Photoluminescent nanosensors capped with quantum dots for high-throughput determination of trace contaminants: Strategies for enhancing analytical performance

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Abstract

High-throughput determination of trace contaminants has attracted a great deal of attention due to their high toxicity, hyperstability and ultra-low level. Among various analytical methods developed during the past few decades, nanosensing techniques have become increasingly popular due to their potential for portable, rapid and real-time detection. Quantum dots (QDs) are colloidal semiconductor nanocrystals with excellent photoluminescent properties, high quantum yields and high resistance to photobleaching. Recently, QD-based photoluminescent nanosensing (pnanosensing) techniques have provided new advances in the field of contaminant determination for environmental monitoring and food quality control. This review focuses on the improvements in the analytical performances of QD-based pnanosensing techniques in order to achieve on-site rapid screening of multiple contaminants. Critical factors along with some difficulties in high-throughput determination of trace contaminants are summarized. Furthermore, the main strategies for enhancing the analytical performance of QD-based pnanosensors based on the characteristics and difficulties of trace analysis are highlighted. Finally, we discuss the difficulties in association with the use of QD-based optosensors in trace analysis and the prospective applications of this novel analytical technique in the future.

Keywords: Quantum dots; Pnanosensors; Trace contaminants; High-throughput analysis; Analytical performance enhancement; Environmental and food safety

1. Introduction

Over the past few decades, a large crop of exogenous harmful materials (mycotoxins, pesticides, heavy metals, etc.) regarding their contamination in complex matrices such as foods, feeds and medicinal plants have received considerable attention due to their high occurrence in these matrices and potential toxicological risks to human and animal health and the environment, as well as the enormous challenges involved in quantifying low concentrations at ppm (mg/kg), ppb ($\mu\text{g/kg}$) or ppt (ng/kg) levels. Current analytical methods for these materials are largely restricted to laboratory instrumental analysis [1, 2] and enzyme-linked immunosorbent assay (ELISA) [3, 4]. The former requires rigorous sample preparation steps prior to analysis, including extraction, clean-up, enrichment and possible derivatisation [5] in order to improve the sensitivity and selectivity by eliminating interferences with the matrix. However, these essential steps may also decrease the analytical accuracy of various techniques due to the potential loss of trace contaminants and the increase in both cost and time associated with professional operation. In the case of ELISA, specific reactions between enzyme and antibody may face challenges of poor tolerance due to the complexity of the matrices and therefore easily produce cross-reactions and false-positive results. Therefore, convenient, ultra-sensitive and -fast analytical platforms that do not require complex preparation steps may play a significant role in multiplex high-throughput screening and on-site monitoring of trace contaminants.

Despite the fact that traditional optical analytical techniques have been widely applied for decades as potential analytical tools for the detection of trace contaminants, the matrix effects (enhancement/suppression) in complex samples for ultratrace contaminants have not been well studied. Recently, photoluminescence (PL) properties of colloidal semiconductor nanocrystals or quantum dots (QDs) in sensors have led to the development of photoluminescent nanosensors (plnanosensors) for trace determination of multiple targets [6-8]. QDs are monodisperse crystalline

clusters with physical dimensions that are smaller than the bulk-exciton Bohr radius in the range of 1-20 nm and contain anywhere from 100 to 100,000 atoms per nanoparticle [9]. Multidisciplinary applications of QDs have been studied due to their unique electro-optical properties, including narrow and symmetric size-tunable PL spectra (25-40 nm), broad absorption spectra, high quantum yields, large and effective Stokes shifts and high resistances to photobleaching and chemical degradation. In addition, multi-functionalization of QDs has been achieved for bioconjugating bio/chem-ligands [10, 11]. However, multiplex high-throughput determination using QDs remains challenging due to the coexcitation of multiple QD emission wavelengths by a single excitation wavelength, since the tunability of their PL emission bands depends on both the nanoparticle size (1-12 nm) and composition, which is determined by atoms in groups II-VI, III-V or IV-VI (e.g., CdSe, CdTe, InP, PbS and CdSe/ZnS) [12]. Additionally, QDs can be applied in many other techniques, such as biosensors, intelligent gene chips and nanotechnology, etc, as well as a large crop of fields, such as chemistry, microbiology, and biochemistry, to enhance specificity, sensitivity and detection speed [13-17].

