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REVIEW ARTICLE

Carbon nanotubes and graphene in analytical sciences

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Abstract Nanosized carbon materials are offering great opportunities in various areas of nanotechnology. Carbon nanotubes and graphene, due to their unique mechanical, electronic, chemical, optical and electrochemical properties, represent the most interesting building blocks in various applications where analytical chemistry is of special importance. The possibility of conjugating carbon nanomaterials with biomolecules has received particular attention with respect to the design of chemical sensors and biosensors. This review describes the trends in this field as reported in the last 6 years in (bio)analytical chemistry in general, and in biosensing in particular.

Keywords Carbon nanotubes · Graphene · Analytical chemistry · Biosensors

General description on carbon nanotubes and graphene

In 1991, when carbon nanotubes (CNTs) were discovered [1], scientists were fascinated with this new form of carbon which changed the paradigm of the three basic forms of carbon: diamond, graphite and amorphous carbon. While research on CNTs was continuing, in 2004 another interesting material, graphene (G) [2] that was later gaining more attention was reported to be obtained at University of Manchester in the UK.

CNTs and G are two carbon allotropes with an identical composition which have a meshwork of sp^2—hybridized carbon atoms [3] but have different structures. CNTs posses a cylindrical nanostructure formed by rolling up graphene sheets with a quasi-one-dimensional structure and G is an unrolled nanotube into a flat two-dimensional sheet. CNTs can be divided into single-walled CNTs (SWCNTs) and multi-walled CNTs (MWCNTs). The size and structure of CNTs and G can be analyzed by transmission electron microscopy (TEM) and atomic force microscopy (AFM) [4], as can be seen in the Fig. 1.

Owing to their identical composition, the properties of both materials would also be similar, although is not always the case, and the differences in their structure open new ways for further developments in biosensors. For example, G shows a better mechanical adhesion than CNTs, because CNT is a tubular structure and the contact area is minimized due to the curvature, whereas the contact area is maximal in graphene [5]. Furthermore, small changes in the charge environment caused by the adsorption of biomolecules can give measurable changes in their properties [3].

Based on the remarkable electronic and optical properties, CNTs and G have been extensively explored for chemical and biological sensing applications beside their use as catalyst supports. Tuning the graphene forms production according to (bio)sensing applications is of crucial importance. For electrochemical applications, the approach with chemical/thermal reduction of graphene oxide looks promising. In recent reports, graphene has been produced through the electrochemical reduction of graphene oxide [6–10]. The electrochemically reduced graphene oxide exhibit much better performance for electrochemical applications than chemically reduced one [8, 11].

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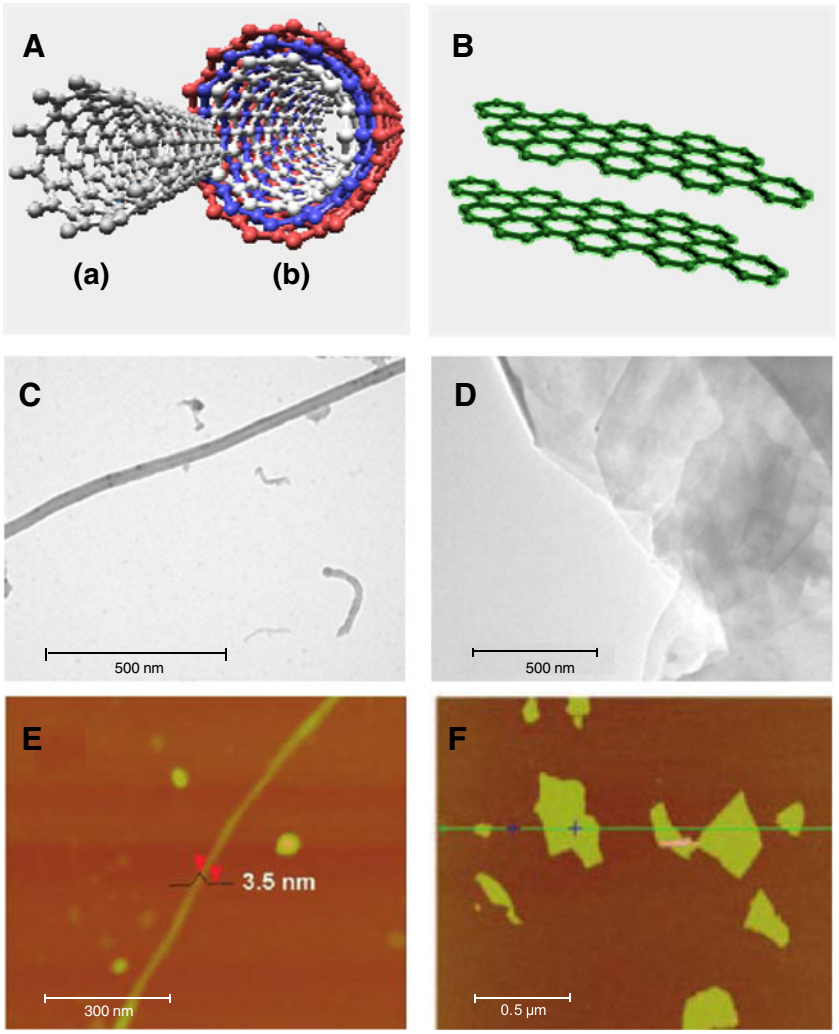

Fig. 1 Structural representation of **A** (**a**) single-wall carbon nanotube (SWCNT) and (**b**) multi-wall carbon nanotubes (MWCNTs) **B** graphene sheets (GS); TEM images of **C** SWCNTs and **D** GS; AFM images of **E** SWCNT and **F** GS on a mica substrate. (**E** and **F** Adapted from reference [14] and [76], respectively)

A key step in CNT and G-based biosensing is the immobilization of biomolecules on their surface for their further use as recognition elements in various kinds of transducers including field-effect transistors (FETs). Two approaches for their functionalization have been reported: (1) noncovalent interaction including physical adsorption or entrapment of biomolecules on/within the material surface and (2) covalent interaction with the functional groups produced via chemical reactions. Thereby, the functionalized CNTs and G exhibit high sensitivity and selectivity in electrochemical, optical, and electronic biosensing systems. Furthermore, thanks to their small size, high electrical conductivity, and high surface-to-volume ratio, devices with fast response and high sensitivity have been developed [3, 5, 12–14]

CNTs and G, used in electrical biosensors [3, 14–20], have shown a high capacity for charge transfer, which makes them suitable to reach lower LODs and higher sensitivity values. These nanomaterials are used as modifiers of transducers ensuring efficient immobilization of biomolecules or other synthetic receptors which are the principal components to improve the performance of biosensors. Particularly, graphene is offering high benefices relative to CNTs [21, 22] in terms of Förster resonance energy transfer (FRET) quenching efficiency for biosensing applications, although if considering FET-style biosensors CNTs could present better results [3, 14]. New opportunities for generating or even amplifying the analytical signals by using these carbon nanoforms in biosensing are being opened [12, 15–17, 23, 24].

Another aspect to be considered is the dispersion of CNTs and G in various matrixes. Thanks to their large surface energy and strong interaction, both materials are difficult to be dispersed in polymeric matrices [25, 26]. Nevertheless, the use of suitable dispersing agents such as surfactants and polymers can preserve their original structures and intrinsic electrical properties, and improve their solubility in aqueous medium. Under these conditions these carbon nanomaterials can be transformed/integrated into various stronger, conductor and flexible devices with interest to be used in various applications. Of particular interest,

for CNTs and G applications in analytical sciences, is the research related to electroanalysis field. The large specific surface area, good biocompatibility and a high adsorption capacity are some of the properties which make these materials suitable to be used in enzymatic sensors, immunosensors and genosensors (DNA sensors).

Considering the huge amount of publications concerning to analytical applications of CNTs and graphene, this review shows some of the most significant contributions appeared in the literature since 2006, particularly in the development of optical and electrochemical sensing systems. For example, some novel (bio)sensing and separation applications related to the electrocatalytic effects of CNTs and graphene, as well as the possibility to obtain composites based on their mixing with polymers or other chemical substances, and also their capability to be used as electrode modifiers, in FETs devices and as detectors in separation techniques such as high performance liquid chromatography (HPLC) or micro-capillary electrophoresis (MCE) are presented in the following sections for each one of these materials. Table 1 displays several examples from CNT and G-based biosensing. Details on the analytes, detection methods, detection limits (LODs) and kinds of applications are also included.

Carbon nanotubes

(Bio)sensing applications

CNT integration into biology based devices is an important trend in the current nanotechnology based analytical sciences [19, 22]. CNTs are offering significant advantages over many existing materials due to their high surface area, the facility for accumulating biomolecules, their excellent conductivity, minimization of surface fouling and electrocatalytic activity that they have. In particular, the unique properties of CNTs make them extremely attractive for the fabrication of electrochemical (bio)sensors [19, 20, 27–29]. Recent studies have demonstrated that CNTs can enhance the electrochemical reactivity of biomolecules and promote the electron–transfer reactions of proteins. The high conductivity of CNTs permits their use as highly sensitive nanoscale sensors and biosensors.

