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Quantum dots assisted laser desorption/ionization mass spectrometric detection of carbohydrates: qualitative and quantitative analysis

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A quantum dots (QDs) assisted laser desorption/ionization mass spectrometric (QDA-LDI-MS) strategy was proposed for qualitative and quantitative analysis of a series of carbohydrates. The adsorption of carbohydrates on the modified surface of different QDs as the matrices depended mainly on the formation of hydrogen bonding, which led to higher MS intensity than those with conventional organic matrix. The effects of QDs concentration and sample preparation method were explored for improving the selective ionization process and the detection sensitivity. The proposed approach offered a new dimension to the application of QDs as matrices for MALDI-MS research of carbohydrates. It could be used for quantitative measurement of glucose concentration in human serum with good performance. The QDs served as a matrix showed the advantages of low background, higher sensitivity, convenient sample preparation and excellent stability under vacuum. The QDs assisted LDI-MS approach has promising application to the analysis of carbohydrates in complex biological samples. **Copyright © 2016 John Wiley & Sons, Ltd.**

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Keywords: MALDI-MS; quantum dots; carbohydrates; glucose; quantitative analysis

Introduction

Carbohydrates have been extensively known as the key regulators in multiple biological processes such as immunity, cell development, differentiation, fertilization, nutrition, cell–cell recognition and adhesion.[1,2] The development of detection methodology for carbohydrates has become an important subject for understanding their roles in biological processes and providing diagnostic tools. Although matrix assisted laser desorption/ionization mass spectrometry (MALDI-MS) has been widely used for the analysis of biomolecules such as peptides, proteins and oligosaccharides,[3–7] the enormous molecular weights of major polysaccharides and poor ionization efficiency limit its application in carbohydrate analysis.[8–10] The matrix selection is a key factor to improve the ionization efficiency and analytical performance.[11–14]

The general matrices for MALDI-MS include 2,4,6-trihydroxyacetophenone,[15] 3-aminoquinoline,[16] 5-amino-2-mercapto-1,3,4-thiadiazole[17] and mefenamic acid.[6] The inhomogeneous crystallization of analytes in these matrices results in poor shot-to-shot and sample-to-sample reproducibility. To overcome these disadvantages, surface-assisted laser desorption/ionization mass spectrometry (SALDI-MS) has been developed by using graphite,[18] fullerene[19] or carbon nanotubes[20,21] as the matrix. This technology has been successfully used for analysis of small molecules, peptides and neutral carbohydrates using gold nanoparticles,[22,23] diamond nanoparticles (DNPs),[24] CHCA-modified Au NPs,[25] DHB@MNP,[26] HgTe nanostructures,[27] magnetic iron oxide,[28] MgO nanoparticles,[29] carbon nanodots[30] and ZnO[31] as the matrices. These nanoparticles possess high surface area and increased local temperature.[32] Under laser irradiation they can transfer charge to the analyte with high efficiency for inducing the desorption/ionization of carbohydrate analytes.

In view of the unique structure and electronic properties of quantum dots (QDs), which are beneficial to the desorption/ionization of analyte in MALDI-MS,[33–35] this work used QDs as the matrix of SALDI-MS to develop a QDs assisted LDI-MS (QDA-LDI-MS) strategy for qualitative and quantitative analysis of a series of carbohydrates (Scheme 1). Four kinds of ligands were used to modify the surface of QDs for exploring their efficacy as SALDI matrices. These carbohydrates showed higher MS intensity than those with conventional organic matrix, leading to high sensitivity. The proposed QDA-LDI-MS approach possesses promising application to the analysis of carbohydrates in complex biological samples.

Experimental

Chemicals

Sucrose, D-(−)-arabinose, D-(−)-ribose, D-(+)-xylose, D-(−)-fructose, D-(+)-galactose, D-(+)-glucose, D-glucose-$^{13}C_6$, D-(+)-mannose, α-lactose monohydrate, D-(+)-maltose monohydrate, *N*-acetyl-D-glucosamine; oligosaccharides including maltotriose,

