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RESEARCH PAPER

Surface tuning laser desorption/ionization mass spectrometry (STLDI-MS) for the analysis of small molecules using quantum dots

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Abstract In most applications of quantum dots (QDs) for surface-assisted *l*aser *d*esorption/*i*onization *m*ass *s*pectrometry (SALDI-MS), one side of QDs is supported by a solid substrate (stainless - steel plate), whereas the other side is in contact with the target analytes. Therefore, the surface capping agent of QDs is a key parameter for laser desorption/ionization mass spectrometry (LDI-MS). Cadmium telluride quantum dots (CdTe QDs) modified with different capping agents are synthesized, characterized, and applied for *s*urface *t*uning *l*aser *d*esorption/*i*onization *m*ass *s*pectrometry (*STLDI-MS*). Data shows that CdTe quantum dot modified cysteine (cys@CdTe QDs) has an absorption that matches with the wavelength of the N_2 laser (337 nm). The synergistic effect of large surface area and absorption of the laser irradiation of cys@CdTe QDs enhances the LDI-MS process for small - molecule analysis, including α-, β-, and γ-cyclodextrin, gramicidin D, perylene, pyrene, and triphenylphosphine. Cys@CdTe QDs are also applied using Al foils as substrates. Aluminum foil combined with cys@CdTe QDs enhances the ionization efficiency and is cheap compared to traditional matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS) with a stainless - steel plate.

Keywords Quantum dots · Surface - enhanced laser desorption/ionization mass spectrometry (SELDI-MS) · Surface capping agent · CdTe QDs

Introduction

Most of the active biological species are small molecules [1–3]. Analysis of small molecules is important for medicine, environment, and our daily life. There are several methods, including nanoporous resonator [4], sandwich assay [5], optical aptasensors [6], and others [7–9], for the analysis of small molecules. Based on their advantages, mass spectrometry-based techniques are promising. Mass spectrometry (MS) provides a wide number of different techniques such as microchip-mass spectrometry [10], electrospray ionization mass spectrometry (ESI-MS) [11–13], infrared matrix-assisted ionization mass spectrometry electrospray ionization (IR-MALDESI) [14, 15], and desorption electrospray ionization mass spectrometry (DESI-MS) [16].

Matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS), a soft ionization laser-based MS, has been intensively applied for large molecules [17–19]. The analysis of small molecules using conventional MALDI-MS is a challenge due to the matrix interferences at low mass range (<500 Da). Thus, nanoparticles have been applied as surface to assist LDI-MS (surface-assisted laser desorption/ionization mass spectrometry (SALDI-MS)) with ultra-clean

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background. Small molecules were analyzed using N-doped graphene [20], N-doped carbon dots [21], gold-carbon dots nanocomposite [22], or other nanomaterials [23–27]. These methods provided sensitive detection of small molecules with a free interference spectrum.

Quantum dots (QDs) or nanocrystals with size below than 10 nm are very interesting and attractive nanomaterials [28]. Quantum dots have been applied as probes [29, 30], for nanomedicine [31], and SALDI-MS [32, 33]. Quantum dot-assisted LDI-MS was reported for the analysis of proteomics [33, 34], peptides [35], metallodrugs [32, 36], carbohydrates [37], and others [38]. QDs offered many advantages compared to conventional organic matrix that usually showed interference peaks at mass range below 500 *m/z* [39–41]. QDs have large surface areas, provided high adsorption capacity, and showed high ionization efficiency. QDs offered a soft ionization method for noncovalent bonds or interactions, showed free background, and effectively can be tuned for laser adsorption.