Herein, we describe in detail the current status and advances in the field of QD-based portable planosensors for the convenient and rapid high-throughput determination of trace contaminants, allowing for enhanced analytical performance and the possibility of on-site rapid screening. In this review, the critical factors and difficulties, together with the requirements and solutions in association with determination levels of trace contaminants in foods and the environment are summarized. The main strategies for enhancing the analytical performance of QD-based planosensors in order to overcome these difficulties in trace determination are subsequently highlighted. Finally, future trends in the field of QD-based planosensors for monitoring trace contaminants are discussed (Fig. 1).

Fig. 1

2. Characteristics of trace determination

Despite the fact that trace contaminants, such as mycotoxins, pesticides, heavy metals, and polycyclic aromatic hydrocarbons, are present in samples at ppm, ppb or ppt level, they are still associated with the disruption of ecological systems, environment hazards and threats to human health. The maximum levels of these contaminants together with the performance criteria for analytical methods have been suggested by some related organizations, such as the European Union (EU) [18].

According to the guidelines introduced by these organizations and previous reports for high-throughput analysis of trace contaminants, sampling procedures must first be optimized in order to accurately and precisely predict contaminant levels depending on lot weight, since different parts within the same sample may possess various contamination levels. In general, homogeneous and representative samples are obtained by evaluating the sampling and analytical variability using a balanced nested design [19, 20].

Moreover, a more sensitive method with a lower limit of detection (LOD) and quantitation (LOQ) will balance the problems induced by the trace and ultra-trace levels through the introduction of an extra enrichment step [21] as well as the addition of a potential derivatization process in order to improve the performance of the analytical technique [22, 5].

Additionally, trace contaminants can be widely found in various matrices which possess enormous complexity and diversity in kinds and compositions and the contaminants will express correlations with the matrices. So, matrix effect should be evaluated to determine the reliability of the analytical method for trace determination, since signal response from contaminants can often be enhanced or suppressed by interference with constituents of the matrix, especially in the case of complex matrices such as agri-foods, medicinal plants and bio-products. Increasing the selectivity of analytical methods or adding an appropriate clean-up step can help eliminate or decrease the influence of matrix effects [23, 24] to avoid the false-positive results and accelerate analytical efficiency to bulk screening.

Finally, due to the fact that most contaminants are derived from enormous species with multifarious physical and chemical properties and usually co-occurred in the same matrix, multiplex high-throughput analysis has become the dominant issue for simultaneously screening matrices and contaminants as much as possible. Therefore, enhancing the selectivity and sensitivity of the analytical method is critical for the rapid determination of trace contaminants without any extra sample pretreatment steps.

3. Strategies for enhancing the analytical performance of QD-based pnanosensors

Owing to the previously mentioned characteristics of trace contaminants, the analytical performances of selected methods for high-throughput analysis must be validated in terms of selectivity, sensitivity, precision, accuracy, stability and repeatability. Selectivity and sensitivity are essential to the reliability and prospective applications of each analytical method. Due to their distinctive optical and bioconjugation properties, QD-based pnanosensors have been increasingly studied for high-throughput analysis of trace contaminants over the past few decades.

3.1. Improving the selectivity of QD-based pnanosensors

Matrix interferences commonly occur in trace analysis, which may lead to inaccurate results particularly in complex matrices. In this case, immobilization of biological materials (enzymes, antibodies, nucleic acids, microorganisms, cells, tissues, etc.) or chemical materials (supramolecular and host cross-linked polymers) as recognition receptors (their characteristics shown in [Table 1](#)), or QDs as signal transducers and amplifiers may minimize matrix effects and improve selectivity [\[25, 26\]](#).

[Table 1](#)

For bio-receptors, enzymes are the earliest bio-recognition elements in QD-based pnanosensors, and enhancing or suppressing the optical response of QDs based on the enzymatic reaction can determine the identities of various contaminants [\[27\]](#).

