of functionalization molecule have been used, such as polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), cellulose, polypeptides, dextran, and silica [2].

CNTs can be functionalized covalently or noncovalently on the tips and side walls, although CNT tips have a higher functionalization affinity compared with the side walls [46]. Noncovalent functionalization, including Van der Waals interactions, π–π interactions, and hydrophobic interactions, causes minimal damage to the CNT surface and maintains the aromatic structure and, consequently, the electronic characteristics of CNTs. However, the disadvantage is that this kind of functionalization is not appropriate for targeted drug delivery applications because of the weak forces formed [47]. By contrast, covalent functionalization of CNTs can be achieved via oxidizing them by strong acids, such as nitric and sulfuric acids [48]. Hence, the forming of carboxylic acid groups because of the high negative charge increases the hydrophilicity, water solubility, and biocompatibility of CNTs [49]. By contrast, the disadvantage is that covalent functionalization damages CNT side walls and, thus, CNTs cannot be used in some applications, such as imaging [37]. Nevertheless, the presence of carboxylic and other oxygen-containing groups on the surface of CNTs also allows the covalent attachment of functional molecules [50]. The covalent surface functionalization of CNTs with amine-terminated PEG stabilizes CNT dispersions in various media and reduces deleterious effects on cultured cells [51], and oxidation debris (i.e., the breaking CNTs during oxidation or oxidizing carbonaceous nontubular structures in pristine CNT samples).

Similarly, the surface characteristics, such as the negative charge at physiological pH caused by the presence of hydroxyl groups on their surface above their isoelectric point (pH 3.7), enable TNTs to react with a variety of functional molecules [52]. The functionalization of TNTs improves their stability for vectorization applications and enables them to carry therapeutic molecules [53]. Tables 3 and 4 detail methods for the functionalization of CNTs and TNTs, respectively.

TABLE 3

Functionalization possibilities of CNTs

Reagent(s)	Aim of functionalization/grafting	Refs
Nitric acid (HNO_3)	Carboxylic groups covered MWNTs; increase solubility	[54]
$NH_2(CH_2CH_2O)_2–CH_2CH_2NH_2$	NH_2 covering of MWNTs; increase solubility; decrease aggregation; decrease cytotoxic effects	[55]
Second-generation poly (amidoamine) dendrimer (G_2-PAMAM)	Increase surface binding ability of DNA probe by supplying large number of amino groups	[56]
Folate moiety	Selective destruction of cancer cells labeled with folate receptor tumor markers; NIR-triggered cell death without harming receptor-free normal cells	[39]
Phospholipid-PEG2000-NH_2	Photothermal cancer treatment in mice by NIR irradiation	[51]
HNO_3 and salicylaldehyde	Reduce reaction step number and reaction time	[50]
HNO_3 and $H2SO_4$ mixture; 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; *N*-hydroxysuccinimide; P-glycoprotein antibody	Specific recognition of multidrug-resistant human leukemia cells (K562R)	[57]

TABLE 4

Functionalization possibilities of TNTs

Reagent(s)	Aim of functionalization/grafting	Res
Dopamine; Tris buffer; bone morphogenetic protein 2 (BMP_2)	Enhance bone osseointegration	[58]
3-isocyanatopropyltriethoxy; PEG; polyethylene imine (PEI)	Enhance TNT dispersion in water and reactivity	[53]
Allyltriethoxysilane; propyltriethoxysilane	Form stable suspensions in tetrahydrofuran (THF)	[59]
Antimicrobial peptides (HHC-36)	Prevent formation of biofilms (based on bactericide and bacteriostatic effect)	[60]
3-aminopropyltriethoxysilane; RGD peptide	Promote initial attachment and proliferation of human mesenchymal stem cells (hMSCs)	[61]
KRSR	Increase osteogenic differentiation and pre-osteoblast adhesion and spread on TNT surface	[62]
N,*N*-carbonyl diimidazole; 11-hydroxy-undecylphosphonic acid; EGF and BMP_2 growth factors	Increasing number and activity of MSCs	[63]
Gelatin-stabilized gold NPs	Improve MC3T3-E1 osteoblast cell adhesion and propagation (achieved)	[64]
Chitosan	Achieve sustained release of loaded drug (selenium or quercetin) from TNTs	[65,66]

Concluding remarks

Drug delivery devices based on nanotubular structures are ideal for modern theranostic applications because of their advantageous properties. However, they can bear the risk of toxicity attributable to their size, surface charge, chemical composition, chemical reactivity, chemical structure, crystal structure, shape, solubility, and degree of agglomeration. Moreover, nanomaterials can cause oxidative stress and damage phagocytosis inside the cells, reduce cell viability, and suppress cell proliferation by producing reactive oxygen species or remaining in the body because of their ability to evade the reticuloendothelial system.

Despite many promising results and numerous advantages, pristine CNTs are insoluble in water and most solvents; thus, they cannot be used immediately in biomedical applications. Furthermore, they bear a considerable risk of toxicity and carcinogenicity because they accumulate in the human body because of their strongly hydrophobic nature and residual metal catalysts, which increases their ability to produce O^{2-} anions, lipid peroxidation, or physical blockage generated from agglomeration at high doses, given that CNTs also have a strong electrostatic attraction.

By contrast, TNTs have exhibited promising toxicological profiles and good biocompatibility in numerous studies and a vital affinity for bone cell adhesion and differentiation, which allows their use in dentistry, orthopedics, and cardiovascular surgery. Therefore, and as a result of their tubular structure, CNT-similar chemical resistivity, mechanical strength, and electron mobility, TNTs might be promising alternatives for developing medical implants and devices. Nevertheless, despite these advantages, TNTs, especially hydrothermally synthetized free TNTs, are poorly studied in terms of their use in drug delivery applications, possibly because of their hydrophilic nature, which improves their biocompatibility and decreases the risk of adverse effects, but also acts negatively on their absorption and cell internalization properties. Thus, functionalization might be key to improving their applicability, given that the range of possibilities is almost as wide as for CNTs. Noncovalent bindings based on van der Waals forces, hydrogen bonds or π–π interactions are easily achievable, which maintain the aromatic structure and electronic characteristics; obtaining covalent functionalization with ether- or esterification of the free surface -OH groups is also possible. With the selection of the appropriate functional groups, the surface properties and, therefore, their absorption and internalization capacity could be improved without the considerable elevation of the risk of toxicity. Furthermore, their similar mechanical, electrical, and optical parameters could provide the same level of processability and range for external stimuli-adjusted targeting possibilities as CNTs.

In terms of their low toxicity and advantageous physicochemical properties, the further investigation, use, and application of hydrothermally synthetized TNTs is recommended for the development of new advanced drug delivery systems.

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