Surface of quantum dots affects dramatically the photo-properties [42], cytotoxicity [43, 44], and chemical [45] and physical properties [46] including band edge positions [47]. Surface of quantum dots represents the first interaction barrier with laser irradiation [48]. Application of QDs for SALDI-MS indicates that one side of QDs is in contact with the target analytes, whereas the other side is in contact with the MALDI-MS target plate. Thus, surface capping or stabilizing agent of QDs is a key and effective parameter for LDI-MS. A few studies highlighted the effect of surface capping of quantum dots on LDI-MS [49]. The surface of quantum dots can be fine-tuned and modified to improve the ionization efficiency. These achievements take place via adjusting the laser absorption. When quantum dots have absorption matches with the laser energy, the technique can be coined as surface enhanced laser desorption/ionization mass spectrometry (SELDI-MS) [48]. This parameter is more critical for small molecule analysis and is interested for further investigation.

Herein, the effect of capping agent of quantum dots (cadmium telluride quantum dots (CdTe QDs)) on the efficiency of LDI-MS for the analysis of small molecules was investigated. CdTe QDs were modified with different capping agents: 11-mercaptoundecanoic acid (MUA), 3-mercaptopropionic acid (MPA), thioglycolic acid (TG), L-cysteine (Cys), 4-mercaptobenzoic acid (MBA), and 4-aminothiophenol (ATP). The materials were synthesized and characterized using transmission electron microscopy (TEM), Fourier transform infrared spectrophotometers (FTIR), UV-vis absorption, and photoluminescence (PL) emission. The material absorption and emission can be tuned using the capping agent. The surface capping affects the material performance of LDI-MS for the analysis of small molecules. Data showed that cys@CdTe quantum dots are the best selection due to the matches of the material UV-vis absorption with the wavelength of N_2 laser (337 nm). The mechanism of the desorption/ionization process of the current method is also investigated.

Material and methods

Tellurium, powder (200 mesh, 99.8%), 11-mercaptoundecanoic acid (95%), 3-mercaptopropionic acid (90%), β-cyclodextrin (98%), thioglycolic acid (98%), L-cysteine, 4-mercaptobenzoic acid (90%), α-cyclodextrin, trifluoroacetic acid (98%), acetonitrile, γ-cyclodextrin, and 3,5-dimethoxy-4-hydroxycinnamic acid were purchased from Sigma-Aldrich (St. Louis, USA). Other chemicals such as cadmium chloride anhydrous (Fluka (USA), 4-aminothiophenol (97%, Alfa Aesar, Heysham, UK), $NaBH_4$ (98%, Chimica), and 2,5-dihydroxybenzoic acid (2,5-DHB, 99%, Acros, Geel, Belgium) were purchased and used directly. Potassium bromide, ammonium bicarbonate, and sodium hydroxide were purchased from Riedel-de Haën (Seelze, Germany). Deionized water (Millipore, Billerica, USA) was used for all the preparation.

Instruments and sample preparation

The spectra of mass spectrometry were reported using MALDI-TOF (Bruker Daltonics, Microflex, Leipzig, Germany). The samples were prepared via spotting of 1 μL drop using micropipette on MALDI sample plate and left for drying before the analysis. All samples have small molecular weight (<5 kDa), so that linear reflectron was used. The laser wavelength is 337 nm (nitrogen laser) with frequency set at 20 Hz and number of shots was set up as 200 shots. UV-visible absorption was recorded using U-3501 (Hitachi, Japan). FTIR spectra were recorded by Spectrum 100 (PerkinElmer) using KBr platelet. The data were recorded in the wavenumber range of 450–4000 cm^{-1}. The particle sizes were determined using transmission electron microscope (TEM), JEOL TEM-3010 (JEOL, Japan). The fluorescence spectrometer (F-2700 FL, model 4J1-0003, Hitachi) was used to record the fluorescence emission.

