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Review

Liberation of drugs from multi-wall carbon nanotube carriers

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ABSTRACT

MWCNTs in the 'nanotube–drug' hybrids can play a role of carriers or additives (enhancers) in the more complex formulations. This work reviews qualitative and *quantitative* analyses of Drug Delivery Systems (DDSs) based on multi-wall carbon nanotubes (MWCNTs) and their chemically modified analogues (mainly oxidised MWCNTs). A special emphasis was placed on the chemical interactions between drug molecules and the nanotube carrier critical both in the stage of preparation/synthesis of the hybrids and liberation of the drug.

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1. Introduction

The worldwide pursuit of more efficient and safer drugs was significantly accelerated alongside with the development of controlled (immediate, sustained, pulsatile and delayed) [1] and targeted (realising the Ehrlich's 'magic bullet' concept) Drug Delivery Systems (DDSs) [2,3]. The drug–carrier conjugates constitute a part of the contemporary pharmacological sciences of at least equal importance to the discovery of novel drugs [4]. Among numerous DDSs tested with the aim of translation to every-day medicine only liposomes, albumin-based and virosomes were successfully commercialised. Other extensively studied drug vehicles are microspheres, protein conjugates, soluble biodegradable (synthetic and natural) polymers, nanofibres, erythrocytes, and the last but not least – raised with the birth of nanotechnology – nanoparticles (NPs) [5]. NPs are currently under a subject of intensive and multidisciplinary studies with a special interest of nanomedicine. However, the initial enthusiasm related to uncommon and frequently extreme properties of NPs, emerging in nanosize but absent (or latent) in bulky materials, was damped by many alarming reports on their potential toxicity [6]. Considerable international efforts were engaged to adjudicate 'how toxic are particular NPs?', nevertheless today the question still remains open. One might claim that the majority of factors influencing on the NPs' cytotoxicity were identified, i.e. chemical structure and composition, dimensions distribution (uniformity of sample and aspect ratios), surface area, surface chemical functionalisation, surface charge, agglomeration state and presence of extraneous materials (catalyst particles, contaminations from the manufacturing processes). On the other hand, the long-term exposure and after-exposure (bio) distributions of NPs on the fauna and flora (environmental toxicity) and humans definitively require further comprehensive investigations. A very recently published review exhausts the current state and prospects of exploitations of NPs as DDSs [7].

Among NPs of a well-founded publicity (metals, metals and non-metals oxides), a family of carbon nanotubes' (CNTs) enjoys a justified and unfading popularity. CNTs as the 1D sp^2-carbon nano-allotrope describable by a seamlessly rolled-up graphene sheet, of a diameter from one up to hundred nanometers and length of microns, exhibit unprecedented chemical and physical properties condensed in just one molecular architecture [8]. Among the CNTs' representatives multi-wall carbon nanotubes (MWCNTs) (Fig. 1), consisting of more than two concentric graphene cylinders with the interlayer distance of 0.34 nm, exhibit a unique combination of physical properties: extremely high Young's modulus (0.95 TPa) [9], high ultimate tensile strength (150 GPa) [10], high electrical conductivity (1.85×10^3 S cm^{-1}) [11], high heat-transfer coefficient (600 W m^{-1} K^{-1}) [12] and a large surface area (see Table 1). Single-wall CNTs (SWCNTs) and double-wall CNTs (DWCNTs) can be also distinguished as they typically display, apart from morphological, enhanced electrical, thermal and mechanical properties and higher chemical reactivity [13].

As for biomedical applications, there are two key properties reserved for MWCNTs as compared to SWCNTs. Firstly, the average price of MWCNTs and SWCNTs is ca. 30 and 1000 € per 1 g (*Sigma Aldrich*, 2012), respectively – MWCNTs can be synthesised today in a large scale via methods enabling full control over their morphology, i.e. c-CVD and Arc-discharge. Secondly, many reports showed that MWCNTs were less cytotoxic than SWCNTs [14–16]. Moreover, it was recently demonstrated that simple chemical functionalisation (oxidative cutting or nitrogen-doping) of MWCNTs (of an appropriate aspect ratio) led to a complete internalisation by cells (after 48 h) connected with practically a loss of toxicity against Human Monocyte Macrophages (with only a slight cytotoxicity observed for pristine, non-modified MWCNTs) [17]. Additionally, since oxidised MWCNTs (O-MWCNTs) (Fig. 1) are enzymatically biodegradable [18] and excretable via kidneys in humans [19], they can be considered as one of the most suited drug nanovehicles.