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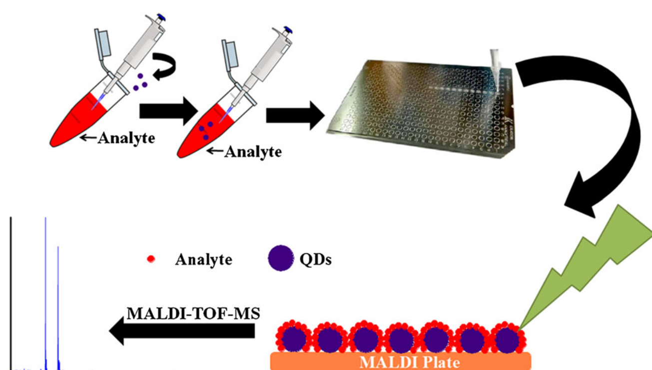

Scheme 1. Schematic illustration of QDs as a matrix for QDA-LDI-MS analysis of carbohydrates.

isomaltotriose, D-(+)-melizitose, D-(+)-raffinose, maltotetraose and strachyose tetrahydrate; and cyclic-oligosaccharides including α-cyclodextrin and β-cyclodextrin were purchased from Sigma-Aldrich (Shanghai). 2,5-Dihydroxybenzoic acid (2,5-DHB) as the matrix was purchased from Sigma-Aldrich (Shanghai). Meso-2,3-dimercaptosuccinic acid (DMSA), 3,3′-dithiodipropionic acid di (N-hydroxysuccinimide ester) (DSP), mercaptopropionic acid (MPA) and thioglycolic acid (TGA) were purchased from Alfa Aesar Ltd (China). The blood samples were obtained from the Hospital of Nanjing University and stored at −20 °C prior to analysis. Ultrapure water obtained from a Millipore water purification system (≥18 MΩ, Milli-Q, Millipore) was used in all assays. All carbohydrates and 2,5-DHB were dissolved in deionized water at an appropriate concentration, respectively.

Apparatus

SALDI-TOF-MS experiments were performed on a 4800 *Plus* MALDI TOF/TOF Analyzer (AB Sciex, USA) with a Nd % YAG laser at 355 nm, a repetition rate of 200 Hz and an acceleration voltage of 20 kV. The transmission electron micrographs (TEMs) were obtained using a JEM-2100 TEM instrument (JEOL, Japan). UV–vis absorption spectra were obtained using a UV-3600 UV–vis-NIR spectrophotometer (Shimadzu, Japan). Photoluminescence (PL) spectrum was obtained on a Jasco FP 820 fluorometer (Jasco Co., Japan).

Synthesis of quantum dots

DMSA-CdTe QDs were synthesized according to our previously reported electrolysis method using an electrogenerated Te precursor.[36] After applying an electricity quantity of 0.5 C to Te electrode at −1.0 V (*vs* Ag/AgCl) in the electrolyte containing Cd^{2+} and DMSA as stabilizer under an N_2 atmosphere, the resulting solution was refluxed at 80 °C for 20 h in the presence of highly pure N_2 to obtain the DMSA-CdTe QDs.

For the preparation of DSP-QDs,[37] the DMSA-CdTe QD solution was first decontaminated with isopropyl alcohol/water (1:1, *v/v*) and centrifuged at 8000 rcf for 5 min. Deionized water was used to dissolve the precipitate, and 0.45 mL of 2 mmol DSP was then mixed with 0.50 mL of QDs to perform ligand exchange reaction under ultrasound for 0.5 h and then incubation for 4–6 h at room temperature. The unreacted DSP was removed by filtration in a Millipore Microcon (10 000 MW) at 8000 rcf for 8 min. The required product was twice washed with acetone and redispersed in deionized water.

The MPA-stabilized CdS QDs were prepared using previously reported method.[38] Briefly, 86-μL MPA was added into 20 mL of 20 mM $CdCl_2$ solution. After the pH was adjusted to 10 with 1 M sodium hydroxide, 20-mL aqueous solution of 20 mM thioacetamide was added with widespread stirring in air for 30 min. The resulting solution was refluxed at 80 °C for 10 h to obtain MPA-CdS QDs solution. The synthesis of TGA-stabilized CdS QDs was performed using a modified method.[39] Briefly, 250 μL TGA was added into 50 mL of 0.01 M $CdCl_2$ solution, which was deoxygenated with highly pure N_2 for 30 min. After the pH was adjusted to 11 with 1 M sodium hydroxide, 5.5 mL of 0.1 M Na_2S was injected in the solution and refluxed for 4 h under N_2 atmosphere to acquire TGA-capped water-soluble CdS QDs.