Synthesis of CdTe modified with different capping agents

Six different capping agents, called 3-MPA, TGA, cysteine, 11-MUA, 4-MBA, and 4-ATP, were used for CdTe stabilization using hydrothermal method [50]. The structures of these capping agents are shown in Fig. S1 in the Electronic Supplementary Material (ESM). The schematic procedures of the samples preparation are shown in Fig. S2 (see ESM). Typically, 32 mg of Te powders and 28 mg of $NaBH_4$ were mixed in 0.2 mL of deionized water (was purged with nitrogen to remove water soluble oxygen). The reaction mixture was stirred under continues nitrogen gases for 20–30 min until the black powder disappeared and white crystals of NaHTe were formed. In a three-necked flask, 229 mg of $CdCl_2$ was added to 100 mL of deionized water (previously purged with N_2 gas to remove oxygen). The pH was adjusted to 9 using 0.1 M NaOH solution. The ligand (surface capping agents) and NaHTe were mixed with Cd^{2+} source in the molar ratio 0.2:0.4:1 and then heated under reflux at 100 °C for 2–3 h. The synthesized nanomaterials were characterized using TEM, UV-vis absorption, FTIR, and fluorescence spectroscopy.

Conventional organic matrices such as sinapinic acid (SA), 2,5-dihydroxy benzoic acid (DHB), and α-cyano-4-hydroxycinnamic acid (CHCA) were used as control and compared with QDs for small molecule analysis. SA and 2,5-DHB (133 mM, 20 mg/mL) were dissolved in mixture of acetonitrile–water (volume ratio 2:1) containing 0.1% of trifluoroacetic acid (TFA). The solution and sample procedure were followed as previous reported [48]. Briefly, 1 μL of sample (with or without QDs) was mixed with an equal volume of SA, CHCA, or DHB. Then, 1 μL of analyte solution was deposited onto stainless steel plates or Al foils. The sample spots were air-dried for 20–30 min and then analyzed in a Mirocflex MALDI-TOF mass spectrometer equipped with a pulsed nitrogen laser (337 nm).

Results and discussion

Material characterization

The systematic representation of CdTe modification with different capping agents is shown in Fig. S2 (see ESM). The prepared materials were characterized using TEM