Different (bio)sensing platforms based on the use of CNTs as electrode modifiers have been developed. Our group has integrated CNTs onto a glassy carbon (GC) electrode by using a matrix based in MWCNTs, tetrahydrofuran (THF) mixed with poly(vinyl chloride) (PVC) and a glutaraldehyde (GA) solution, for β-Nicotinamide adenine dinucleotide (NADH) detection [30]. This CNTs matrix promotes better the electron transfer of NADH minimizing the fouling effect. GC electrode modified with CNTs shows remarkable electrochemical and mechanical advantages compared to bare GC electrode offering future alternatives for biosensors applications due to the ability of the developed design for the covalent binding of biological molecules. Another example based on (bio)sensing platforms using CNTs has been reported by Reuel et al. [31]. They developed a sensor array employing recombinant lectins as glycan recognition sites tethered via Histidine tags to Ni^{2+} complexes which act as fluorescent quenchers for semiconducting SWNTs embedded in a chitosan hydrogel spot. This detection platform is based on near-infrared (near-IR) fluorescent detection which allows measuring of binding kinetics of model glycans in real time in a similar way as the surface plasmon resonance (SPR). The absolute detection limit for the current platform was found to be 2 μg of glycosylated protein or 100 ng of free glycan to 20 μg of lectin.

On the other hand, CNTs mixed with magnetic nanoparticles (MNPs) functionalized with enzymes can provide magneto-switchable bioelectrocatalysis by using an external magnetic field. MNP-enzyme-CNT conjugate can simplify magneto-switching and open the door to a wide range of novel electrocatalytic and bioelectrocatalytic applications for magnetocontrolled redox enzymes. Based on this concept, a novel biosensor has been developed. This uses a MNPs-tyrosinase conjugate in operational synergy with MWCNTs, where an on—off external magnetic field is applied to a screen-printed electrode used as a transducing platform (see Fig. 2) [20]. The response of the biosensor to catechol is evaluated obtaining a limit of detection (LOD) around 7.61 μM (S/N=3) with a relative standard deviation (RSD) of 4.91 % (n=3).

Another study based on magnetic particles (MPs) has been performed for the specific detection of ferrocene labels used for the immunodetection of dopamine in artificial and real samples [32]. Here, CNTs are adsorbed onto the surface of the beads and used as wiring tools for electrochemical biosensing. These CNT/MP complexes attached onto the electrode surface allow straightforward electrochemical sensing of the MP surface by exploiting CNT wiring.

Nanomaterials are also offering new opportunities in the development of new -based (bio)sensing systems for applications in food industry, environmental monitoring, clinic diagnostics and safety and security. In this context, an impedimetric detection method of a DNA sequence related to Influenza A (H1N1) virus using CNTs platform and AuNPs so as to improve the sensitivity and rapidity of analysis is reported [33]. This device uses colloidal gold for labelling of DNA oligonucleotides and the impedimetric signal of AuNPs onto screen printed carbon nanotubes electrode is measured and correlated to the DNA target concentration.

CNTs can be used as efficient transducers in solid-contact ion-selective electrodes [34]. CNTs must be connected with a suitable receptor to selectively detect a specific analyte. Aptamers are good receptor candidates for the selective and high-proficiency detection of a wide range of molecular

Table 1 Some reported examples for carbon nanotubes and graphene-based biosensing systems

Material	Analyte	Detection method	LOD	Application	Ref
CdS–G nanocomposite	Carbaryl	Amperometric, by inhibition of OPs on AChE activity	0.7 ng mL^{-1} (S/N=3)	Amperometric biosensor	[24]
GO-MWCNTs	H_2O_2	Electrocatalytic reduction for H_2O_2	1.17 μM (S/N=3)	Electrochemical sensing platform	[91]
MWCNTs	Catechol	Magneto switchable bioelectrocatalytic	7.61 μM (S/N=3)	Electrocatalytic Magnetoswitchable biosensor	[20]
GO	DA in biological fluids	Label-free PCT	94 nM	NIR fluorescent biosensor	[58]
SWCNTs	Glycosylated protein	NIR fluorescence	2 μg	NIR fluorescent sensor	[31]
MWCNTs	Phenol	Amperometric reduction of *o*-quinone	1.35 μM (S/N=3)	Amperometric biosensor	[19]
MWCNTs	DA	Amperometric	37 μM (S/N=3)	Amperometric biosensor	[92]
SWCNTs	*ST*	Potentiometric	0.2 CFU mL^{-1} (S/N=3)	Potentiometric aptasensor	[93]
CMG	Thrombin	Label-free electrochemical impedimetric	10 nM	Impedimetric aptasensor	[15]
rGO	2-CP, 3-CP, 2,4-DCP, 3,4-DCP, 2,4,6-TCP, 4-CP, 2,3,5-TCP and 2,3-DCP	HPLC-UV	0.2, 0.2, 0.2, 0.2, 0.4, 0.1, 0.4, and 0.2 ng^{-1} (S/N=3), respectively	Adsorbent in SPE	[79]
MWCNTs	2,6-dichloroaniline, 2-nitrophenol and naphthalene	HPLC	0.1–3 ng mL^{-1} (S/N=3)	Sorbent for μ-SPE	[48]
MWCNTs-R-NH_2	Acetone, ethyl acetate, toluene, methyl isobutyl ketone, n-butyl acetate, 2-butanol, 1-butanol, 1,3,5-trimethylbenzene, n-undecane, n-dodecane	GCS	–	Stationary phase	[47]
rGO	Lead	FAAS	0.61 μg L^{-1}	SPE	[85]
Graphene	PBDEs, MeO-PBDEs OH-PBDEs (in soil samples)	LC–ESI-MS/MS	5.9–28.7, 14.3–46.6, and 5.3–212.6 pg g^{-1}, respectively	Sorbent in MSPD	[87]

GO graphene oxide; *CdS–G* CdS–decorated graphene; *MWCNTs* multi-wall carbon nanotubes; *SWCNTs* single wall carbon nanotubes; *GO-MWCNTs* graphene oxide-MWCNTs hybrid nanocomposite; *OPs* organophosphates; *AChE* acetylcholinesterase; *DA* dopamine; *ST Salmonella Typhi*; *CFU* colony-forming units; *SPE* solid-phase extraction; *μ-SPE* micro-solid-phase extraction; *MWCNTs-R-NH_2* Amino-terminated alkyl MWCNTs; *HPLC* High-performance liquid chromatography; *FAAS* Flame atomic absorption spectrometry; *rGO* reduced graphene oxide; *CMG* chemically modified graphene; *GCS* gas chromatographic separation; *MSPD* matrix solid-phase dispersion; *LC–ESI-MS/MS* liquid chromatography–electrospray-tandem mass spectrometry; *PBDEs* polybrominated diphenyl ethers; *MeO–* methoxylated; *OH–* hydroxylated; *2-CP* 2-Chlorophenol; *3-CP* 3-chlorophenol; *2,4-DCP* 2,4-dichlorophenol; *3,4-DCP* 3,4-dichlorophenol; *2,4,6-TCP* 2,4,6-trichlorophenol; *4-CP* 4-Chlorophenol; *2,3,5-TCP* 2,3,5-trichlorophenol; *2,3-DCP* 2,3-Dichlorophenol; *HPLC-UV* HPLC with multi-wavelength ultraviolet; *PCT* photoinduced charge transfer; *NIR* near-infrared; *LOD* limit of detection