Quantitative analysis of glucose in human serum samples

Molecules larger than 10 kDa in human serum were first separated using micofilter under centrifugation at 12 000 *g* for 30 min. The supernatant without further pretreatment was used for quantitative analysis of glucose using a standard addition method. The linear relationship for glucose detection was examined with glucose-spiked serum samples. All data were the averages of eight individual measurements.

QDA-LDI-MS measurements

The SALDI-TOF-MS experiments were performed in a linear low mass positive ion mode. During MS analysis, the laser power was adjusted slightly above threshold to obtain the better resolution and higher S/N ratio. Each mass spectrum was acquired as an average of 500 laser shots with a laser pulse energy of 17 μJ.

Results and discussion

Characterization of QDs

The QDA-LDI-MS strategy was developed for detection of three types of carbohydrates, including small neutral carbohydrates, oligosaccharides and cyclic-oligosaccharide by using QDs functionalized with four kinds of ligands as the matrix. The size and morphology of four different QDs were characterized by transmission electron microscopy (TEM), UV–vis absorption and PL spectra (Fig. S1), which showed the size of 4.0–6.5 nm for DSP-CdTe QDs, around 20 nm for MPA-CdS QDs, 4.5 nm for TGA-CdS QDs and 20 nm for DMSA-CdTe QD. The UV–vis spectrum of DMSA-CdTe QDs showed a wide absorption band at 460 nm, while the absorption peak of DSP-CdTe QDs significantly blue-shifted to 437 nm. Meanwhile, the PL spectrum of TGA-CdS QDs showed an excitonic emission peak centered at 510 nm, and MPA-CdS QDs showed a relatively narrow emission peak at 576 nm.

These modified QDs could interact with carbohydrates or oligosaccharides through hydrogen-bonding as reported previously,[40,41] which led to the adsorption of these compounds on QDs. After QDs absorbed the energy at 355 nm under the laser irradiation, the desorption/ionization process took place by the energy transfer from QDs for selective ionization of carbohydrates. As a result, these QDs acted as matrix for the analysis of carbohydrates. Moreover, the mass spectra of these QDs showed the background peaks only in the m/z region lower than 215.4 (Fig. S2), which did not interfere with the detection of carbohydrates with relatively large molecular weights.

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Method optimization and effect of QD concentration

The amount of QDs used as the matrix greatly affects both the adsorption capacity of analyte and the energy transfer efficiency for the ionization of the analyte[28,29] and the ratio of matrix to analyte greatly influences the matrix suppression effect (MSE).[42] Thus the MS signal depends on both the concentration of QDs and the sampling format. Using DSP-CdTe QDs as the matrix, the analytical performance was first examined at three sampling formats, dried-droplet, layer-by-layer with analyte first and QDs first, respectively.[3,6,29] At the same concentrations of QDs and analyte, the mass spectrum with a dried-droplet sampling showed the three-times larger intensity than those with layer-by-layer methods because of the fact that more analyte could be adsorbed on the surface of QDs during the mixing of analyte with QDs (Fig. 1). The dried-droplet method shows the highest intensity at *m/z* 995.6 because of the fact that more α-CD can be adsorbed on the surface of QDs during the mixing of analyte and QDs. Thus this sampling method was appropriate for the detection of different types of neutral carbohydrates.

When QD solution was mixed with the analyte solution at a ratio of 0.5:0.5 (*v/v*) in the well of the target plate and dried at room temperature, the MS peak intensity increased with the increasing QD concentration and trended a maximum value at 10 μM (Fig. S3), which was selected as the optimal amount of DSP-CdTe QDs for carbohydrate analysis.