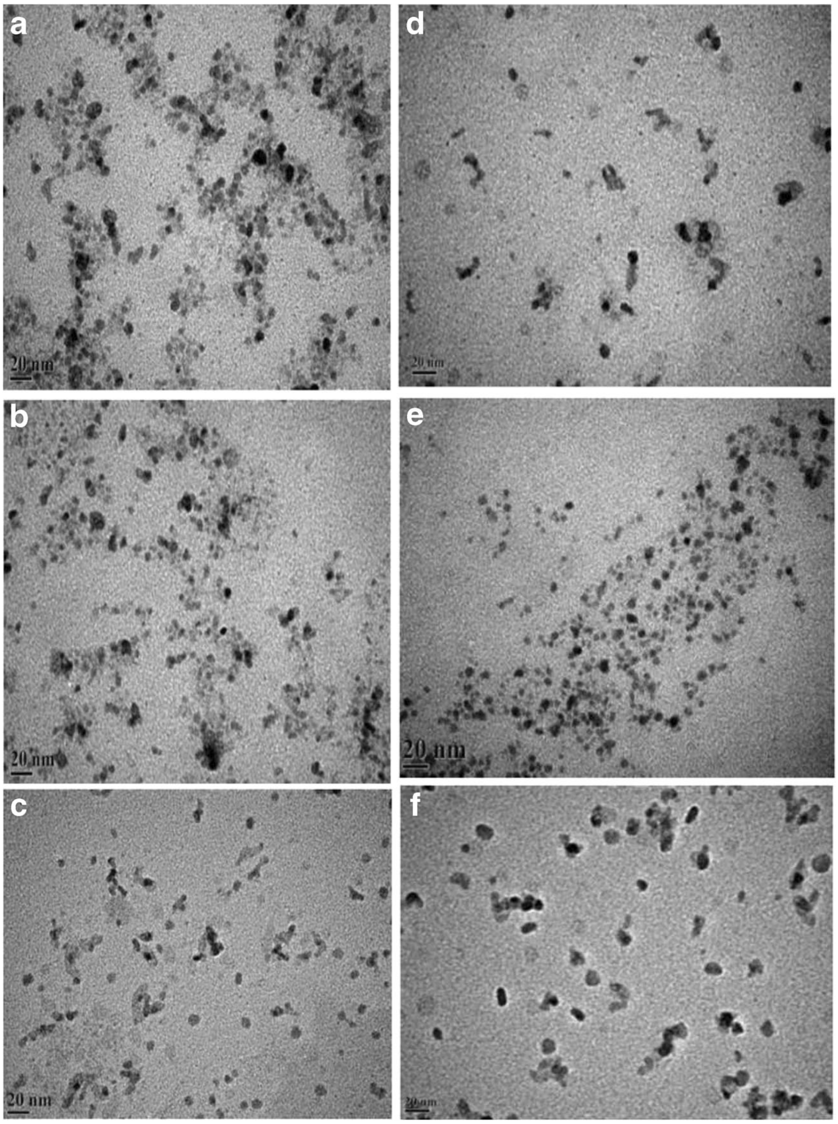

Fig. 1 TEM images for (**a**) TGA@CdTe, (**b**) MPA@CdTe, (**c**) Cys@CdTe, (**d**) MBA@CdTe, (**e**) ATP@CdTe, and (**f**) MUA@CdTe

(Fig. 1), UV-vis absorption and fluorescence emission (Fig. 2), and FTIR (ESM Fig. S3). TEM images show the average sizes of the nanocrystal are about 1–4 nm (Fig. 1). The particle sizes depend on the capping agents: 3.8 nm (TGA@CdTe QDs), 3.4 nm (MPA@CdTe QDs), 4.0 nm (cys@CdTe QDs), 3.1 nm (MBA@CdTe QDs), 3.3 nm (4-ATP@CdTe QDs), and 4.8 nm (MUA@CdTe QDs). The UV-vis absorption of these QDs shows variable absorption from 200 to 500 nm depending on the capping agents (Fig. 2). The absorption at 337 nm makes Cy@CdTe QDs to be the most effective QDs for surface tuning desorption/ionization mass spectrometry (STLDI-MS). The fluorescence emission shows an emission in the range of 200–400 nm for absorption at 400, 270, 300, 337, 250, and 250 for TGA@CdTe, MPA@CdTe, cys@CdTe, MBA@CdTe, ATP@CdTe, and MUA@CdTe, respectively (Fig. 2). The changes of photophysical properties are due to the change of charging and local environment [51]. Infrared absorption (FTIR) was recorded for CdTe QDs with different capping agents to confirm the capping process as shown in Fig. S3 (see ESM). ATP@CdTe shows peak at 1656 cm^{-1} for the benzene ring, while vibration absorbing at 3400 and 1590 cm^{-1} are assigned as $–NH_2$ and N–H, respectively. The materials display peaks at 1710–1725 cm^{-1} corresponding to C=O and 3400–3600 cm^{-1} corresponding to O–H. The absence of thiol group (–SH) stretching band at 2495 cm^{-1} confirms the absence of free 3-MPA. FTIR confirm the functionalization of CdTe by ATP, Cys, MAP, MBA, MUA, and TGA (ESM Fig. S3).

Applications of cys@CdTe for the analysis of small molecules

Analysis of small molecules using conventional organic matrices is a major challenge. Conventional matrices, such as DHB or CHCA, show the formation of several cluster ions due to the matrix's self-ionization. Thus, they generate background interferences for samples with low molecular weight <500 Da. Furthermore, the ionization of organic matrices causes detector saturation, resulting in the reduction of target analyte's signals (ion suppression effect). We select cysteine-modified CdTe (cys@CdTe) because it shows maximum absorption that matches with the wavelength of N_2 laser (337 nm). This method is coined as STLDI-MS. The efficiency of ionization mass spectrometry/ionization process was significantly enhanced due to the large surface area of QDs and absorption on QDs matches with the laser wavelength (337 nm). The analysis of α-, β-, and γ-cyclodextrin (Fig. 3a) and gramicidin D (Fig. 3b) using DHB and CHCA is compared with cys@CdTe QDs. The optimization of cys@CdTe QDs concentration was carried out for α-, β-, and γ-cyclodextrin as shown in Fig. 4. Data show decrease of the analyte ionization with the decrease of the concentration of cysteine@CdTe QDDs (Fig. 4). The lowest concentration of α-, β-, and γ-cyclodextrin is 12.5 nM as shown in Fig. S4 (see ESM). The data observations reveal 10 times sensitivity superior than those of the conventional matrices that require higher concentration of organic matrix. It was reported that nanoparticles such as gold nanoparticles showed high loading capacities