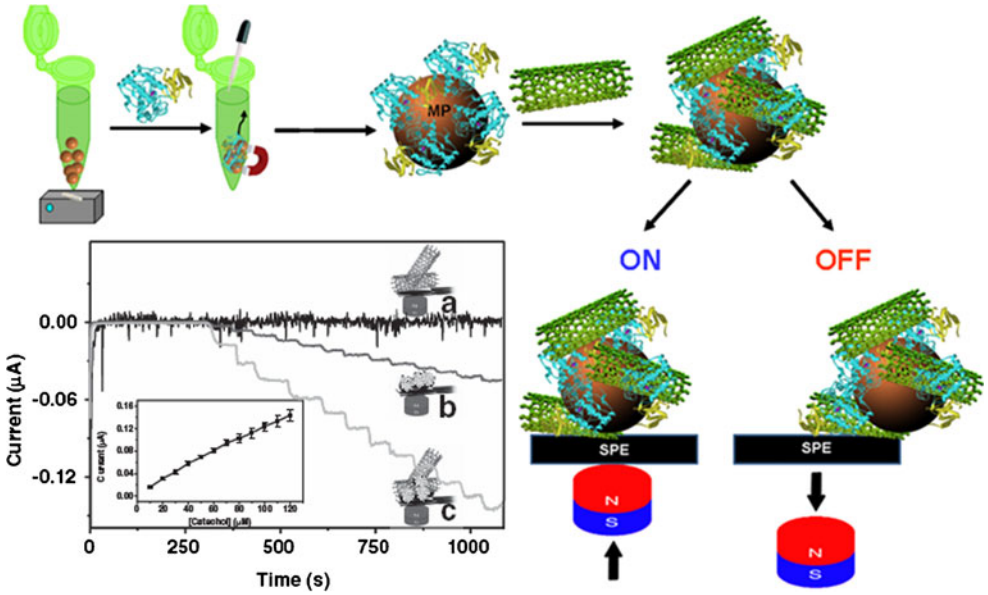

Fig. 2 Scheme of a tyrosinase-modified magnetic nanoparticles (MNPs) (size: 100 nm) conjugate in operational synergy with multi-wall carbon nanotubes (MWCNTs) by applying an on-off external magnetic field under a screen printing electrode (SPE). The insets show the current–time recordings for the catechol response from the SPE modified with **a** MWCNTs; **b** the bioconjugate of MNPs and tyrosinase; and **c** the bioconjugate of MNPs, tyrosinase, with MWCNTs, as well as the corresponding calibration plot. (Adapted from reference [20])

targets, including bacteria [35]. In this way, a rapid and sensitive strategy for detection of living bacteria at ultralow concentrations using a CNT based potentiometric aptasensor has been reported by Rius's group [35]. It takes advantages of CNTs with respect to the traditional culture detection method. The authors demonstrate that aptamer-based SWCNT potentiometric sensors are highly selective and can be successfully used to detect living microorganisms in an assay in real time (see Fig. 3). The most important advantage of this biosensor is that simple positive/negative tests can be carried without cross reaction with other types of bacteria. The easy way with which measurements are performed using a potentiometric sensor opens the door to simpler microbiological analysis.

Furthermore, the development of simultaneous multiplex assays is showing a great efficiency in clinical applications, which shortens the analysis time and consequently decreases detection cost in comparison with the traditional single analyte assays. For example, a novel sandwich-type electrochemical aptasensor has been fabricated for simultaneous sensitive detection of platelet-derived growth factor (PDGF) and thrombin based on dual signal amplification of SWCNTs and multi-labeled graphene sheets using as redox probes toluidine blue (Tb) and ferrocene (Fc) attached with reduced graphene oxide (rGO) sheets respectively, which are subsequently coated with platinum nanoparticles (PtNPs) to form the PtNPs-redox probes-rGS nanocomposites. Thus, a signal amplification strategy based on bienzyme (glucose oxidase and horseradish peroxidase) modified PtNPs-redox probes-rGS nanocomposites as the tracer labels for secondary aptamers (Apt II) through sandwiched assay was described. AuNPs functionalized SWCNTs (AuNPs@SWCNTs) as the biosensor platform enhance the surface area to capture a large amount of primary aptamers (Apt I), thus amplifying the detection response. The results showed that the multi-labeled PtNPs-

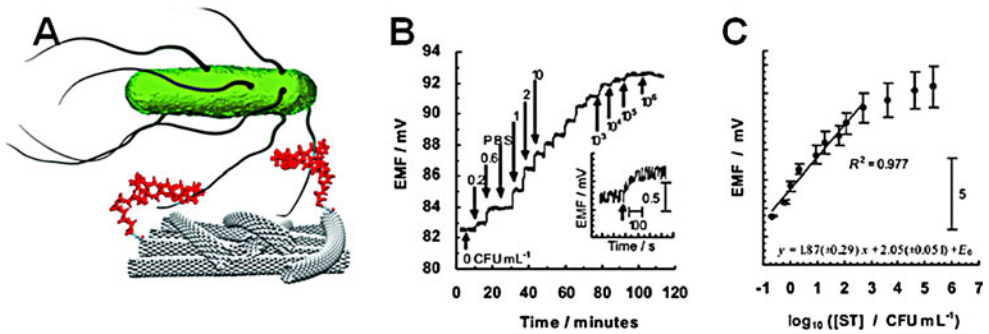

Fig. 3 **A** Schematic representation of the interaction between the target bacteria and the aptamer–SWCNT hybrid. **B** Potentiometric responses of the SWCNT electrode functionalized with aptamer for different concentrations of *Salmonella Typhi* (*ST*). Inset shows the fast response time (in seconds) of the inoculation step at 0.2 CFU mL^{-1} **C** Electromotive force (EMF) response versus log of concentration of *ST*. (Adapted with permission from reference [93]). For more details, see text

redox probes-rGS nanocomposites display satisfying electrochemical redox activity and highly electrocatalytic activity of PtNPs and bienzyme, which exhibit a LOD of 8 pM for PDGF and of 11 pM for thrombin [36].

Moreover, electrochemical detection using CNTs modified electrodes as detecting systems in separation techniques such as HPLC or capillary electrophoresis (CE) has also been reported [37–39]. For example, Pingarron's group has modified a GC electrode with MWCNTs for amperometric detection of tetracycline (TC) antibiotics (tetracycline, oxytetracycline, chlortetracycline and doxycycline). They have demonstrated the possibility to carry out multiresidue analysis in samples containing tetracyclines and sulfadrugs (see Fig. 4). This HPLC with electrochemical detection was applied to the analysis of fish farm pool water and underground well water samples spiked with the four TCs at 0.2 μM. Thus, solid-phase extraction (SPE) was accomplished for the preconcentration of the analytes and clean-up of the samples [38].

Separation applications

Preconcentration is an important step in various analytical process technologies used for trace-level determination; thus a variety of sample pretreatment techniques are being developed. Among the most promising technique for application in analytical chemistry is the SPE, which has provided an efficient tool using a large number of materials. In this context CNTs have been also reported to be used as adsorbents in SPE, and as stationary phases coupled with gas and liquid chromatography (LC) [37, 40–46]. CNTs provide an active surface for the adsorption/desorption of organic molecules that make them suitable as SPE adsorbents.

Analysis and speciation for cobalamins (various forms of vitamin B12) has been performed in seafoods by using LC that contains a MWCNT-packed mini-column system for on-line sample introduction [40]. Such system was tested to be an excellent alternative to trace-level determination.

On the other hand, gas chromatography (GC) has improved the selectivity of compounds detection by using modified CNTs as stationary phase. Speltini et al., [47] studied the separation of esters and chloroaromatic hydrocarbons by using chemically modified MWCNTs as stationary phase. Amino-terminated alkyl MWCNTs (MWCNTs-R-NH_2) were synthesized by chemical modification of the nanotube

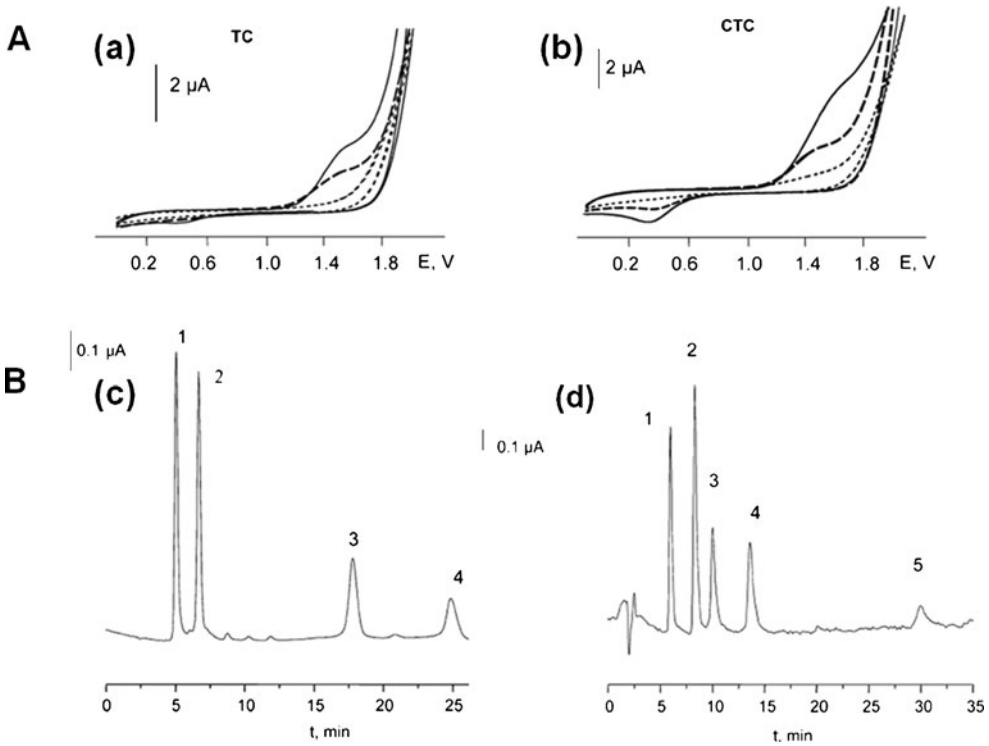

Fig. 4 **A** Cyclic voltammograms of 0.1 mM **(a)** tetracycline (TC) and **(b)** chlortetracycline (CTC) at a glassy carbon electrode modified with MWCNTs (MWCNT-GCE) (solid line); at a unmodified glassy carbon electrode (dashed line); and a background voltammogram in 0.05 M phosphate buffer solution of pH 2.0 (dotted line), ν=50 mV s^{-1}. **B** Chromatograms obtained from a **(c)** standard solution containing 10^{-4} M each of oxytetracycline (1, OTC), tetracycline (2, TC), chlortetracycline (3, CTC) and doxycycline (4, DC) with amperometric detection at a MWCNT-GCE. Mobile phase, 18:82 acetonitrile/0.05 M phosphate buffer of pH 2.5; flow rate, 1.0 mL min^{-1}; Eapp=+1.20 V; **(d)** a water sample containing 20 mM each of sulfadiazine (1), sulfamerazine (2), OTC (3), TC (4) and sufamethoxazol (5), with amperometric detection at a MWCNT-GCE. (Adapted with permission from reference [38])