Detection of carbohydrates

The conventional mass spectroscopic analysis of carbohydrates using 2,5-dihydroxybenzoic acid (2,5-DHB) as the matrix always suffers from the strong matrix ion interference and low ionization efficiency, which significantly affect the performance. With the help of these QDs, small monosaccharides, including arabinose, ribose, xylose, fructose, galactose and mannose, showed sodium and potassium adducts at the amount down to 1 nM (Fig. 2). When DSP-CdTe QDs were used as matrix, the amino group contained monosaccharides such as *N*-acetyl-D-glucosamine showed detectable signals even at 1 nM. Moreover, as most carbohydrates,[3,8–10] *N*-acetyl-D-glucosamine also showed Na^+ or K^+ adducts, and the peak for Na^+ adduct was stronger than that for K^+ adduct (Fig. 3A). The mass spectrum of sucrose at 1 pM showed well defined Na^+ or K^+ adducts and significantly suppressed matrix signals (Fig. 3B), which was much better than the previously reported data,[27] indicating QDA-LDI-MS provided excellent sensitivity. This appearance was also verified in the mass spectra of 1-nM α-lactose monohydrate when using DSP-CdTe QDs or 2,5-DHB as the matrix (Fig. 3C and

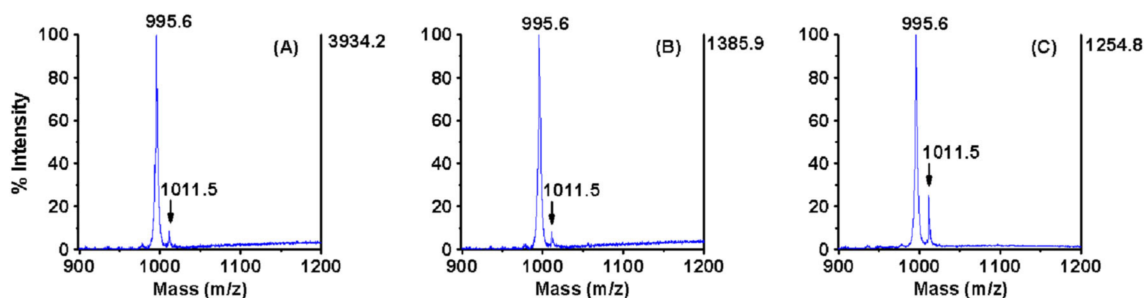

Figure 1. QDA-LDI mass spectra of 1-μM α-CD using DSP-CdTe QDs as matrix with the sample preparation methods of (A) dried-droplet, (B) analyte first and (C) QDs first. The peaks correspond to the adducts of $[\alpha\text{-CD} + Na]^+$ at *m/z* 995.6 and $[\alpha\text{-CD} + K]^+$ at *m/z* 1011.5, respectively.