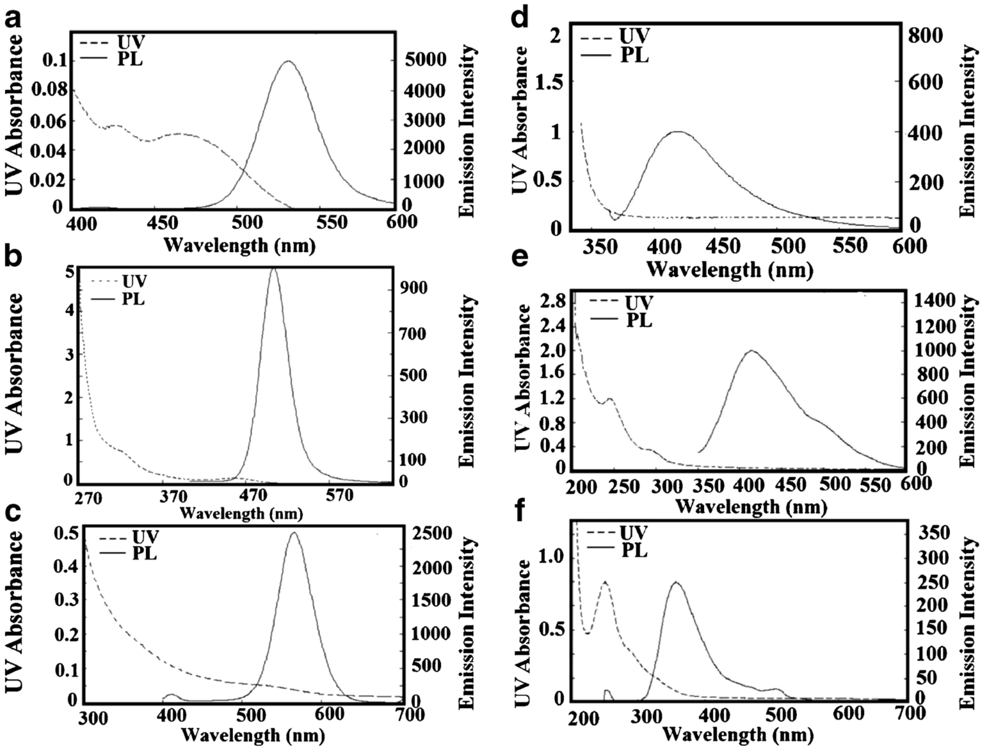

Fig. 2 UV-vis absorption and photoluminescence (PL) of cadmium telluride quantum dots (CdTe QDs) modified with (**a**) TGA, (**b**) 3-MPA, (**c**) cysteine, (**d**) 4-MBA, (**e**) 11-MUA, and (**f**) 4-ATP