skeleton by nucleophilic substitution with 2,2′-(ethylenedioxy) diethylamine. The so-prepared stationary phase was used for analysis of a synthetic mixture containing different classes of analytes, such as esters, ketones, alcohols, alkanes, and aromatic hydrocarbons. Good chromatographic profiles were obtained, with satisfactory resolution and peak shape, even for the most retained analytes. MWCNTs-R-NH_2 had higher selectivity and resulted in enhanced resolution and better sorption–desorption behavior than non-functionalized MWCNTs (nf-MWCNTs).

Both SWCNTs and MWCNTs have been explored as high performance sorbents for μ-solid phase extraction in packed and self assembled formats. For example, Sae-Khow and Mitra [48] have reported the implementation of the μ-solid phase extraction in the needle of a syringe for integrating sampling, analyte enrichment and sample introduction into a single device. This device was constructed by using a syringe attached to a removable capillary probe (0.53 mm in ID) containing CNTs (as shown in Fig. 5). The CNTs were used in self-assembled (open tubular) as well as in packed formats. The analytical signals of the HPLC chromatograms of the original samples and samples enriched by μ-solid phase extraction with MWCNTs resulted significantly higher than the direct injection of a standard solution. MWCNTs provided the lowest LODs for naphthalene which was 0.1 ng mL^{-1} compared with 10 ng mL^{-1} from C-18 (S/N=3). These results clearly indicate that CNTs have outstanding enrichment capabilities, and can be successfully used for trace analysis.

Recently, CNTs are applied for preconcentration of heavy metals [42, 49], organics [50], and biological impurities [51] due to the large specific surface area. Cui and co-authors modified MWCNTs for preconcentration of Pb (II). The MWCNTs were grafted by the tris-(2-aminoethyl) amine (TAA), which has been proved as a good chelating reagent for metal ions [52]. TAA-grafted MWCNTs (MWCNTs-TAA) were employed as extractants for Pb(II) through a SPE process using a microcolumn packed with MWCNTs-TAA. The results show that the dispersibility of the MWCNTs-TAA is obviously increased compared with pristine MWCNTs and show good selectivity for adsorption of Pb(II) ions. A maximum adsorption capacity of 38 mg g^{-1} of Pb(II), a LOD 0.32 ng mL^{-1}, an enrichment factor of 60 and RSD of 3.5 % (n=6) were obtained.

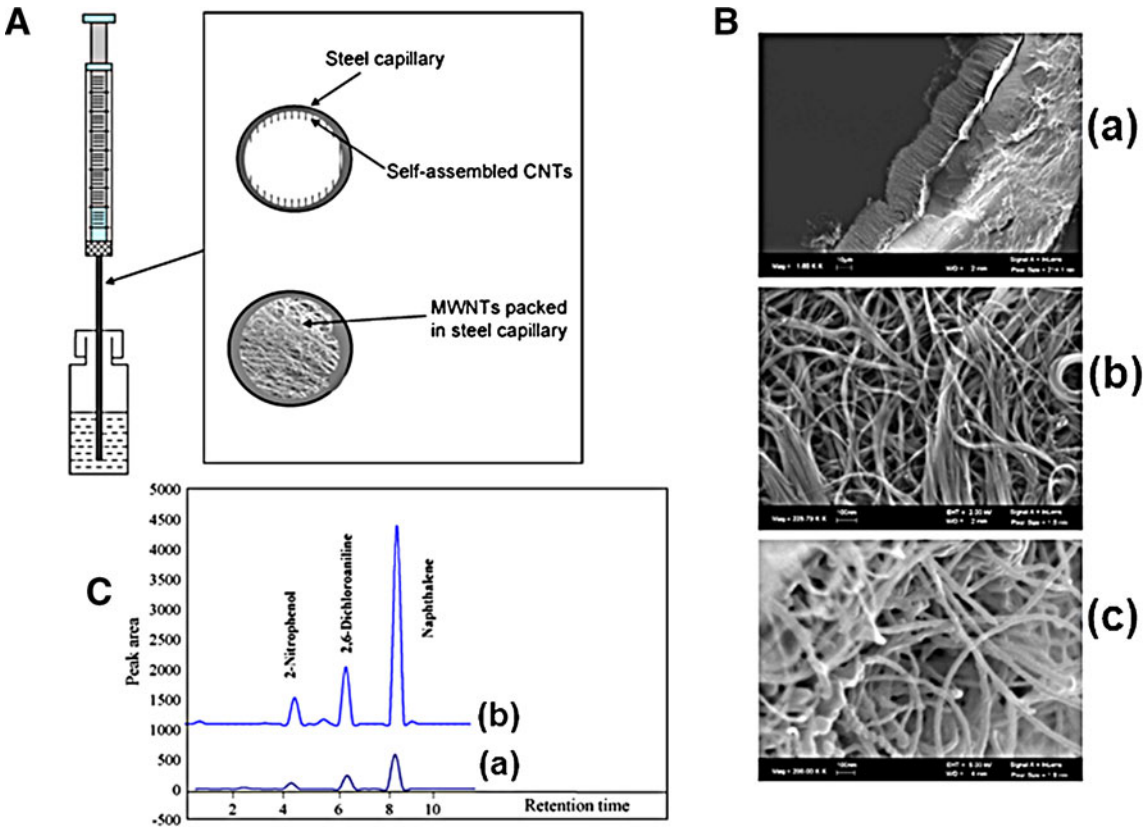

Fig. 5 **A** Scheme of the μ-solid phase extraction device; **B** SEM images of **(a)** CNTs in self-assembled in the capillary probe, **(b)** SWNTs, and **(c)** MWNTs used for packing the μ-solid phase extraction probe; **C** HPLC chromatograms of **(a)** original samples and **(b)** samples enriched by μ-solid phase extraction with MWCNTs. (Adapted with permission from reference [48]). For more details, see text

Graphene

(Bio)sensing applications

A significant number of publications reporting graphene-based biosensors [12, 53–57] which have been used for improving the sensitivity and selectivity of biosensing systems based on the unique chemical, optical, electrical and electrochemical properties of G [3, 16, 21, 58–62] have appeared.

G is reported to decrease overpotentials of electrochemical reactions, ensure a better reversibility of some redox reactions, and bring novel labelling opportunities including multidetection capabilities.

The graphene's electrical and optical properties are affected by several important factors such as number of layers, the used substrate, adsorbed impurities, flatness, defects, size of sheet, edge types and functionalization. These factors need to be considered and controlled where possible during the fabrication of graphene-based biosensing. The first factor, the number of layers, has special importance due to the fact that by its increasing the complexity of the electronic band structures, thereby the electrical and optical properties should change [3].

Graphene have been employed in various optical and electrochemical biosensors. In these applications, detection techniques such as fluorescence (FL), electrochemiluminescence (ECL) and FETs in addition to the use of G either as transducer or as biomolecular labels have been reported [16]. For example, Chen and co-authors [58] have studied the fluorescence quenching capacity of G and its potential for (bio)sensing. They have evaluated a graphene oxide (GO)-based photoinduced charge transfer (PCT) label-free near-infrared fluorescent biosensor for dopamine (DA), as shows the Fig. 6. The multiple noncovalent interactions between GO and dopamine (DA) resulted in effective self-assembly of DA on the surface of GO, and significant fluorescence quenching, allowing development of a simple label-free PCT-based near-IR fluorescence biosensor for selective and sensitive detection of DA in biological fluids with a LOD of 94 nM and a RSD of 2.0 %.