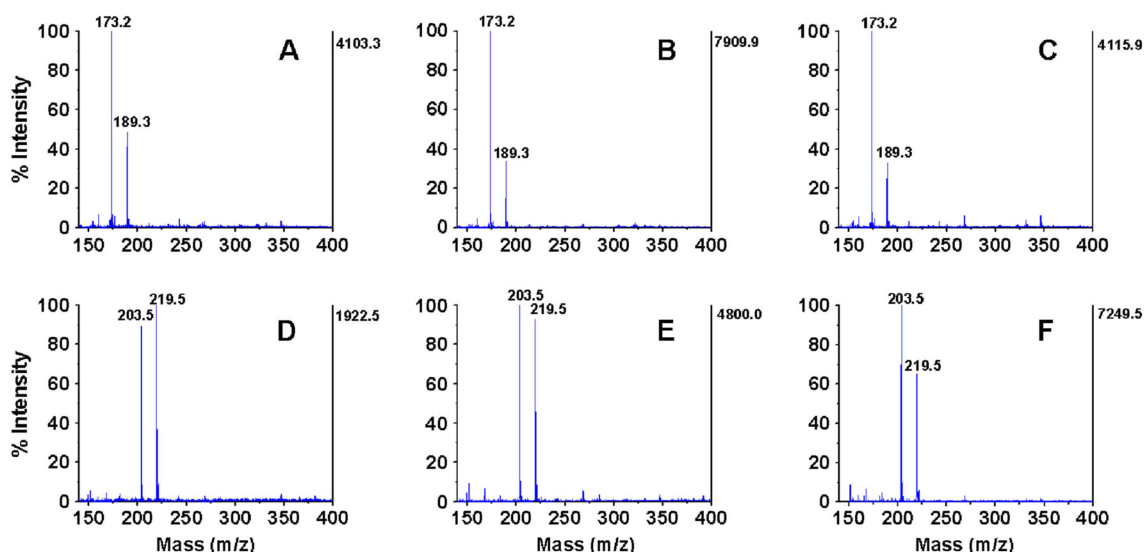

Figure 2. QDA-LDI mass spectra of small monosaccharides with DSP-CdTe QDs as matrix. (A) 1-nM arabinose at *m/z* 172.3 and 189.3 for $[\text{arabinose} + Na]^+$, $[\text{arabinose} + K]^+$ (B) 1-nM ribose at *m/z* 172.3 and 189.3 for $[\text{ribose} + Na]^+$, $[\text{ribose} + K]^+$ (C) 1-nM xylose at *m/z* 172.3 and 189.3 for $[\text{xylose} + Na]^+$, $[\text{xylose} + K]^+$ (D) 1-nM galactose at *m/z* 203.5 and 219.5 for $[\text{glactose} + Na]^+$, $[\text{glactose} + K]^+$ (E) 1-nM fructose at *m/z* 203.5 and 219.5 for $[\text{fructose} + Na]^+$, $[\text{fructose} + K]^+$ (F) 1-nM mannose at *m/z* 203.5 and 219.5 for $[\text{mannose} + Na]^+$, $[\text{mannose} + K]^+$.

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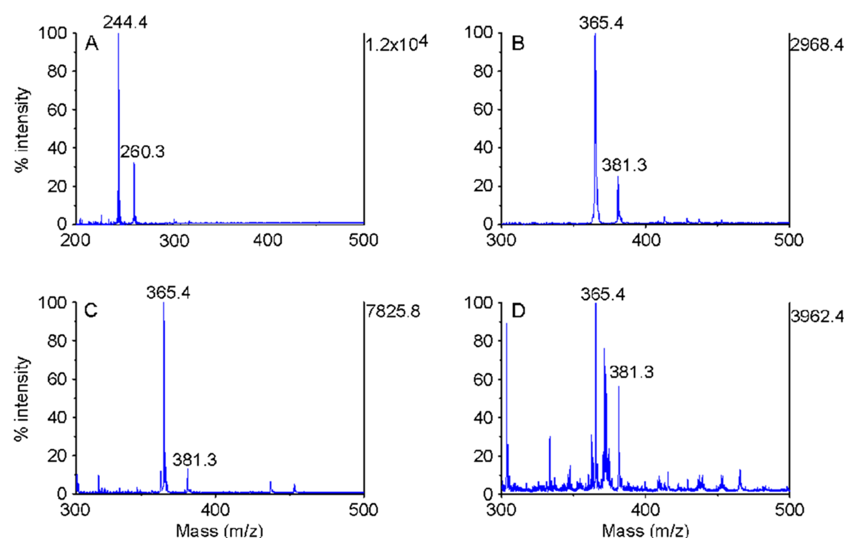

Figure 3. QDA-LDI mass spectra of (A) 1-nM *N*-acetyl-D-glucosamine and (B) 1-pM sucrose using DSP-CdTe QDs as the matrix. $[A+Na]^+$ at *m/z* 244.4, $[A+K]^+$ at *m/z* 260.3, $[B+Na]^+$ at *m/z* 365.4 and $[B+K]^+$ at *m/z* 381.3. Mass spectra of 1-nM α-lactose monohydrate using (C) DSP-CdTe QDs and (D) 2,5-DHB as the matrix [α-lactose monohydrate-H_2O + Na]$^+$ at *m/z* 365.4 and [α-lactose monohydrate-H_2O + K]$^+$ at *m/z* 381.3.

3D). DSP-CdTe QD matrix showed not only higher signal intensity than 2,5-DHB matrix, but also negligible background or matrix signals. Thus QDA-LDI-MS could achieve high ionization efficiency for analysis of neutral carbohydrates.

