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Current Opinion in Biomedical Engineering

Recent advances in carbon nanomaterials for biomedical applications: A review

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Abstract

With the emergence of new pathogens like coronavirus disease 2019 and the prevalence of cancer as one of the leading causes of mortality globally, the effort to develop appropriate materials to address these challenges is a critical research area. Researchers around the world are investigating new types of materials and biological systems to fight against various diseases that affect humans and animals. Carbon nanostructures with their properties of straightforward functionalization, capability for drug loading, biocompatibility, and antiviral properties have become a major focus of biomedical researchers. However, reducing toxicity, enhancing biocompatibility, improving dispersibility, and enhancing water solubility have been challenging for carbon-based biomedical systems. The goal of this article is to provide a review on the latest progress involving the use of carbon nanostructures, namely fullerenes, graphene, and carbon nanotubes, for drug delivery, cancer therapy, and antiviral applications.

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Current Opinion in Biomedical Engineering 2021, **17:**100262

This review comes from a themed issue on **Biomaterials: Futures of Biomaterials**

Edited by **Aldo Boccaccini, Himansu Sekhar Nanda,Syam Nukavarapu** and **Vinoy Thomas**

For complete overview of the section, please refer the article collection - Biomaterials: Futures of Biomaterials

Received 1 October 2020, revised 31 December 2020, accepted 4 January 2021

https://doi.org/10.1016/j.cobme.2021.100262

Keywords

Graphene, Carbon nanotubes, Drug delivery, Cancer therapy, Antiviral activity.

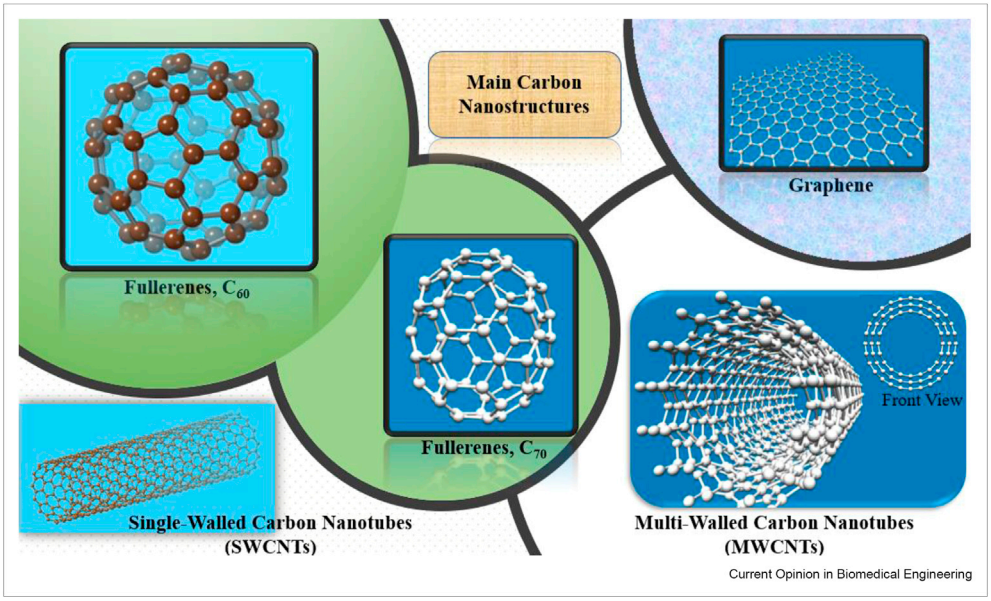
Introduction

Selecting the appropriate materials for drug delivery, cancer therapy, and antiviral applications has been a challenge for biomedical researchers. Carbon nanomaterials have appealing properties for many biomedical applications because of the diversity in their structures, large ratios of surface area to volume, facile functionalization, unusual optical properties, and biocompatibility [1]. The diversity of nanoscale carbon structures is impressive. In nanoscale dimensions, carbon nanotubes (CNTs), graphene, fullerenes, carbon dots (CDs), graphene quantum dots (GQDs), carbon fibers (CFs), nanodiamonds, carbon nanoonions, and amorphous carbon nanostructures represent alternative structures and allotropes of only one element, carbon [2,3]. The classification of carbon nanomaterials is typically determined by the number of dimensions exceeding nanoscale (100 nm) [4]. Accordingly, CDs, GQDs, and fullerenes are zero-dimensional nanomaterials. CNTs and CFs are classified as one-dimensional nanomaterials, and layered structures like graphene are classified as two-dimensional nanomaterials. Finally, nanodiamonds are classified as three-dimensional carbon nanostructures.