Furthermore, visualization of signal enhancement/suppression effects can be achieved in two ways. One way is based on the temporary inhibitory effect of enzymes by contaminants during the catalytic reaction of acetylcholinesterase (AChE) inhibited by organophosphorus pesticides [28-31] (Fig. 2A), the catalyzed oxidation of alcohol oxidase (AO) inhibited by Cu^{2+} [32], and during the catalytic reaction of horseradish peroxidase inhibited by phenols and H_2O_2 [33]. The other ways focuses on using contaminants as enzyme-substrates rather than inhibitors, such as the ability of organophosphorus hydrolase (OPH) to hydrolyze P-O, P-F, P-S, and P-CN bonds in organophosphorus compounds to produce acids and alcohols. This reaction quenches the PL of QDs as the phenols are oxidized by tyrosinase (TRS) to form quinones [34-38]. Through the inner filter effect on fluorescence of QDs, a new type of 2,3-dihydroxybiphenyl 1,2-dioxygenase (BphC)-based fluorescent biosensor was developed for catechol and 2,3-dihydroxybiphenyl, which could be employed as a robust support for the construction of other enzyme-based biosensors [39] (Fig. 2B).

Fig. 2

Antibody or antigen-coated immunoassays have been widely used in QD-plnanosensors based on their specific recognition reactions with a K level of μM . Due to the abundant conjugation of amino acids in the protein, active esters, fragmented antibodies, avidin/protein G bridges, polyhistidine peptides, and various polyclonal/monoclonal antibodies (pAb/mAb) for the specific binding of contaminants, are considered to the ligands that preferentially bonded to QDs [11]. Furthermore, by optimizing the antibodies/QDs ratio, many assay formats have been developed, such as direct/indirect competition and sandwich modes. Indirect competition generally exhibits better selectivity and specificity compared to direct competition due to the fact that homogeneous immunoassays are known to be less sensitive than heterogeneous assays. The sandwich immunoassay needs double-antibodies and is therefore more suitable for analyzing pathogens rather than smaller sized contaminants since it requires immunogenicity by integrating carrier

proteins (e.g. bovine serum albumin), which may decrease selectivity [40-42].

Nucleic acid-based QD-plnanosensors (also known as gene-plnanosensors) have recently emerged as materials with high affinities and specificities at a K level of about nM. Gene-plnanosensors are formed by fabricating functional nucleic acid elements (DNAzymes, oligonucleotides, aptamers) as bioreceptors, which are selected by an *in vitro* selection process through the systematic evolution of ligands by exponential enrichment (SELEX) procedure. A novel electrochemical sensing system based on DNAzymes and rolling circle amplification has been developed for the detection of Pb^{2+} . Due to dramatic signal amplification by numerous QDs, high sensitivity (7.8 pM) was achieved. More importantly, by taking advantage of the recognition process and cleavage efficiency of the metal ion dependent DNAzyme, the sensing system also demonstrated good selectivity against other divalent metal ions, such as Zn^{2+} , Mg^{2+} , Cu^{2+} , Mn^{2+} , Hg^{2+} and Cd^{2+} . In addition, no masking agents are necessary, thereby simplifying the detection process [43]. By using aptamers, this method can also be expanded to detect mycotoxins [44, 45]. DNAzyme-stimulated chemiluminescence resonance energy transfer to CdSe/ZnS QDs has been used for the detection of Hg^{2+} based on the Hg^{2+} -induced self-assembly of nucleic acid subunits into the hemin/G-quadruplex catalytic label [46]. It is well known that ions can form stable complexes by bridging specific oligonucleotides (oligos). For example, Hg^{2+} ions can specifically bridge thymine bases (T- Hg^{2+} -T) and Ag^{+} ions can specifically bridge cytosine bases (C- Ag^{+} -C)]. In previous studies, T- or C-rich modified QDs were introduced for the selective detection of Hg^{2+} and Ag^{+} ions using an electron-transfer-quenching path, where Hg^{2+} and Ag^{+} ions are used as inputs that activate logic gates to implement QDs as optical readout signals for logic gate operations [47]. The substitution of aptamers and QDs for antigens and AuNPs, respectively, led to the development of a fluorescent strip for monitoring ochratoxin A. This substitution effectively enhanced the specificity and sensitivity (LOD of 1.9 ng/mL) in complicated samples. The sensitivities and specificities of these fluorescent

strips containing aptamer and QDs are improved compared to traditional gold immunochromatographic assays [48].

In the case of chem-receptors, supramolecular polymers receptors, such as azamacrocycles (Azas) [49], cyclodextrins (CDs) [50] and calixarenes [51-53], have been used to form molecular cavities in order to trap analytes on the surface of QDs. The recognition pattern is similar to the host-guest interaction and therefore can improve the detection selectivity in complex matrices through the synthesis and immobilization of **the host and the guest** and relevant QDs [54].