A novel self-assembled homogenous immunoassay has been developed by Liu et al. [63], which explores nanoscale-graphene sheets as excellent FL acceptors and CdTe QDs as donors for ultrasensitive detection of trace amounts of the target glycoprotein α-fetoprotein (AFP), a potential diagnostic biomarker for hepatocellular carcinoma. They demonstrated that the radiative quenching efficiency was distance independent on a wide dynamic range due to the effect of the two-dimensional G-based material, which significantly broke the distance limit in traditional Förster Resonance Energy Transfer (FRET) or Photoinduced Electron Transfer (PIET)-based biosensors.

Chemically modified graphene (CMG) is an ideal nanomaterial for the construction of FET transistors for sensing charged molecules. Therefore, CMG-based FETs can be employed for DNA sensing since DNA has a charged phosphate backbone [64]. The generation of holes is attributed to the negative-charge molecular gating from the phosphate ions of the complementary DNA. The change in conductivity due to hybridization/dehybridization varied from 60 % to 200 % for different graphene-DNA (G-DNA) samples. Immersing the G-DNA device in a solution of non-complementary DNA did not change the conductivity. Even though the DNA hybridization/dehybridization measurements were made in dry nitrogen conditions, they were effective in producing the negative-charge-gating. The results elucidate the high sensitivity of CMG nanostructures which function effectively as a label-free DNA detector and a molecular transistor. With these studies, Mohanty and Berry have demonstrated the interfacing of CMGs with biological systems to build a novel live-bacterial-hybrid device and a DNA-hybridization device with excellent sensitivity. CMGs, with their two-dimensional nanostructures and adjustable surface chemistry, can strongly interface with the biological systems without geometric restrictions and without compromising the integrity of the microbial attachment.

Other studies related with the detection of DNA hybridization based on CMG platforms has been developed by Pumera's group [65, 66]. They have compared for the first time different graphene platforms modified with hairpin-DNA (hpDNA) probes for the sensitive detection of single nucleotide polymorphism (SNP) correlated to the development of Alzheimer's disease. Graphene as transducer and electrochemical impedance spectroscopy (EIS) as a highly sensitive detection technique have been used. The LOD for each of the three different platforms was 50 nM for graphene nanoribbons consisting mostly of single- and double-layered graphene (G-SL), 6.6 pM for triple and four layer graphenes (G-FL), and 66 μM for multilayer graphene nanoribbons (G-ML) [65].

Several (bio)sensing systems have been reported to date involving several kinds of "graphene", e.g., GO, chemically-rGO and graphene produced by direct in-liquid exfoliation (dG) [67]. For instance, Lu et al. [68] have reported a novel glucose biosensor by combining exfoliated graphite nanoplatelets (xGnPs) decorated with platinum (Pt) and palladium (Pd) nanoparticles, glucose oxidase (GOx), and Nafion. Pt-xGnP and Pd-xGnP-based glucose biosensors showed LODs of 1.0 and 4.0 μM (S/N=3); detection limits of around 20 and 10 mM and sensitivities of 61.5±0.6 and 47.9±3.2 μA $(mM \cdot cm^2)^{-1}$ upon the addition of 0.5 mM glucose solution in 50 mM phosphate buffer solution at 700 mV, respectively.

Shan and co-authors [69] developed another novel method for glucose detection. They have exploited the high surface area and electrical conductivity of rGO to attempt direct electron transfer (DET) between the GOx and the electrode. The polyethylenimine-functionalized ionic liquid (PFIL) has been used to construct the biosensor. High biocompatibility and exchangability of the counter-anions in PFIL, e.g., with negatively charged GOx, are favorable in order to immobilize

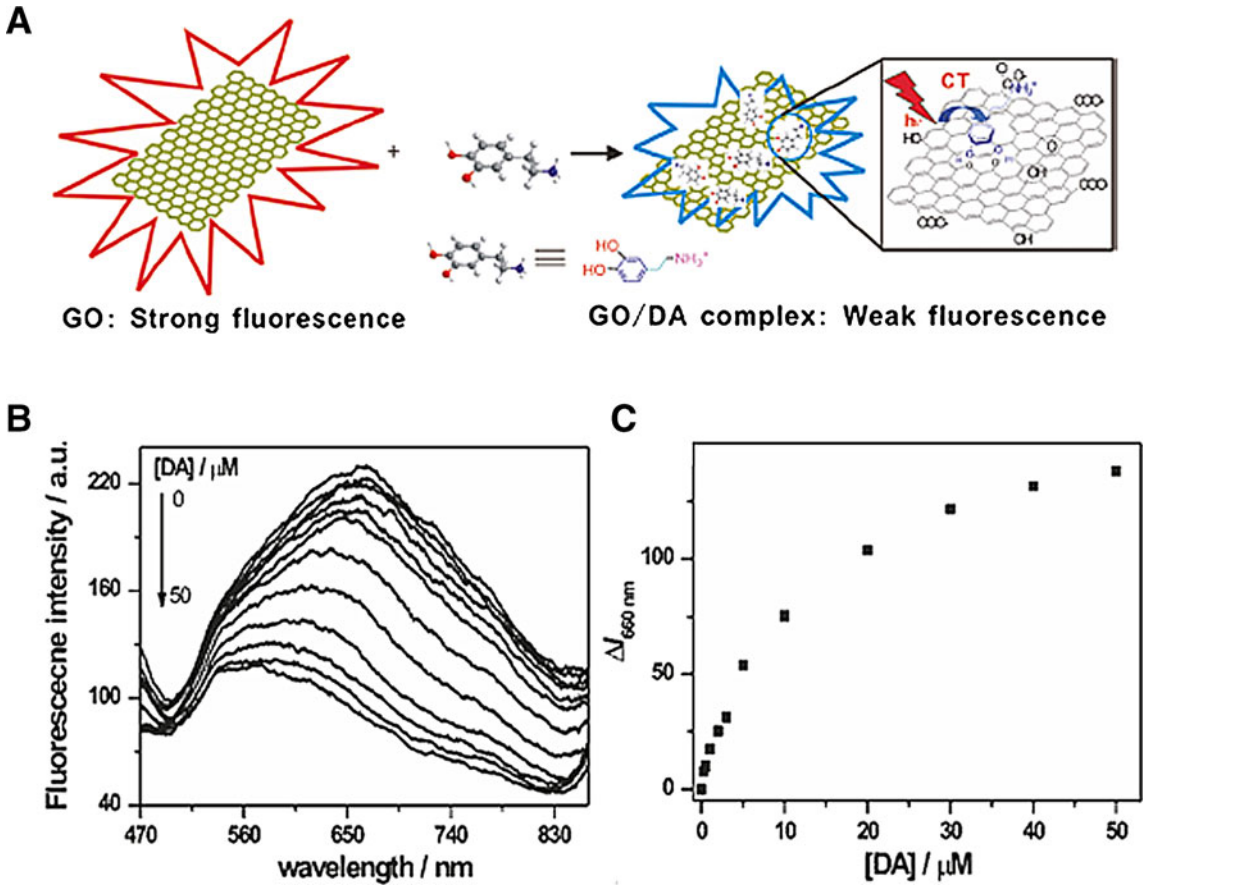

Fig. 6 **A** Schematic representation for the graphene oxide (GO)-based photoinduced charge transfer fluorescent biosensor for dopamine (DA). **B** Fluorescence spectra of GO (25 μg mL^{-1}) in presence of different DA concentrations (0, 0.25, 0.5, 1.0, 2.0, 3.0, 5.0, 10, 20, 30, 40, and 50 μM) under excitation at 450 nm and with a 5.0 mM Tris–HCl solution, pH=5.0; **C** Quenched fluorescence intensity at 660 nm (ΔI) vs DA concentration ([DA]). (Adapted with permission from reference [58])

biomolecules. Thereby, a graphene-PFIL solution (2 μL) was dropped and dried onto a GC electrode at room temperature for 24 h. Then, the graphene-PFIL modified GC electrode was impregnated in GOx solution (2 mg mL^{-1}) for 24 h at 4 °C to obtain the graphene-GOx-PFIL modified GC electrode. This electrochemical biosensor achieved the DET of GOx maintaining its bioactivity and showing a potential application in the construction of novel glucose biosensors with linear glucose response up to 14 mM.

The determination of phenolic compounds is very important for evaluating the toxicity of environmental samples. Song et al. [70] developed a biosensor based on GO conjugated with tyrosinase assembled AuNPs for the determination of catechol. A screen-printed electrode was modified by using covalent attachment between 1-pyrenebutanoic acid, succinimidyl ester (PASE) adsorbing on the GO sheets and amines of tyrosinase-protected gold nanoparticles (Tyr–AuNPs). They detected catechol with a high sensitivity, good reproducibility and acceptable stability with a linear range of 8.3×10^{-8} to 2.3×10^{-5} M with a correlation coefficient (R^2) of 0.9980 and a LOD of 2.4×10^{-8} M (S/N=3).