Fullerenes were first discovered in 1985; the inventors of this new carbon allotrope won the 1996 Nobel Prize in Chemistry [5]. This achievement is considered as revolutionary in the synthesis of carbon allotropes [2]. Fullerenes are sp^2-carbon-atom cages of different sizes with single or double bonds (Figure 1) [6]. Fullerenes enjoy the highest symmetry among the various carbon nanostructures and thus exhibit a high structural and chemical stability. Fullerene surfaces can be decorated with various functional groups for targeted delivery in drug delivery, diagnosis, imaging, and biosensing applications [1,6]. The photoelectrochemical properties of fullerenes, particularly C_{60}, make them suitable for photodynamic therapy [7]. Fullerenes are hydrophobic; the low solubility of fullerenes in polar solvents such as water is an obstacle to their use in biomedical applications, and numerous methods, including synthesizing fullerene derivatives, have been used to overcome this obstacle [6,7].

Graphene is an individual layer of densely packed sp^2 carbon atoms. The hexagonal arrangement of this material is indicated in Figure 1 [1]. Geim and Novoselov described the synthesis and characterization of this carbon nanostructure in 2004 [8]; thy were recognized for this effort with the 2010 Nobel Prize in Physics. In comparison with bulk structures, this nanostructure has a large relative surface area. Graphene can be functionalized chemically and dispersed in different solvents, including water. It has a great electrical and thermal conductivity as well as unique optical properties

Figure 1



The schematic of main carbon nanostructures: fullerenes (C_{60}, C_{70}), graphene, and carbon nanotubes (SWCNTs and MWCNTs).

[1,9]. In graphene, all the atoms are located on the surface, which provides locations for attachment for many types of biomaterials [9]. Graphene endowed with all these features is a great candidate for biosensing, drug delivery, tissue engineering, genetic engineering, bioimaging, and therapeutics [1,9].

CNTs, as the cylindrical form of fullerenes, are rolled graphene sheets (Figure 1); these materials consist of single or multiple graphene layers called single-walled carbon nanotubes (SWCNTs) and multiwalled carbon nanotubes (MWCNTs), respectively [1]. Initially, CNTs were reported in 1991 by Iijima, who synthesized fullerenes through the arc discharge method [10]. CNTs are stretchable and flexible with excellent strength [11]. They have high electrical and thermal conductivity as well as significant chemical reactivity. There are some barriers that impede CNTs from large scale use such as the absence of a technique to synthesize CNTs with a repeatable structure for mass production [11].

The use of carbon nanostructures for treating new viruses such as coronavirus disease 2019 (COVID-19) and established ones such as Ebola virus along with cancer has been a focus of recent research activity. Several studies on the use of carbon nanostructures for COVID-19 therapy have recently been published. Numerous researchers have tried to bring the carbon-based materials closer to clinical drug delivery applications through functionalization and conjugation of carbon nanostructures with biological molecules. In this article, we will focus on the latest studies that involve the use of graphene, fullerene, and CNTs for advanced drug delivery, cancer therapy, and antiviral applications.

Drug delivery and cancer therapy

The biodistribution, pharmacokinetics, and excretion properties of the compound play a vital role in the efficacy of the drug delivery system [12]. Carbon nanostructures are attractive candidates for drug delivery systems because of their dimensions being close to those of viruses and other biological structures. Carbon nanostructures may linger inside biological structures with poor drainage (e.g. tumors), whereas they may not linger inside healthy cells with normal drainage [13]. As carbon nanostructures may be functionalized in a straightforward manner, they may be conjugated with chemotherapeutic agents, antibodies, antitumor drugs, and other therapeutic agents [3,13].