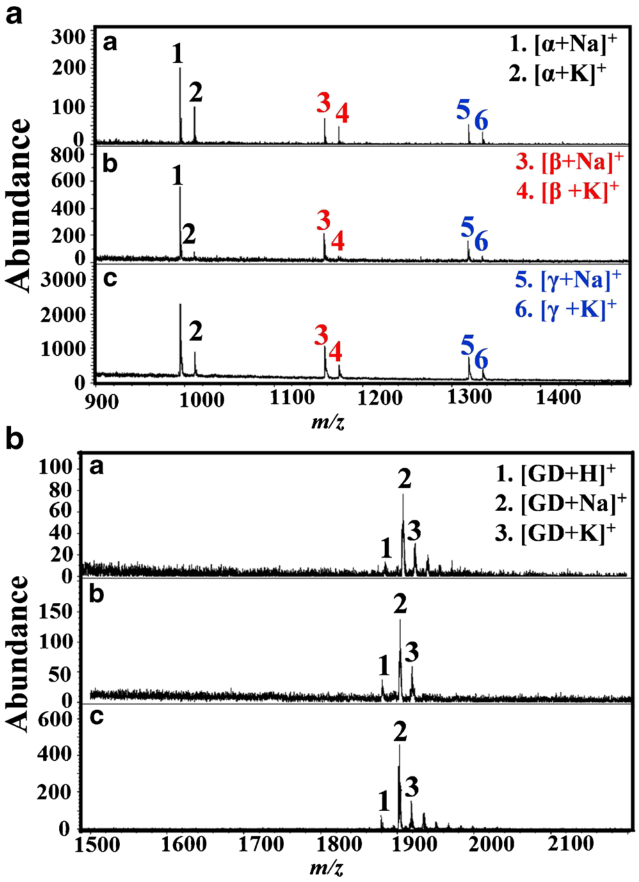

Fig. 3 Analysis of (**A**) α-, β-, and γ-cyclodextrin and (**B**) gramicidin D using (**a**) DHB, (**b**) CHCA as matrixes, and (**c**) cysteine@CdTe for STLDI-MS

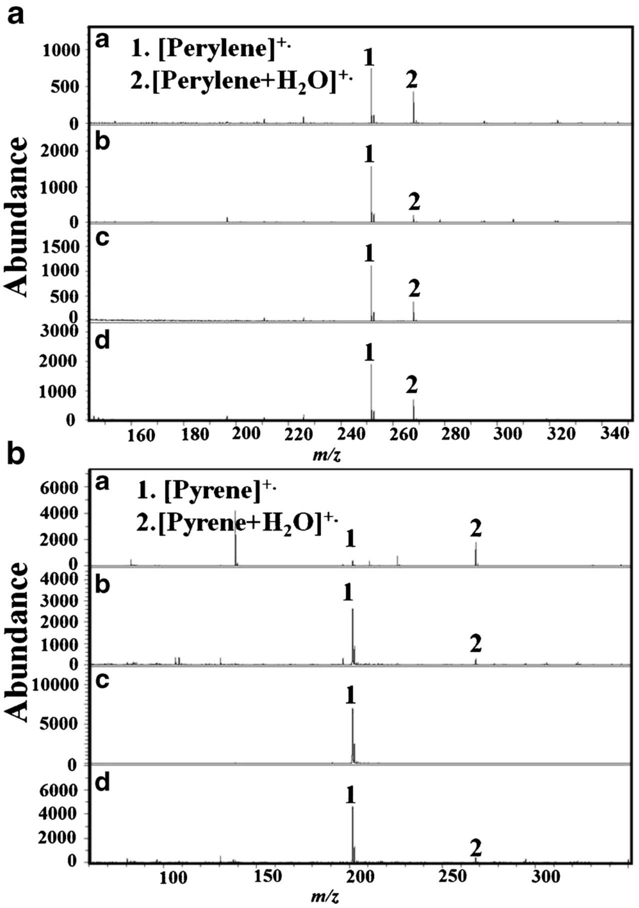

Fig. 5 Analysis of (**A**) perylene and (**B**) pyrene using (**a**) LDI, (**b**) cys@CdTe, (**c**) cys@CdTe combined with glucose, and (**d**) cys@CdTe + benzoquinone. Laser energy is fixed at 32.1 μJ

(e.g., >1000 small molecules per NP) [52]. In contrast, 1000 molecules are required to ionize only one molecule of the target analyte. The gramicidin (GD) analysis as shown in spectrum shows peaks at 1880, 1903, and 1919 Da that are assigned as $[GD+H]^+$, $[GD+Na]^+$, and $[GD+K]^+$, respectively (Fig. 3b) [53]. Comparing to conventional matrices, cysteine@CdTe shows high intensity of the protonated peak (i.e., $[GD+H]^+$) with a high resolution spectrum.