Molecularly imprinted polymers (MIPs) are host cross-linked materials that can be artificially synthesized by the induced copolymerization of functional and cross-linking monomers using analytes as templates. By taking advantages of their high specificities, chemical and thermal stabilities, and tolerance to organic reagents, MIPs have been successfully applied in QD-based planosensors. Due to the imprinting effect, diphenolic acid (DPA)-MIP-QDs optosensors have excellent selectivities and binding affinities of K at 10180 M^{-1} to tetrabromobisphenol A in water and soils by using DPA as dummy template molecule to graft onto the surface of Mn^{2+} : ZnS QDs [55]. Due to weak interactions including van der Waals and hydrophobic forces, the Mn^{2+} : ZnS QDs-based MIP composite nanospheres, which can be prepared via a facile and versatile ultrasonication-assisted encapsulation method, demonstrated excellent recognition selectivity of diazinon compared to similar chemical analogues (phoxim, primiphos-methyl, quinalphos, dichlofenthion, and fenthion) [56]. **Moreover, MIPs-QDs were also fabricated in order to detect mycotoxins [57], pesticides [58, 59], 4-nitrophenol [60], and pentachlorophenol [61].**

A turn-on fluorescent probe based on “ion-imprinted” sites and generated by ethylene diamine tetraacetic acid (EDTA)-etched-CdTe QDs has also been reported for the detection of Cd^{2+} . In this probe, specific Cd^{2+} ionic imprinted polymers (IIPs) sites were created on the surface of the QDs to selectively bind Cd^{2+} leading to the repair of surface defects and restoration of the QD fluorescence (FL). Other common

transition metal ions had a negligible influence on the FL of the unetched QDs. Therefore, IIPs not only retain all the virtues of MIPs, but also reduce interference by other ions due to their high specificity [62].

3.2. Improving the sensitivity of QD-based plnanosensors

Usually, extra clean-up and enrichment steps and potential derivatization processes are critical during laboratory analyses of trace or ultratrace contaminants, leading to more time and cost consumption. By introducing and optimizing the appropriate PL transduction pathways, many sensitive methods based on QD-plnanosensing can effectively eliminate complex sample preparation steps and derivatization processes to ensure the reliability of the method and save time.

ELISA has received considerable attention over the past few years due to its simplicity, relatively low cost, easy operation and suitability for high-throughput analysis. However, commercially available ELISA, which is mostly based on the competitive assay format, is only suitable for qualitative analysis, since it possesses narrow sensitivity, poor reproducibility and is limited to less complex matrices. Additionally, enzyme-based labels suffer from problems of instability due to denaturation and degradation over time [63, 64]. Conjugating organic fluorescein or rhodamine to a substitute enzyme in fluorescence-linked immunosorbent assay (FLISA) can overcome these disadvantages, whereas traditional organic fluorescent materials exhibit narrow excitations and broad, trailing emissions. Compared to organic dyes, QDs possess the dramatically better FL properties with one-third of the emission width, 20 times the brightness, and 100 times more stable against photobleaching [16, 65]. As labels, QD-based FLISA provides substantial advantages in improving sensitivity and lowering the LOD. Utilizing CdSe/ZnS QDs to perform the FLISA array for detecting ZEN has led to a fourfold decrease in the IC_{50} value (0.1 ng/mL) compared to ELISA with a LOD of 0.03 ng/mL, even in complex food matrices [66]. By using CdTe QDs as labels for mAb, the cFLISA method for aflatoxin B₁ (AFB₁) was developed with a LOD of 0.016 ng/mL [67]. By the use of

multicolored (red, orange, and green) CdSe-based QDs and the immobilization of two different types of antibodies into the same well (double-analyte multiplex) or each mycotoxin antibody into separate well, two easy-to-operate QD-based FLISA techniques (single- and double-analyte multiplex) were developed to give ultra-low LODs for target mycotoxins. Real application demonstrated excellent applicability of the multiplex assays for simultaneous on-site screening of several mycotoxins in cereals [68]. CdTe QDs-coated streptavidin (QDs-SA) was also employed to improve the sensitivity of QDs-SA-cFLISA for the detection of chlorpyrifos in drinking water with a LOD of 3.8 ng/mL. This technique also resulted in a 5.5-fold increase in sensitivity and reduction in detection time of 1 hour compared to ELISA [69]. Two types of QD sensors based on icFLISA and icELISA have been integrated for simultaneously screening multiple structurally different molecules in milk. Combined with icFLISA, the hybrid immunoassay was able to simplify sample pretreatment with LOD values of 0.18 ng/mL for quinolones, 0.17 ng/mL for sulfonamides and 7.5 ng/mL for melamine [70], which is low enough for trace determination of multiple analytes in complex matrices.