Fullerenes

Numerous derivatives of fullerenes with improved water solubility for advanced drug delivery systems have been developed. The size of fullerenes together with their amphiphilicity enable them to penetrate almost all biological entities and barriers. Conjugated fullerenes may be used for localized drug delivery, which avoids damage to other body organs. For instance, ibuprofen is a common prescribed drug for pain relief and inflammation with side effects such as gastrointestinal hemorrhage, ulcer, digestive aggravation, and vomiting when it is consumed orally. Recent density functional theory (DFT) calculations show that C_{60} fullerenes with a porphyrin-like transition metal-N4 can be used as

ibuprofen carriers. Quantum studies confirmed the release of the drug in the acidic environment of unhealthy cells [14].

The use of fullerenes for nucleic acid delivery systems has receiving attention recently. In a recent *in vitro* study, tetra(piperazino)[60]fullerene epoxide (TPFE) was used for stabilization and delivery of unstable siRNA molecules [15]. *In vivo* studies have already shown that TPFE is nontoxic, unlike the commonly used lipofectamine 2000, for siRNA delivery and has a higher knockdown efficiency [16]. As depicted in Figure 2, the *in vitro* study involved the use of TPFE-siRNA particles with a submicrometer size to deliver siRNA to the lung cells; an immediate agglutination with the plasma proteins occurred. TPFE-siRNA-plasma protein materials were initially stable and accumulated in the lung capillaries; they later became unstable after blocking the lung capillaries, which culminated in the release of siRNA into the cells. The TPFE residues in the form of micelles were under 10 nm and were removed from the lung capillaries with a high clearance rate [15].

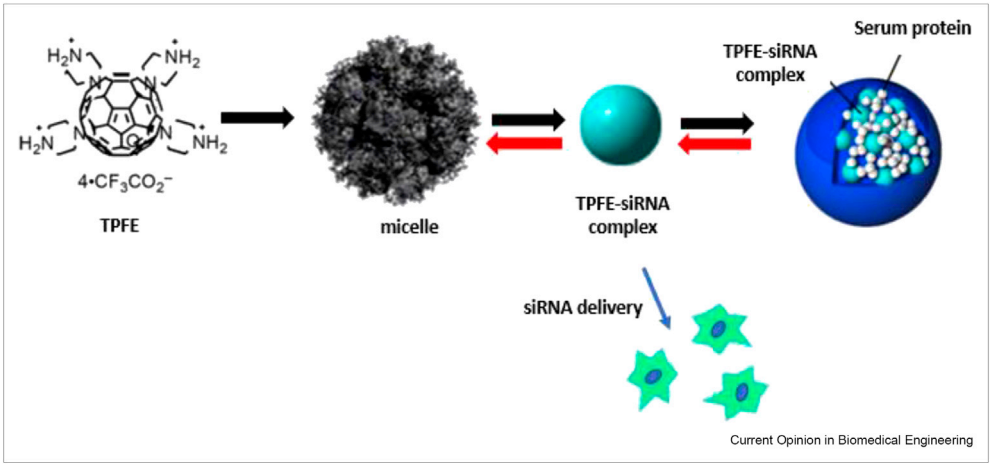
The blood–brain barrier (BBB) contains tight junctions that serve as a barrier to the delivery of highly polar drugs to the central nervous system (CNS). Fullerenes-based carriers have been shown to enable penetration of the BBB. For example, the effect of fullerene compounds on penetration of the BBB by polar hexamethonium benzosulfonate was explored. In this study, "virtually solvent-free planar lipid bilayer" phosphocholine membranes were prepared [17]. Without the fullerene, the addition of hexamethonium benzosulfonate to the lipid bilayer membrane did not produce any observable transmembrane current. However, with the presence of the fullerene compounds (IEM-2143 and IEM-2144), ion permeability through the phosphocholine bilayers, lipid disorder in the phosphocholine membranes, and movement through the lipid bilayers were enhanced [17].

Studies of the COVID-19 pandemic indicate that chloroquine (CQ) may be an efficient medicine to combat the COVID-19 infection [18]. DFT studies show that Al- and Si-doped C_{60} are stable CQ carriers for COVID-19 treatment because of the well-matched energetics between these species; fullerene serves as the electron acceptor and CQ serves as the electron donor [18].