On the other hand, G has also received significant attention as new and advantageous nanomaterial for electrochemical (bio)sensing in microfluidic devices. Martin and co-workers [71] evaluated GO amperometric detectors in microfluidic devices for detection of dopamine, catechol and nitroaromatic explosives, such as 2,4,6-trinitrotoluene (TNT), 2,4-dinitrotoluene (DNT) and 1,3-dinitrobenzene (DNB). They have reported that GO as electrochemical detector in the tested microchip doesn't show any advantage in terms of sensitivity or selectivity over graphite microparticles, as showed in Fig. 7.

The optical properties of G have also been of great interest in (bio)sensing applications [72, 73]. Graphene oxide has been explored as acceptor of quantum dots (QDs) FRET donors into liquid phase and as acceptor of QDs FRET individual donors [63, 74]. According to Kim et al. [75] "the strong quenching by GO is likely due to the residual graphitic domains in the basal plane that survived the severe chemical oxidation". For GO or reduced GO, as acceptors, the FRET effect can be independent of the emission spectra of the donor. Recently, a simple FRET evidence for the ultrahigh QD quenching efficiency by GO compared to graphite, carbon nanofibers and carbon nanotubes

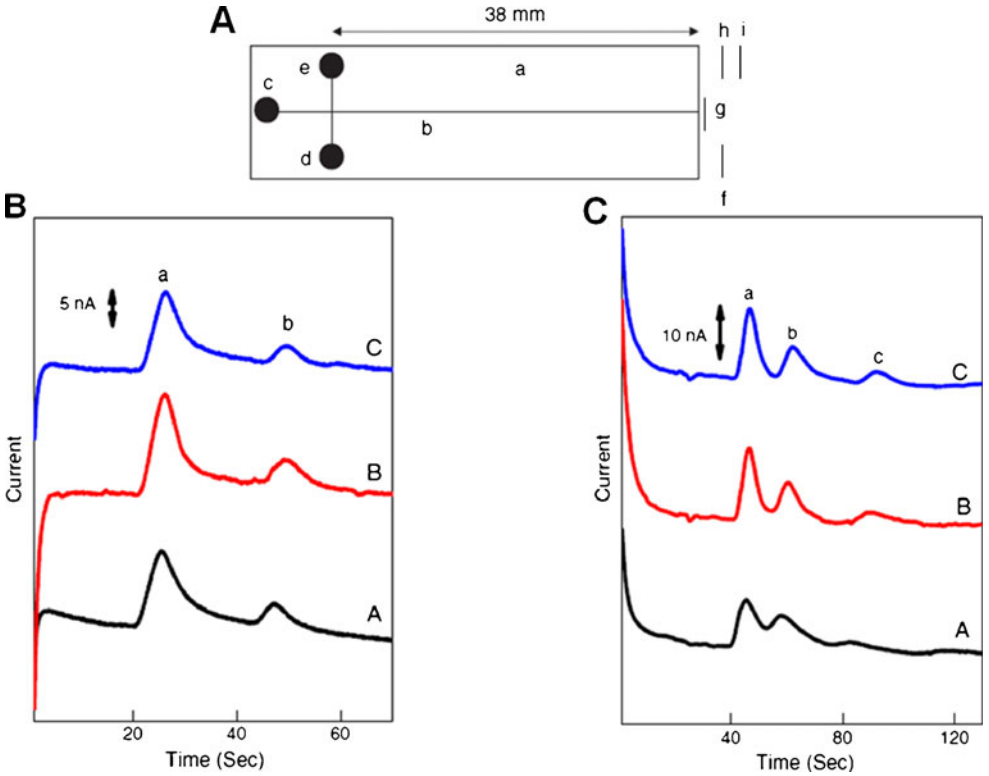

Fig. 7 **A** Scheme of the microchip: (a) the glass chip, (b) separation channel, (c) buffer reservoir, (d) run buffer reservoir, (e) sample reservoir, (f) platinum cathode for separation, (g) detection electrode, (h) Ag/AgCl reference electrode, and (i) platinum counter electrode. **B** Electrophoregrams of a mixture of (a) dopamine and (b) catechol at bare glassy carbon (GC) (A), graphite microparticles (B), and GO (C) modified electrodes. Conditions: Dopamine and catechol at 400 and 100 μm respectively; 25 mM MES (pH 6.5); separation voltage, +1500 V; injection voltage, +1500 V; injection time, 5 s; detection potential, +0.6 V. Carbon material film loading, 1 μg. **C** Electrophoregrams of a mixture of (a) 1,3-dinitrobenzene (DNB), (b) 2,4,6-trinitrotoluene (TNT) and (c) 2,4-dinitrotoluene (DNT) (20 ppm for all) at bare GC (A), graphite microparticles (B), and GO (C) modified electrodes. Conditions: 15 mM borate buffer (pH 9.2) with 20 mM sodium dodecyl sulphate (SDS); separation voltage, +2000 V; injection voltage, +2000 V; injection time, 3 s; detection potential, −0.5 V. Carbon material film loading, 1 μg. (Adapted with permission from reference [71])

has been demonstrated [21]. The results evidence the fact that GO is the most powerful acceptor of QDs FRET donors.

The ultrahigh quenching efficiency of G opens the way to several interesting applications in the field of biosensing [23, 58, 67, 76], principally in bioimaging, labeling and sensing. For example, Lu and co-authors [76] have demonstrated optical testing of dye-labeled DNA. GO could bind dye-labeled ssDNA and completely quench the fluorescence of the dye. The binding between the dye-labeled DNA and target molecule alter the conformation of dye-labeled DNA, and disturbs the interaction between the dye-labeled DNA and GO, thus the target molecule releases itself from the GO and restores the quenched fluorescence (see Fig. 8). This design could result in a fluorescence-enhanced detection that is sensitive and selective to the target molecule.

Another platform for detecting biomolecules based on graphene has been performed by Chang et al. [77]. The biosensing platform was constructed according to the non-covalent assembly of fluorescent dye labeled aptamer on graphene for thrombin detection, using fluorescein amidite (FAM) as dye and 5′-FAM-GGTTGGTGTGGTTGG-3′ as DNA sequence of thrombin aptamer. In such a configuration, graphene quenched the fluorescence signal due to a transfer of fluorescence resonance energy from dye to graphene. Thereby, the conformation of aptamer on graphene can be changed by quadruplex formation induced by thrombin. The weak binding between quadruplex-thrombin complexes and graphene surface makes the dye to move far away from the graphene surface, inducing the fluorescence recovery. In this way, a highly sensitive and specific FRET aptasensor for thrombin detection was obtained (see Fig. 9). A linear range of 62.5–187.5 pM and a LOD for thrombin of around 31.3 pM, which is two orders of magnitude lower than those by using CNT fluorescent biosensors was reported [78].

Separation applications

Due to its large specific surface area, high adsorption capacity and good chemical and thermal stability graphene is widely applied in analytical techniques such as chromatography [79–81], mass spectrometry [82–84] and atomic absorption spectrometry [85, 86].

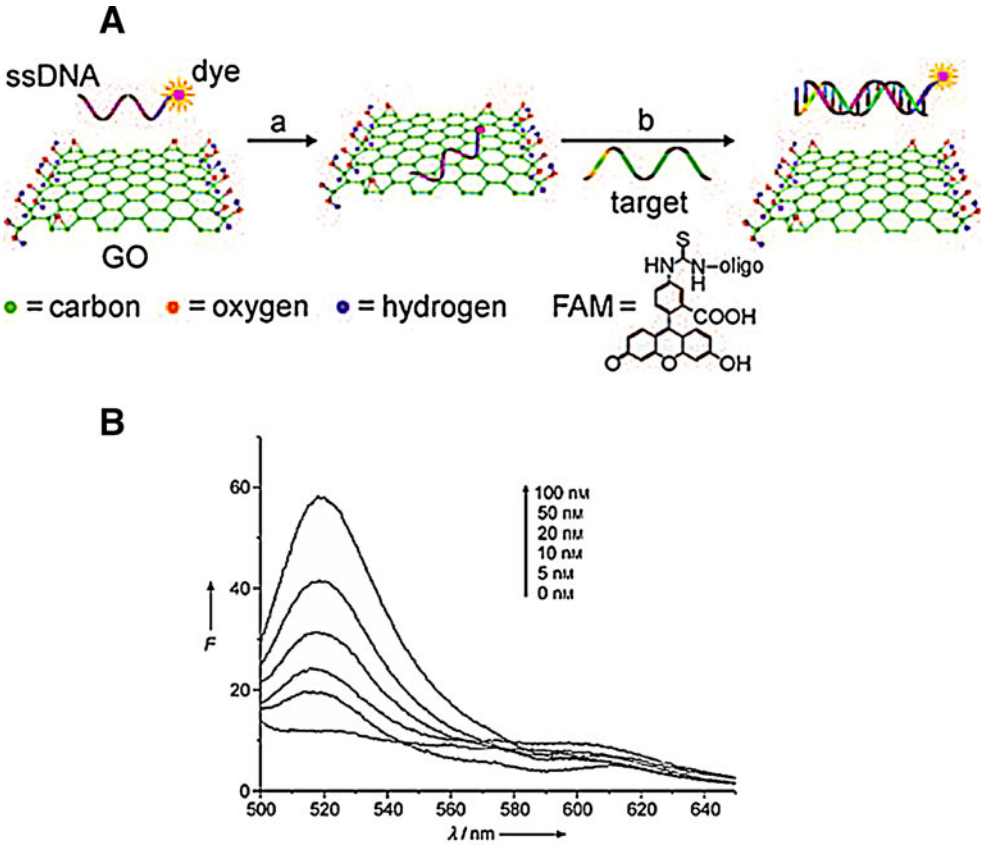

Fig. 8 **A** Schematic representation of the target-induced fluorescence change of the ssDNA-fluorescein-based dye (FAM)-GO complex. **B** Fluorescence spectra of the fluorescein-based dye-labeled aptamer-GO (dye-labeled aptamer 50 nM) in presence of human thrombin (0-100 nM). Excitation: 480 nm. (Adapted with permission from reference [76]). For more details, see text