Fluorescence (Förster) resonance energy transfer (FRET)-based planosensors are also fairly advanced with fast liquid-phase binding kinetics, long-term stabilities, ratio metric measurements and homogeneous assays that do not require additional washing and separation steps [71]. In FRET-coated planosensors, selecting relational and compatible donor-acceptor pairs is essential to sustain high sensitivity. Furthermore, QDs can serve as excellent donors or acceptors as explained by the following FRET mathematical formulas (Fig. 3A): surface multifunctionalizations dramatically increase conjunctive patterns with the acceptors, thereby shortening the distance (r) between the donor-acceptor pair. The symmetric, size-tunable and narrow emissions ensure a large donor-acceptor spectral overlap integral (J) and the equivalence of the FRET efficiency (E). In addition, high quantum yields are essential for maximizing the Förster distance (R_0) [72].

Substantial detection based on QD-assisted FRET-plnanosensors has been carried out with signal-on/off modes as shown in Table 2 and Fig. 3 (Fig. 3B, 3C). For the signal-on mode, the intrinsic sensitivity of FRET is associated with small changes in the donor-acceptor distance from effective forces, such as electrostatic interactions [73-78] and π - π stacking interactions [79]. Adding analytes to disrupt the equilibrium of the FRET system will lead to PL recovery of quenching QDs due to hypercompetitive assays. Additionally, the selectivity is improved by specific interactions with antibodies [80-82], sDNA [83], aptamers [84], nicking endonucleases (NEase) [85] and DNAzymes [86]. Time-gated FRET sensors have also been studied based on the longer fluorescence lifetime of Mn^{2+} :CdS/ZnS and Hg^{2+} -induced conformational changes in the thymine-rich oligo. This sensing system possessed ultra-sensitivity and efficiently reduced background noise with a LOD of 0.18 nM by a time-gated mode. The system also had excellent selectivity even with interference by high concentrations of other metal ions [83]. For the signal-off mode (Fig. 3D, 3E), donor-acceptor pairs of heterogeneous donor QDs as donors, such as CdSe/ZnS [87], Mn^{2+} : CdS/ZnS [88], CdTe [89], and commercialized QDs [90], in association with specific ligands were reported to decrease matrix effects while improving sensitivity. Recently, researchers have found the effective energy transfer occurring from QDs to analytes, which simplified the determination steps as being refrained from finding extra As and potential modifications [56]. Significant FRET is observed on benzo(a)pyrene (BaP)-loaded TiO_2 NTs when they are modified by CdTe QDs. This leads to a 15 fold enhancement in FL emission of BaP on CdTe- TiO_2 NTs resulting in higher sensitivity for BaP in the FRET based method than in direct solid and liquid FL spectroscopies [91]. These results suggest that using CdTe QDs as the acceptors and fluorescent brighteners as the donors can provide a unique FRET system which utilizes electrostatic interactions for the analysis of Hg^{2+} [92].

Table 2

Fig. 3

Unlike FL, phosphorescence is a long lived process resulting from radiative recombination of the triplet excited state T_1 returning to the singlet state S_0 . This can lead to superior PL properties such as long emission lifetimes, large Stokes-shifts, and minimum interference from short-lived auto-FL and scattered light. Although phosphorescence usually occurs in low quantum yields, there have been numerous studies on the use of phosphorescence to enhance sensitivity and reliability by eliminating the interference of similar fluorescent emissions in matrices. Yan et al have developed room-temperature phosphorescence (RTP) sensing based on Mn^{2+} : ZnS QDs for the detection of persistent organic pollutants [93] and drug residues [94], which is unaffected by auto-FL and scattered light. The method has good sensitivity (LODs of 86 and 58.6 nM, respectively) without the need of any inducers or derivatization step. Rayleigh scattering enhancement of defect-related emission makes RTP of Mn^{2+} : ZnS QDs well-suited for sensing 2, 4, 6-trinitrotoluene in water with a LOD of only 0.8 nM [95]. Additionally, RTPs of Fe_3O_4 magnetic- Mn^{2+} : ZnS [96, 97], Mn^{2+} : ZnSe [98], Mn^{2+} : CdTe/ZnS [99] QDs have been successfully introduced for sensing trace contaminants.