Lung cancer chemotherapy methods suffer from an inadequate concentration of the drug interacting with the tumor cells and the toxicity of the drug. Various water-soluble fullerene derivatives for drug delivery were investigated for their anticancer potential as an alternative to conventional lung cancer chemotherapy [19]. It was found that a stronger cytotoxic ability of fullerene derivatives against lung cancer cells corresponds to the presence of less aliphatic single bonds attached to the fullerene cage, the absence of chlorine in the structure, and the presence of 2-phenoxyacetate residues [19].

A very effective drug for the pancreatic cancer is gemcitabine; however, this agent shows some chemoresistivity and poor distribution inside the tumor. Therefore, an alternative mechanism to deliver gemcitabine is an important focus of current research efforts. One potential solution is the conjugation of gemcitabine with [60]fullerene for improved water solubility [13]. The compound exhibits cytotoxicity that can be boosted

Figure 2



Schematic of producing TPFE-siRNA-plasma protein for siRNA delivery (adapted from Ref. [15]).

Table 1

A Summary of the recent progress in drug delivery and cancer therapy using carbon nanomaterials.

Carbon nanomaterial	Application	New progress	Reference
Fullerene, C_{60} with porphyrin-like transition metal-N4	Drug delivery, Ibuprofen	Predicts the release of Ibuprofen in acidic environment of unhealthy cells	[14]
Fullerene, Al- and Si-doped C_{60}	Drug delivery, Chloroquine	Possible COVID-19 treatment by drug delivery	[18]
Water-soluble fullerene derivatives	Cancer therapy	Water-soluble fullerene derivatives with cytotoxicity for lung cancer	[19]
[60]Fullerene-glycine derivative	Cancer drug delivery, gemcitabine	New synthetic approach for a highly water-soluble [60] fullerene-glycine derivative	[13]
C_{60}-serinol	Cancer drug delivery, paclitaxel	Synthesizing a novel C_{60} derivative	[20]
C_{60}	Cancer drug delivery, Doxorubicin and Boronic Chalcone	The possibility of functionalizing C_{60} with B and N atoms and loading with Doxorubicin and Boronic Chalcone	[21]
Glycoconjugated C_{60} derivatives	Cancer therapy	Glycolfullerenes act as photodynamic cytotoxic agents	[23]
Functionalized graphene with choline chloride	Cancer drug delivery, Doxorubicin	First Doxorubicin delivery by graphene	[24,25]
Graphene with attached folic acid and indocyanine green	Cancer drug delivery, Doxorubicin	Multifunctional graphene synthesis with improved anticancer activity	[29]
Fluorinated graphene	Cancer drug delivery, curcumin	Synthesis of fluorinated graphene with ionic liquid for the first time and curcumin delivery	[30]
Folic acid functionalized graphene	Combined drug delivery, Doxorubicin and Camptothecin	Enhance the efficacy of cancer therapy	[32]
Graphene	Combined drug delivery, Paclitaxel and Doxorubicin	Enhance the efficacy of cancer therapy	[33]
Graphene with attached FeN4	Drug delivery, Ibuprofen	High chemical bonding potential to target bio-entities	[34]
Carboxylated CNTs	Drug delivery, Droxidopa	Uniformly dispersed and biocompatible with great system stability	[35]
SWCNTs	Drug delivery, Isoprinosine	Enhanced anti-NNV ability	[37]
SWCNTs	Drug delivery, bath vaccine	Enhanced the efficacy of bath vaccine	[38]
Functionalized SWCNTs and MWCNTs with PPGP	Cancer drug delivery, Doxorubicin	Foster the uniform dispersibility and biocompatibility of CNTs, and easier evaluation of cytotoxicity	[39]
PEGylated multiwalled discrete CNTs	Cancer drug delivery, Doxorubicin	Successful anticancer delivery systems	[40]
Oxidized MWCNTs by HNO_3/H_2SO_4 covered by ɣ-Fe_2O_3 nanoparticles	Cancer drug delivery, Doxorubicin	Successful anticancer delivery systems	[41]
Polyampholytic alternating polymers (PMT) functionalized SWCNTs	Cancer drug delivery, Doxorubicin	Successful anticancer delivery systems	[42]
CNTs conjugated with glycoblock copolymers and folic acid	Dual targeting system	Increase the efficiency of antibreast cancer activity	[43]

PPGP, pyrrole polypropylene glycol.

through the oxygen species generated by blue LED-irradiated C_{60} [13].