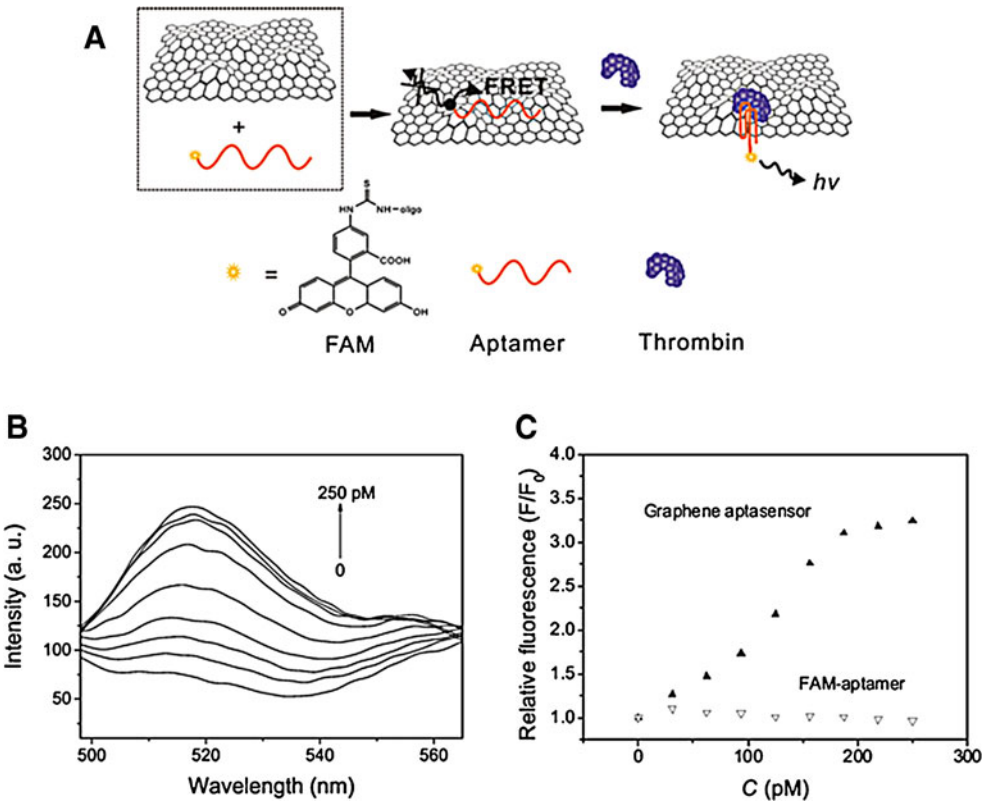

Fig. 9 **A** Schematic representation of graphene Fluorescence Resonance Energy Transfer (FRET) aptasensor for the thrombin detection; **B** Fluorescence recovery of graphene FRET aptasensor in the presence of different concentrations of thrombin (0, 31.3, 62.5, 93.8, 125, 156.3, 187.5, 218.8, and 250 pM) in 20 mM PBS buffer (pH=7.0); **C** Relative fluorescence changes with thrombin concentration from 0 to 250 pM, where F_0 and F are the fluorescence intensity without and with thrombin, respectively. FAM-aptamer concentration: 20 nM. Excitation wavelength: 470 nm. (Adapted with permission from reference [77]). For more details, see text

Recently, Liu et al. [79] have used G as adsorbent in SPE for water samples monitoring with interest for environmental applications. Eight chlorophenols (2-Chlorophenol (2-CP), 3-chlorophenol (3-CP), 2,4-dichlorophenol (2,4-DCP), 3,4-dichlorophenol (3,4-DCP), 2,4,6-trichlorophenol (2,4,6-TCP), 4-Chlorophenol (4-CP), 2,3,5-trichlorophenol (2,3,5-TCP) and 2,3-Dichlorophenol (2,3-DCP)) as model analytes were extracted on a graphene-packed SPE cartridge, and then eluted with alkaline methanol. HPLC with multi-wavelength ultraviolet (UV) detection has been used to determine the concentrations of the elutes, obtaining a high sensitivity (LODs=0.2, 0.2, 0.2, 0.2, 0.4, 0.1, 0.4, and 0.2 ng mL^{-1} (S/N=3), respectively) and good reproducibility (RSDs=5.9, 4.6, 5.3, 2.9, 4.8, 5.4, 7.7, and 2.2 % for run-to-run assays, respectively). By using graphene higher recoveries than other adsorbents including C18 silica, graphitic carbon and CNTs, owing to the large surface area and unique chemical structure have been achieved (as shown in Fig. 10). A similar method based on the separation and fluorescent detection by HPLC has been developed to extract neurotransmitters from rat brain, using graphene as a sorbent for SPE [81].

A novel graphene-assisted matrix solid-phase dispersion (GA-MSPD) method has been developed by Liu et al. [87] for extraction of polybrominated diphenyl ethers (PBDEs) and their methoxylated (MeO–) and hydroxylated (OH–) analogs from different kinds of spiked environmental samples, including soil, tree bark and fish. They found that grinding the solid sample with chemically converted graphene (CCG) powder yielded a tight contact and sufficient dispersion of the sample matrix due to the large surface area and flexible nanosheet morphology of CCG. The resultant blend was eluted using a two-step elution strategy: PBDEs and MeO-PBDEs were eluted firstly by hexane/dichloromethane and analyzed by gas chromatography–electron capture detection (GC–ECD), and then OH-PBDEs were eluted by acetone and determined by liquid chromatography–electrospray-tandem mass spectrometry (LC–ESI-MS/MS) (see Fig. 11). The method LODs of five PBDEs, ten MeO-PBDEs and ten OH-PBDEs (in soil samples) were in the