It is worth mentioning that some novel formats have been established based on QD PL for sensitivity enhancement of analytes at trace levels as well as avoidance of matrix effects in the environment, such as ratiometric fluorescence [100], surface enhanced raman scattering [101], and surface plasmon resonance [102]. Wang et al. [103] hybridized two differently sized CdTe QDs, which emitted red and green fluorescence, by embedding red-emitting QDs in silica nanoparticles and covalently linking QDs with the silica surface to form a dual-emissive fluorescent hybrid nanoparticle. Variations in the dual emission intensity ratios display continuous color changes from green to red, which can be clearly observed by the naked eye. This method provides significantly enhanced visual detection selectivity and sensitivity compared with single QD-based probes, and has been successfully applied in detecting residues in complex environmental samples and herbal products.

3.3. Simultaneously high-throughput screening of multi-contaminants

Usually, numerous contaminants co-exist within one sample, making it necessary for detection methods to screen for multiple contaminants in a single run and be both accurate and cost-effective for displaying levels of various contaminants. Moreover, high-throughput screening of food products, medicines and environmental samples is essential for determining the characteristics of the contaminated materials and maximum residue levels, as well as the potential resistances of constituents in the same matrix. These requirements can be achieved in tandem by utilizing QDs in groups II-VI, III-V and IV-VI, and multiple size-dependent PL signals in suspended or planar arrays ([Table 3](#)).

[Table 3](#)

Flow cytometry (FCM) is a high-throughput analytical technique for most prominent suspension microarrays and can virtually discriminate between each analyte in a sample while simultaneously measuring multiple analytes based on light-scattering and fluorescence-based detection. By integrating biofunctionalized dualcolor QDs of 525 nm (green) and 655 nm (red), Yu et al. extended the capabilities of multicolor FCM for the prescreening of environmental hazards [\[104\]](#). Compared to conventional analytical methods, the hyphenated technique provides significant improvements with respect to sensitivity and analysis time. This method also simplified sample manipulation on the basis of suspended bead-based competitive immunological reactions, rapid and simultaneous FCM readouts as well as high throughput, and QD-based amplification of the optical signal using a single excitation source ([Fig. 4](#)). This proposed format provides another potential platform by choosing the suitable analytes-aptamers in FCM [\[105\]](#).

Microfluidic technology is a new planar assay that possesses advantages of portability, minimal sample/reagent use, fast reaction times, and considerable parallel processing of samples. Zhang et al. [\[106\]](#) reported the combination of efficient sample handling of microfluidics with high-throughput parallel analysis of microbead based

arrays for the detection of multiple contaminants. This microfluidic beads-based array chip obtained picomolar sensitivity. In addition, approximately 500 times the signal enhancement was obtained when adenosine sensing was performed on chip due to the enhanced mass transport capabilities inherent to microfluidics and multienzyme-linked AuNPs amplification and QD labels. Compared to conventional planar arrays, the incorporation of a microbead into a single and sealed micro-channel requires only a small amount of reagents and sample injection with minimal sample contamination.

Fig. 4

4. Conclusions and prospectives

Continuous concerns over hazards in association with contaminants have provide an urgent need to develop novel techniques that can quickly and accurately detect harmful contaminants in the environment, food materials, feeds, plants, medicinal herbs and other matrices. Because of their superior PL characteristics, QDs have been attained a variety of applications ranging from biological imaging, drug delivery systems design, and medical diagnoses to the detection of trace contaminants [107-115]. QD-based plnanosensors have demonstrated satisfactory performance criteria for the qualitative and quantitative analysis of various trace contaminants with enhanced selectivity and sensitivity, while also achieving simultaneous high-throughput screening of multiple contaminants and complex samples. Based on these novel QD-based plnanosensing technologies, plnanosensing platforms containing QDs can be developed for laboratory analysis, as well as on-site, fast and real-time analysis of numerous contaminants in complex matrices. However, it is important to consider the drawbacks of this method, therefore the problems and future trends relating to the development of QD-based plnanosensors for monitoring trace contaminants are discussed here.