C_{60} conjugated with serinolamide can permeate liver cancer cells; C_{60}-serinol conjugated with paclitaxel reduces the size of tumor without the side effect of weight loss. A study of the *in vivo* function of C_{60}-serinol shows that its biodistribution and excretion from kidney in mice is rapid and efficient [20]. Based on computational results, C_{60} can be successfully loaded with the chemotherapeutic drug doxorubicin (DOX) and anti-tumor agent boronic chalcone [21].

A novel drug delivery system was described by Shi et al. for advanced cancer therapy using C_{60} [22]. Unlike the traditional drug delivery systems, this 'off—on' type drug delivery system does not suffer from an uncontrolled drug release. In this approach, the fullerene is conjugated with DOX using reactive oxygen species (ROS) and a hydrophilic shell is attached to its surface, which has a tumor-targeted feature. In the 'off' mode, DOX is stably entrapped at environments with pH ~5.5. However, in the 'on' mode, ROS are produced by fullerenes, which consequently release DOX. The switching between the 'on' and 'off' modes is controlled remotely by a 532 nm laser [22].

Some C_{60} derivatives are able to produce ROS under light exposure. One example is glycoconjugated C_{60} derivatives that are used for targeting cancer cells [23]. Cancer cells tend to accumulate glucose and lure the glycoconjugated C_{60} into themselves. Based on recent studies, these glycolfullerenes absorbed by cancer cells act as photodynamic cytotoxic agents when exposed to blue and green light [23].

Graphene

Although graphene has potential use as a drug carrier, it has a toxicity effect on human organs as it can aggregate in tissues and produce oxidative stress. To overcome this issue, surface modification of graphene is important. Various functional groups can be attached to the graphene surface through the deep eutectic solvent (DES) method to overcome these issues. The functionalization of graphene enables wider applications of this material for advanced drug delivery. In addition, the large surface-area-to-volume ratio of graphene is beneficial for drug carrier applications.

Zainal-Abidin et al. described DES functionalization of graphene with choline chloride and loading with DOX. This material showed good dispersibility and DOX loading capacity. It exhibits superior anticancer activity as DOX is captured by the functionalized graphene more efficiently than pristine graphene [24,25].

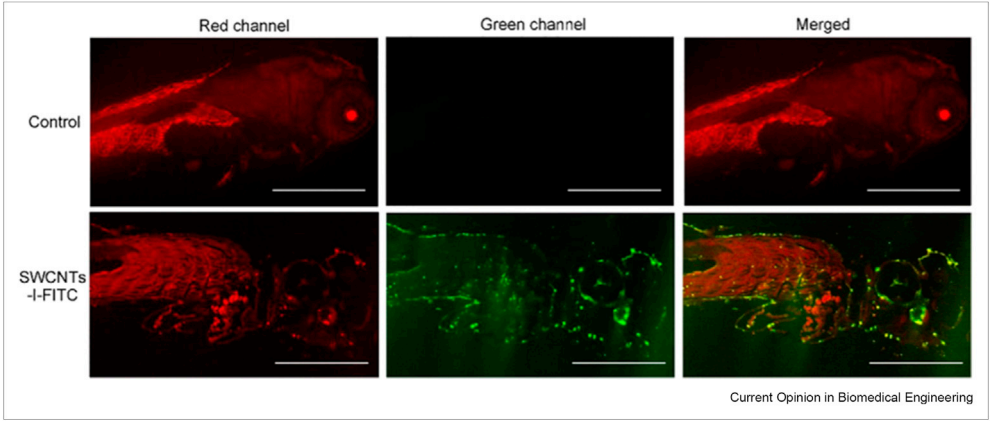
Graphene materials have recently been developed for pH-responsive drug delivery. Unlike normal cells, the cancer cells possess acidic environment. As such, pH-responsive materials may be useful for drug delivery systems. For example, a rubber-like nanohybrid hydrogel containing pristine graphene was developed for pH-responsive drug delivery applications [26]. This material exhibited drug release with changes in pH; in addition, the conductive nature of the hydrogel enabled tunable and pulsatile drug delivery. The pH-oscillatory response of the hydrogel was demonstrated by measuring the swelling and deswelling behavior of the hydrogel in a buffer solution as the pH of the buffer solution was adjusted between 7.8 and 1.7. This study indicated that the nanohybrid hydrogel was pH-responsive and conductive because of the acrylic acid contribution and graphene components of the structure [26].