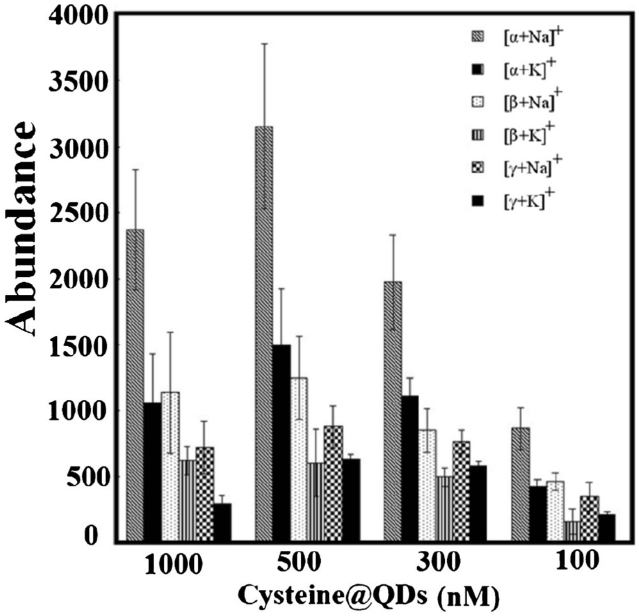

Fig. 4 Effect of the concentration of cysteine@CdTe QDs on the ionization of α-, β-, and γ-cyclodextrin

Mechanistic study of cysteine@CdTe for laser desorption/ionization mass spectrometry

So far, the mechanism for laser desorption/ionization using organic matrices or nanoparticles is ill defined. However, the laser absorption for organic matrices is the reasonable mechanism for laser desorption/ionization process. This indicates that the performance of organic depends on wavelength of the laser irradiation. In contrast, inorganic materials such as nanoparticles are wavelength independent. Thus, it is mainly due to large surface areas of the nanoparticles. The large surface area of QD nanocrystals contributes to the laser desorption/ionization process. Furthermore, the wide absorption of CdTe QDs enhances this process. The laser desorption/ionization processes of QDs absorbed laser energy (337 nm)