First, how can we achieve on-site detection from laboratory analysis? In general, laboratory analysis is indispensable for detection of various contaminants. However,

professional operation of these instruments requires greater amounts of time and higher costs. Integration of nanotechnology, microfluidics technology and gene microarrays in QD-based plnanosensors provides advantages of on-site, dynamic and real-time analysis, meeting the analytical demands of miniaturization and practicality with short analysis time, small costs and reagent consumption.

Another important question is how can we suppress matrix effects and improve the accuracy of on-site detection? Interference in complex matrices, particularly from components of containing similar structures to the target structure is a difficult problem in chromatographic analysis. Appropriate pretreatments on samples can be effective but are often time-consuming and lead to a loss of the targets and inaccurate results. Interferences from the matrix pose similar problems for QD-based plnanosensors. Currently, the combination of biological and chemical ligands, such as Apts, DNAzymes, MIPs and IIPs, as well as some compatible formats, such as FLISA, FRET, RTP, in QD-based plnanosensors can effectively enhance both selectivity and sensitivity and reduce or eliminate interferences. Therefore, the development of various specific receptors and compatible formats for the surface functionalization and signal amplification of QDs in the future will be important.

The final question we need to answer is how can we ensure the stability of analytical methods for simaltenous detection of trace contaminants? The synthesis and surface modification of QDs may meet these stability requirements. For example, the development of quantum-sized carbon analogues, such as carbon quantum dots (CQDs, C-dots or CDs) [115-120] and graphene quantum dots (GQDs) [121-123] can build excellent probes that may be superior since CQDs and GQDs can maintain the original features of QDs but with exceptional multi-photon excitation (up-conversion) property, lower toxicity, high photostability, excellent biocompatibility, ease to be functionalized with biomolecules, and chemical inertness. As a fascinating class of “zero-dimensional” carbon nanomaterials, C-dots are spherical nanoparticles with sizes below 10 nm and have a great potential for widespread applications in the fields

of biomedicine, optronics, catalysis and sensor issues. Zhou et al. [117] prepared new water-soluble fluorescent CQDs with diameters of about 3 nm using a facile microwave pyrolysis approach in minutes. They discovered that the CQDs could dramatically enhance the chemiluminescence intensity of potassium peroxomonosulfate-sodium sulfite-hydrochloric acid reactions. Satisfactory results were obtained through the successful application of the CQDs sensitized chemiluminescence system for the determination of aliphatic primary amines in real water samples. GQDs is a class of graphene nanomaterials with exceptional luminescence properties. Peng et al. [121] have reported a facile synthesis of GQDs on a large scale with acidic exfoliation and etching of pitch carbon fibers, which were rich in distributed graphitic domains in their original frameworks. We believe that additional studies on quantum-sized carbon analogues will be the next big small things and get more exciting applications in other areas, such as energy storage and conversion, photocatalysis, and display technologies.

In conclusion, QDs are promising nanoparticles that show excellent potential for various applications in the fields of high-throughput determination of various trace contaminants.

Acknowledgements

The authors are grateful for the support from the National Science Foundation of China (81274072, 81473346) and Xiehe New Star project.

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Figure legends

Figure 1. Requirements and solutions of QD-based sensors for high-throughput determination of trace contaminants.

Figure 2. Strategy of enzyme-based QD plnanosensors for high-throughput determination of trace contaminants.

(A: Enzymes inhibition [28-32]; B: Enzymes catalytic oxidation [34-39])

Figure 3. Schematics and strategy of QD-based fluorescence resonance energy transfer (FRET) plnanosensors for high-throughput determination of trace contaminants.

(A: FRET mathematical formulas; B, C: Signal-on mode [73-79, 85, 86]; D, E: Signal-off mode [56, 87-91])

Figure 4. Multiplex competitive microbead-based flow cytometry (FCM) using dualcolor QD labels [104].

Figure 1

Figure 2

Figure 4

Photoluminescent nanosensors capped with quantum dots for high-throughput determination of trace contaminants: Strategies for enhancing analytical performance