In another study, GQDs were conjugated with the reverse transcriptase inhibitors CHI499 and CDF119 for use in human immunodeficiency virus (HIV) treatment [27]. GQDs have also been shown to permeate the BBB [28].

Lucherelli et al. attached folic acid to graphene with a PEG chain for targeted delivery of DOX; they used indocyanine green for tracking the compound inside cancer cells to observe its dispersity and anticancer activity. *In vitro* and *in vivo* studies showed reduced toxicity for the multifunctionalized graphene [29]. A novel method for fluorination of graphene by an ionic liquid was studied for curcumin delivery. The functionalized material showed higher drug loading efficiency and stronger anticancer behavior [30].

Combination drug delivery plays a pivotal role in cancer therapy as therapy methods involving only one anticancer drug are not always successful. Owing to its straightforward functionalization and large relative surface area, graphene is a promising material for combination drug delivery [31]. Computational studies show that graphene can be conjugated with paclitaxel and DOX simultaneously. Folic acid functionalized graphene is capable of co-delivery of DOX and camptothecin through strong $\pi-\pi$ interactions [32,33].

Figure 3



Tissue section observation that confirms the effective delivery of isoprinosine using the conjugated system. The first row shows the zebrafish exposed to FITC, which served as the control material. The second row shows the zebrafish exposed to SWCNTs-I-FITC. No clear green fluorescence can be seen in the control system, whereas the green fluorescence in the conjugated system shows effective internalization (the green fluorescence corresponds to the FITC labeling and the red fluorescence corresponds to dyed cell membrane) (with permission from Ref. [37]).

Recent DFT calculations show that graphene with attached FeN_4 serves as an excellent adsorptive carrier for ibuprofen; the ibuprofen/FeN_4-graphene system possesses a high chemical bonding potential to target biological structures [34].

Carbon nanotubes

CNTs are hydrophobic materials that exhibit nonuniform dispersity in biological environments; functionalization of the CNT surface can overcome this limitation. When exposed to oxidative agents, CNTs form carboxylated surfaces. The carboxylated CNT materials are uniformly dispersed and biocompatible materials that can be loaded with drugs. Carboxylated SWCNTs can be loaded with droxidopa using amine and carboxylate groups; droxidopa is used as a treatment for orthostatic hypotension and Parkinson's disease. Molecular dynamic simulations predict good stability for this material [35].

A cell-penetrating cancer-targeting functionalized MWCNT has been described [36]. The results with material indicated showed an increase in ROS level supporting anticancer activity, elevated BBB permeability, and efficacy against glioma tumors. The BBB penetration and the selectivity of the compound toward glioma cells were associated with the antitumor functionality of the material [36].

Viral nervous necrosis disease, which is caused by nervous necrosis virus (NNV), target the CNS in fish; accessing this affected tissue with drugs is a technical challenge. Fluorescein isothiocyanate (FITC) and isoprinosine, an anti-NNV agent, were conjugated with SWCNTs to boost the effectivity of isoprinosine delivery (Figure 3) [37]. A delivery system composed of bovine serum albumin, isoprinosine, and SWCNTs was investigated both *in vitro* and in zebrafish larvae and showed enhanced anti-NNV ability with significantly reduced fatality [37].

SWCNTs were also successfully used to enhance the efficacy of a bath vaccine for juvenile pearl gentian grouper against iridovirus. The efficacy of the immune genes was improved through the use of SWCNTs as the vaccine carrier [38].