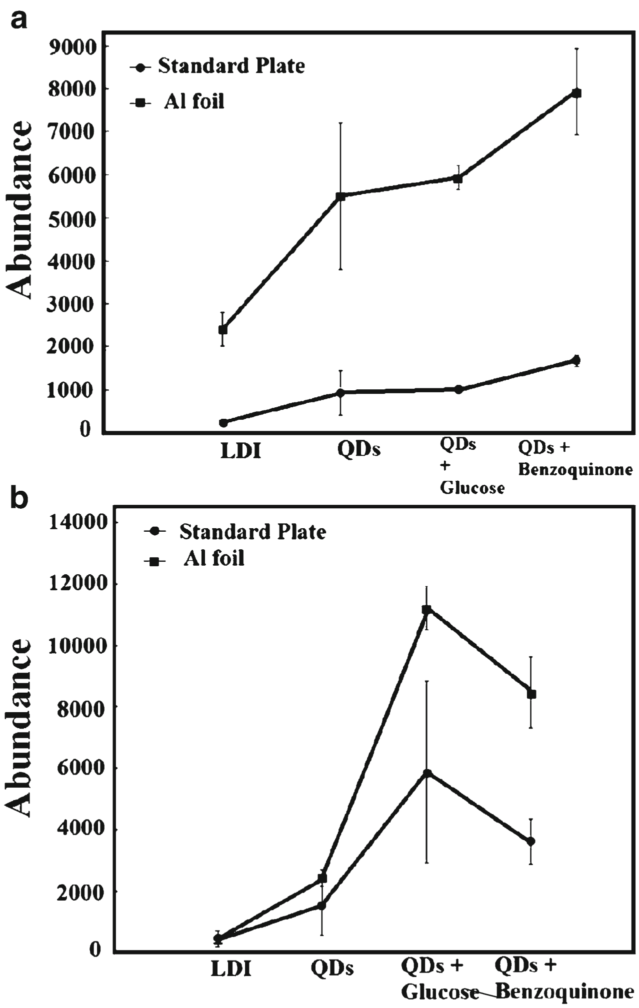

Fig. 6 The intensity improvement for (**a**) perylene (M.Wt., 252.32 Da) and (**b**) pyrene (M.Wt., 202.5 Da) using LDI, cys@CdTe, cys@CdTe combined with glucose, and cys@CdTe combined with 1,4-benzoquinone

lead to the formation of excited QDs*. These species ionize the target analytes such as analytes (A) via protonation or form cationic species, i.e., $[A+H]^+$ or $[A+Na]^+$.

$$\mathrm{QDs} + h\upsilon \rightarrow \mathrm{QDs}^*$$
$$\mathrm{QDs}^* + \mathrm{A} + \mathrm{Matrix} \rightarrow \mathrm{QDs} + \mathrm{Matrix} + [\mathrm{A}+\mathrm{H}]^+$$

In order to support this proposal, different analytes that work for laser desorption/ionization process (LDI), such as perylene (M.Wt., 252.32 Da, Fig. 5a), pyrene (M.Wt., 202.25 Da, Fig. 5b), and triphenyl phosphine (M.Wt., 262.29 Da, ESM Fig. S4), were investigated. The selected material could work without matrices, i.e., LDI. The electron-rich matrices assist the ionization using the laser irradiation directly via radical formation. The same analytes were investigated using cys@CdTe as shown in Fig. 5 and ESM Fig. S4. The spectra reveal an increase of the peak intensities in the presence of cys@CdTe. The intensity of the ionized peaks shows dramatic improvement when additives such as glucose and benzoquinone (BQ) were added (Fig. 6). It was reported that the addition of sugars minimizes the transfer of excess laser energy to investigated species such as DNA molecules and the deterioration of the laser energy [54]. These additives improved the sample homogeneity, signal strength, and signal duration [55].

The application of a cheap Al foil (which was purchased from local market) as a new plate was also investigated (Fig. 6). The new approach shows significant improvement of the peak signal as shown in Fig. 6. These observations indicate that the main reasonable mechanism is charge transfer of the QDs to the investigated analytes. The Al foil is cheap and effective for small molecule analysis. However, Al foil shows low resolution compared to the standard plate (Table 1).

Conclusions

The selection of effective capping agents for CdTe QDs applied for surface tuning laser desorption/ionization is of paramount importance. Cysteine-modified CdTe (cys@CdTe) showed potential and promising future for STLDI-MS for small molecule analysis. Cys@CdTe QDs offered many advantages, such as large surface area and absorption matching with the wavelength of N_2 laser. Laser desorption/ionization of small molecules using CdTe QDs provided background free, sensitivity, and simple sample preparation. Mechanistic study of cys@CdTe showed that the laser desorption/ionization is mainly due to charge transfer that improves by species such as benzoquinone or glucose. The laser desorption/ionization process from Al foil is higher than the traditional standard MALDI stainless steel plates and is cheap.

Table 1 FWHM summary of small molecule analysis using LDI, QDs, and QDs with additives (glucose and benzoquinone (BQ))

Analyte	Plate	LDI	STLDI-MS	STLDI-MS + glucose	STLDI-MS + BQ
Perylene	Standard plate	223	917	1003	1667
	Al foil	2400	5500	5933	7933
Pyrene	Standard plate	443	1510	5867	3617
	Al foil	413	2407	11,200	8467
Triphenyl phosphine	Standard plate	70	151	12	24
	Al foil	202	517	467	347

We did not observe any interaction or cluster formation of the investigated species and the capping agents of QDs.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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