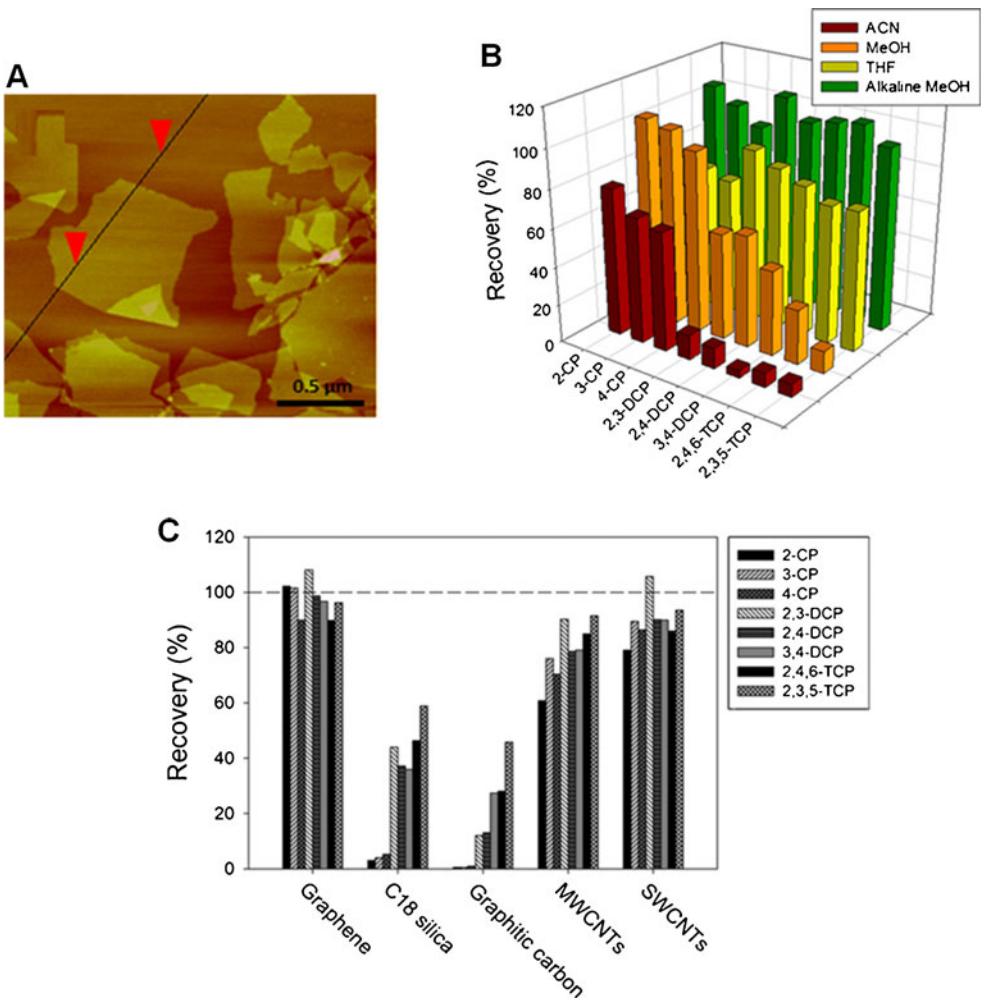

Fig. 10 **A** AFM image of grahene oxide (GO) sheets on a mica substrate; **B** Effect of eluent type on the recoveries of 2-Chlorophenol (2-CP), 3-chlorophenol (3-CP,), 2,4-dichlorophenol (2,4-DCP), 3,4-dichlorophenol (3,4-DCP), 2,4,6-trichlorophenol (2,4,6-TCP), 4-Chlorophenol (4-CP), 2,3,5-trichlorophenol (2,3,5-TCP) and 2,3-Dichlorophenol (2,3-DCP); **C** Comparison of graphene versus C18 silica, graphitic carbon, SWCNTs, and MWCNTs, as adsorbents for the solid-phase extraction of eight chlorophenols. (Adapted with permission from reference [79]). For more details, see text

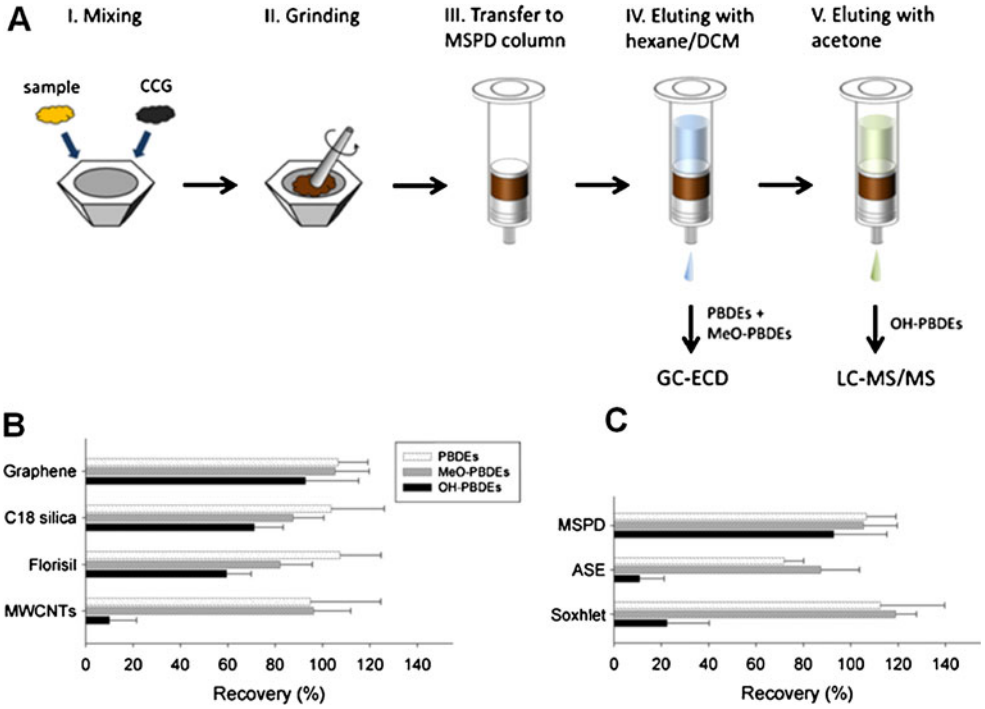

Fig. 11 **A** Scheme of the graphene-assisted matrix solid-phase dispersion (GA-MSPD) method to extract polybrominated diphenyl ethers (PBDEs) and their methoxylated (MeO–) and hydroxylated (OH–) analogs from environmental matrices; **B** Comparison of chemically converted graphene (CCG) with C18, Florisil and MWCNTs as sorbents (20 mg) for extraction of PBDEs, MeO-PBDEs and OH-PBDEs from soils; **C** Comparison of GA-MSPD with other extraction techniques (ASE and Soxhlet extraction). (Adapted with permission from reference [87]). For more details, see text

range of 5.9–28.7, 14.3–46.6, and 5.3–212.6 pg g^{-1} dry weight, respectively. According to the authors [79, 87] graphene in comparison with other absorbents including C18 silica, graphitic carbon, florisil and CNTs gives improvements as SPE adsorbent owing to its high sorption capacity, good compatibility with various organic solvents, good reusability, no impact of sorbent drying, and fine reproducibility.

Solid-phase extraction has also been proposed for separation and preconcentration of trace metal ions in environmental samples combined with flame atomic absorption spectrometry. Ma's group [85, 86] has developed a new method for the preconcentration of trace amounts of lead (Pb) in water samples based on the use of a column packed with graphene as the sorbent, prior to its determination by flame atomic absorption spectrometry. G, as sorbent material used, is considered the core of SPE because it determines the selectivity and sensitivity of the method owing to its ultrahigh specific surface area and high adsorption capacity. They also showed that G is superior to other adsorbents including C18 silica, graphitic carbon, and single- and multi-walled CNTs for the extraction of Pb [85].

More recently, GO bonded fused-silica fiber has been applied in solid phase microextraction (SPME) of polycyclic aromatic hydrocarbons (PAHs) in water samples coupled with GC, achieving good results. The GO/SPME fiber provide good stability towards organic solvent, acidic and alkali solutions and high temperature, wide linearity range (from 0.05 to 200 mg L^{-1}) with a R^2=0.9954 and low LODs (less than 0.08 mg L^{-1}) for extracting six PAHs couple with GC. The repeatability and fiber to fiber reproducibility were less than 6.13 and 15.87 %, respectively [80].

Conclusion & future prospects

CNTs and graphene offer significant advantages as analytical tools for biosensing systems. Graphene and chemically modified G sheets possess a high electrical conductivity, high surface area, and outstanding mechanical properties comparable with or even better than CNTs. The advantages of either CNTs or G would sometimes depend on the application field.

A wide variety of researches have demonstrated that GO can be used in a similar mode as CNTs as platforms for fast, sensitive, and selective biosensing. CNT and G-based composites seem to be suitable candidates to satisfy the requirements in biomedical devices, chemical analysis, time-resolved spectroscopy, environmental related sensing, and in optical devices. Composites infused with graphene are stronger, stiffer, and less prone to failure than composites infused with CNTs or other nanoparticles, according to reported studies [12, 88, 89]. This means that graphene, in relation to robustness, could be a key enabler in the development of next-generation of nanocomposite materials.

Despite the large amount of recent publications on CNTs and graphene-based biodetection, the advantages of those novel biosensing platforms over conventional bioassay tools remain to be clarified. Although high detection sensitivities have been achieved by many graphene-based biosensors,

their reliability and reproducibility must be carefully studied following the corresponding electrochemical or optical techniques. However, graphene due to the low cost and large production scale is widely believed to be the material with interest to design and fabricate future devices. Of special interest seems to be the biosensing applications of graphene oxide in relation to optical techniques [72].

CNTs have been extensively and successfully used for sample treatment and preconcentration to overcome certain difficulties in analytical chemistry, such as unsatisfactory LODs and removing matrix interferences. It is expected that CNTs will be placed in the leading role as sorbent for SPE and replacing probably previous sorbents. Nevertheless graphene is also being demonstrated as a possible replacer of CNTs in the same field [90]. However, still much work is needed so as to definitively decide if either graphene or CNT is the ideal candidate for such applications.

The differences between CNTs and graphene could be associated with the surface chemistry, conductivity and their redox properties. A better understanding of the structure/property relationship with interest for fundamental research but also for developing effective biosensing platforms based on these carbon nanomaterials is still necessary. In general, the development of CNTs and graphene-based platforms with interest for analytical chemistry applications is still growing, and significant efforts are still showing to bring graphene to the same stature as CNTs. The future of graphene is bright and its amazing potential will surely be the focus of many researchers during the coming years.

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