Besides the increasing toxicity for healthy tissues, the aggregation of CNTs prevents straightforward estimation of the cytotoxicity of an anticancer delivery system. To facilitate the uniform dispersibility and biocompatibility of CNTs, Pennetta et al. functionalized SWCNTs and MWCNTs with pyrrole polypropylene glycol (PPGP) covalently (CNT/$PPGP_c$) and noncovalently (CNT/$PPGP_s$) and conjugated these materials with DOX. The novel CNT/PPGP/DOX systems were associated with melanoma and lung cancer cell death at a lower dose of DOX. The uniformly distributed CNT/PPGP/DOX also facilitated easier evaluation of cytotoxicity [39].

Other novel, successful anticancer delivery systems containing CNTs and DOX include PEGylated multiwalled discrete CNTs [40], oxidization of MWCNTs by HNO_3/H_2SO_4 and coverage by ɣ-Fe2O3 nanoparticles for magnetic drug delivery [41], and polyampholytic alternating polymer (PMT) functionalized SWCNTs [42].

CNTs exhibit exceptional capability to target a special receptor or molecule. A dual targeting system has been proposed to increase the efficiency of antibreast cancer therapy. In this system, both the glucose transporter protein and the folic acid receptor of cancer cells were targeted simultaneously through loading of CNTs with DOX-conjugated glycoblock copolymers and folic acid [43]. A summary of the recent progress in drug delivery and cancer therapy using the aforementioned carbon nanomaterials is provided in Table 1.

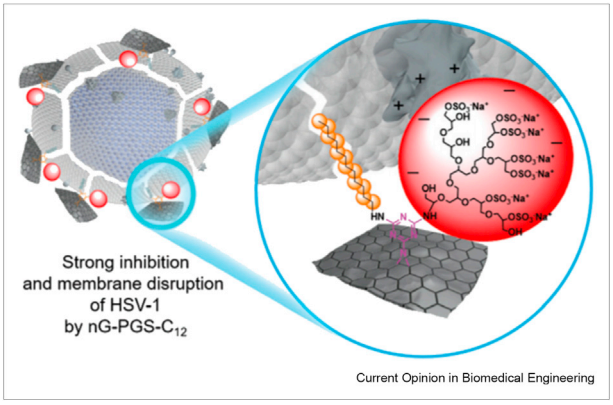
Antiviral applications

With the emergence of new viruses such as COVID-19, the development of new antiviral systems, including drugs and vaccines, has recently attracted significant attention from the research community. Carbon nanostructures have shown promising antiviral features such as viral inhibition activity and virus enzyme blocking to combat against viruses such as HIV, influenza, herpes simplex virus (HSV), and COVID-19 [44,45]. The use of carbon nanomaterials for antiviral applications is currently at an early stage and requires more comprehensive investigation.

Fullerenes

Hydrophilic fullerenes are of special interest for antiviral applications. The biological properties of fullerenes directly correspond to the type of functional groups linked to the fullerene cage. The most water-soluble fullerene derivative is $C_{60}[P(O)\ (OK)_2]_5H$ with C—P

Figure 4



A representation of inhibitory interaction of C_{12} with HSV-1 (with permission from Ref. [54]).

connected to the cage; the synthesis of this material has recently been significantly simplified [46]. *In vitro* studies of the antiviral effect of $C_{60}[P(O)(OK)_2]_5H$ show strong activity against influenza A and feline coronavirus [46]. Klimova et al. reported that the water-soluble C_{60} (ndC_{60}) has activity against type 1 of Herpes simplex virus (HSV-1) and human cytomegalovirus. *In vitro* and *in vivo* studies indicated that ndC_{60} inhibits virus entry into the host cells by blocking virus–receptor interactions [47].

The outer layer (envelope protein) of coronavirus is a hydrophobic phospholipid that is responsible for interaction with the host. The aqueous colloidal fullerene releases singlet oxygen under UVA irradiation, which damages the lipid layer of coronavirus. As such, a C_{60} coating may serve as an antiviral surface. In addition, the adhesion of the virus on the surface can be minimized. Fullerene-coated surfaces take advantage of the lipid structure of the virus and the hydrophobic properties of fullerenes by decreasing the contact area of the virus on the surface [45]. A computational study indicated that fulleropyrrolidine derivatives may interrupt the main mechanism by which the coronavirus protects itself against antibodies, in which the antibodies are neutralized by a receptor-binding domain of the spike protein on the coronavirus [48].