Progressive oxidation of MWCNTs introduces mainly carboxyl (COOH) and hydroxyl (OH) groups — primarily in place of the nanotube structural defects (e.g. Stone–Wales defects, fullerenoid hemisphere cups) and, subsequently, by a gradual degradation of graphene walls. The process chemically resembles oxidation of *C*-aromatic compounds and results also in opening of the nanotubes' ends ('uncapping') and, further, the nanotube cutting (Table 1). Apart from carboxyl and hydroxyl groups, other functionalities were found after oxidative treatment of MWCNTs including lactone, ketone or anhydride [20].

Unmodified (pristine) MWCNTs tend to agglomerate and form so-called 'nanotube bundles' via weak but 3-D abundant π–π interactions. Due to this phenomenon, MWCNTs are practically non-dispersible either in water or a whole set of organic solvents. Oxidative introduction of hydrophilic carboxyl and hydroxyl groups onto the MWCNTs' surface significantly increases dispersibility of nanotubes in water (and other polar systems) since it allows for multiple hydrogen bonding and dipole–dipole interactions — stability of the aqueous dispersions of O-MWCNTs can amount up to years.

Oxidation of MWCNTs is usually performed under harsh conditions like refluxing in mixtures of HNO_3 and H_2SO_4 [21], prolonged ozonolysis [22], etc. This process generates multiple structural defects undesirable in many applications, especially in mechanical and electronic devices. A development of controllable, less destructive, more effective and reversible after de-bundling functionalisation methods still remains a challenge [23]. Fortunately, and as the reader will ascertain further, O-MWCNTs of the altered morphology can be safely applied in the construction of DDSs.

The prospects of application of MWCNTs (and their chemical analogues) as controlled DDSs and the preceding *in vitro* studies covering drug loading and unloading mechanisms are a subject of this review. Since there were published many papers on qualitative into-cell drug delivery studies based mainly on direct observation of fluorescently labelled MWCNTs, here, for a change, we wish to put a special emphasis on MWCNT–drug interactions of a broad scale of bond energy and quantitative analysis of liberation of drugs from MWCNT-based and MWCNT-added carriers.

2. 'MWCNTs–drug' hybrids

MWCNTs have numerous unusual features marking them out from other NPs. Due to cylindrical shape and a high aspect ratio they have a large surface area. These characteristics, combined additionally with an optionally hollow structure of MWCNTs, can result in the excellent drug loading capacity [24]. External and internal surfaces of (MW) CNTs can be straightforwardly functionalized or manipulated. Drugs can be exposed to the environment after tethering to the most outer nanotube wall (exohedral functionalisation) — or entrapped inside the nanotubes' cavity via capillary forces, after the 'uncapping' procedure (endohedral functionalisation) (Fig. 2).

Moreover, the MWCNTs' surface can be chemically modified (oxidation, 1,3-dipolar cycloaddition, Diels–Alder reaction, carbene and nitrene ddition etc.) or physically (adsorption via hydrophobic interactions or π–π stacking, wrapping by polymer chains, surfactant-assisted debundling, etc.) [25]. O-MWCNTs are also capable of drug loading/anchoring via ionic and hydrogen bonds. The modifications allow to: (1) uniformly disperse nanotubes in aqueous media, (2) introduce a variety of drug linkers, (3) improve drug loading capacity, and (4) tailor unique drug carriers by attaching targeting agents (homing peptides, magnetic nanoparticles). In turn, extraordinary thermal and electrical conductivities of MWCNTs could be employed in the enhancement of electrically or thermally stimulated drug release. The 'nano-needle' morphology makes MWCNTs particularly efficient through-cell conveyors [26]. All the above premises prompted the scientific society to verify usefulness of 'MWCNT–drug' hybrids in the realisation of the MWCNT-based DDSs, especially in cancer targeting [27].