The dimensions of fullerene derivatives match well with the HIV protease active sites and can block HIV enzymes. The requirements for fullerene derivatives with efficient anti-HIV activity are hydrophilicity and a balance between cytotoxicity and antiviral action. Voronov et al. introduced five new water-soluble [60]fullerene derivatives as HIV inhibitors [49] by the reaction between $C_{60}Cl_6$ and dimethyl 2,2'-(1,4-phenylenebis-(oxy))diacetate. They found that the five derivatives acted against R5 and X4 strains of HIV-1 virus.

Graphene

Aside from conjugation with antiviral materials, graphene can directly interact with viruses. Graphene may interact with the virus via electrostatic and hydrophobic interactions to affect the viral envelope [50]. A newly explored direct interaction mechanism was reported by Matharu et al. [51]. They investigated the antiviral activity of graphene nanoplatelets (110 nm × 170 nm) by 24-h incubation of a suspension of graphene in *Escherichia coli* T4 bacteriophage, a double-stranded DNA virus. Graphene nanoplatelets significantly reduced the population of the virion and prevented infection completely within 3 h. They ascribed the antiviral effect of graphene to its morphology and the generation of ROS [51]. Another recent study indicated that a hybrid containing graphene and copper inhibited influenza A virus attachment and entry to the host cell within 30 min by destroying the virus envelope [52].

Graphene can be conjugated with negatively charged antivirals (e.g. negatively charged sulfates) [53]. This type of conjugation enhances the interaction between graphene and the positively charged residues of virions [53]. Donskyi et al. [54] functionalized graphene to enhance its antiviral activity. They synthesized graphene derivatives that were conjugated with polyglycerol sulfate and alkyl chains (C_3–C_{18}). Graphene with the C_{12} alkyl chain acted as the best HSV-1 inhibitor (Figure 4); however, it showed strong toxicity toward Vero cells. The chains shorter than C_{12} were nontoxic for Vero cells yet served as good HSV-1 inhibitors.

There are some suggestions regarding the use of graphene as a COVID-19 inhibitor based on computational simulations and experimental results from other RNA viruses in the coronaviruses family [55,56]. They suggested that graphene can destabilize COVID-19 virus; the strong light absorption properties of graphene may serve as a disinfectant [55,56].

Carbon nanotubes

The RNA-binding domain (RBD) of the nonstructural protein 1 (NS1) in influenza A facilitates virus survival and prevents export of the mRNA of the host cell. Molecular dynamic simulations predicted that CNTs are able to adsorb and stretch the RBD very quickly and interrupt the virus protection system [57]. The effect of nonfunctionalized SWCNTs and hydroxylated MWCNTs on influenza H1N1 strain A/Mexico/4108/2009 (IAV) in lung tissue were evaluated by Chen et al. They noted that body exposure to MWCNTs and IAV changes the antiviral response to the virus without changing the viral titers or causing significant lung injury; SWCNTs generate greater viral titers with lung damage under the same *in vivo* conditions [58]. MWCNTs show phagocytosis through macrophages; the excretion properties of MWCNTs are considerably faster than SWCNTs [58]. Using SWCNTs as an antiviral coating on surfaces was suggested based on the results of DFT studies [59]. According to the DFT results, Ru-, Pt-, and Cu-functionalized SWCNTs strongly adsorb H_2O_2 molecules, which are lethal to viruses such as coronaviruses.

Conclusions and future perspectives

In this article, recent progress in using fullerenes, graphene, and CNTs for drug delivery, cancer therapy, and antiviral activity in recent years has been reviewed. Owing to their nanoscale dimensions, these materials possess high surface-area-to-volume ratios and high chemical reactivity. These nanosized structures can penetrate many biological structures and membranes to facilitate drug delivery. There have been remarkable advancements in the chemical modification of carbon nanostructures and the introduction of new derivatives to improve solubility, enhance biocompatibility, reduce

toxicity, boost antineoplastic activity, and obtain stable loading of drugs (e.g. antiviral agents). Although most studies emphasized the benefits of localized drug delivery and reducing the side effects through the use of carbon nanostructures, the toxicity and safety of these materials still need to be more carefully addressed.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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** of outstanding interest

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