Low ionization efficiency of the analyte is one of the most challenging aspects for the analysis of oligosaccharides. The QDA-LDI-MS signals of six oligosaccharides with the molecular mass ranging from 500 to 700 Da, such as melizitose, isomaltotriose, maltotriose, raffinose, maltoteterose and strachyose tetrahydrate, were first examined. The lowest energy setting sufficient for ionization of an analyte was typically applied because it ensured the strongest analyte signal and maximum resolution. The QDA-LDI mass spectra of these oligosaccharides showed the adducts of $[M+Na]^+$ or/and $[M+K]^+$ (Fig. S4–S7). At the same amounts of these oligosaccharides, DSP-CdTe QDs as matrix led to the strongest MS signals, indicating the highest sensitivity and desorption-ionization efficiency of analytes. Although the $[M+K]^+$ did not occur when using TGA-CdS QDs as matrix, the mass spectra showed weaker signals than those using MPA-CdS QDs as matrix. Both maltoteterose and strachyose tetrahydrate showed the loss of glucose ($C_6H_{12}O_6$), $C_6H_{10}O_5$ and H_2O, when using these QDs as matrix, while raffinose showed the same loss when using DMSA-CdTe QDs or TGA-CdS QDs as the matrix. Interestingly, different oligosaccharides showed greatly different signal intensities, even if the same QD matrix was used. For example, when DSP-CdTe QDs were used as matrix the mass spectrum of melizitose showed sensitive signal at 1-pM level, while the signal of strachyose tetrahydrate was negligible, even at 1-mM level. This appearance was also been observed for other matrices. These results provided reference for the selection of QDs and analysis of these oligosaccharides.

To further demonstrate the feasibility of QDA-LDI-MS for qualitative and quantitative analysis of carbohydrates, the mixture including ribose, mannose and sucrose, were examined (Fig. 4A). The mass spectrum showed all the Na^+ and K^+ adducts of these carbohydrates, and the matrix-related interference was negligible. In addition, α-CD and β-CD, displayed clear signals of Na^+ and K^+ adducts (Fig. 4B), even stronger than the carbohydrates with high molecular weight, indicating the advantage of the QDA-LDI-MS for cyclic-

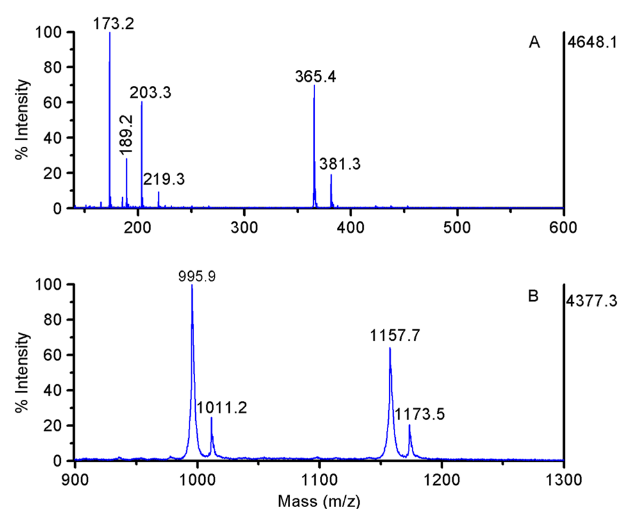

Figure 4. QDA-LDI mass spectra of mixtures of (A) 1-μM three carbohydrates and (B) 1-μM α-CD and β-CD using DSP-CdTe QDs as the matrix. The peaks at *m/z* 172.3 and 189.2 203.3, 219.3, 365.4, 381.3, $[\text{ribose}+Na]^+$, $[\text{ribose}+K]^+$ $[\text{mannose}+Na]^+$, $[\text{mannose}+K]^+$ $[\text{sucrose}+Na]^+$ and $[\text{sucrose}+K]^+$ respectively. $[\alpha\text{-CD}+Na]^+$, $[\alpha\text{-CD}+K]^+$, $[\beta\text{-CD}+Na]^+$ and $[\beta\text{-CD}+K]^+$ are at *m/z* 995.9, 1011.2, 1157.7 and 1173.5.

oligosaccharides. The higher ionization efficiency of cyclodextrin was possibly because of the large number of hydroxyl groups present in the center of the cyclodextrin structure.

The detectable limits of QDA-LDI-MS for cyclic-oligosaccharides were further examined with various QDs as matrices (Fig. 5). When DSP-CdTe QDs were used as a matrix, both α-CD and β-CD showed the detectable limits of 1 pM, lower than those of reported lithium-rich composite metal oxide matrix,[43] and 1 nM for DMSA-CdTe and MPA-CdS QDs. The higher sensitivity of DSP-CdTe QDs over other QDs, as shown in Table 1, could be attributed to its outstanding dispersibility with analytes and the unique structure of DSP for highly efficient ionization of analytes. These results demonstrated the application of QDA-LDI-MS in analysis of various kinds of carbohydrates.

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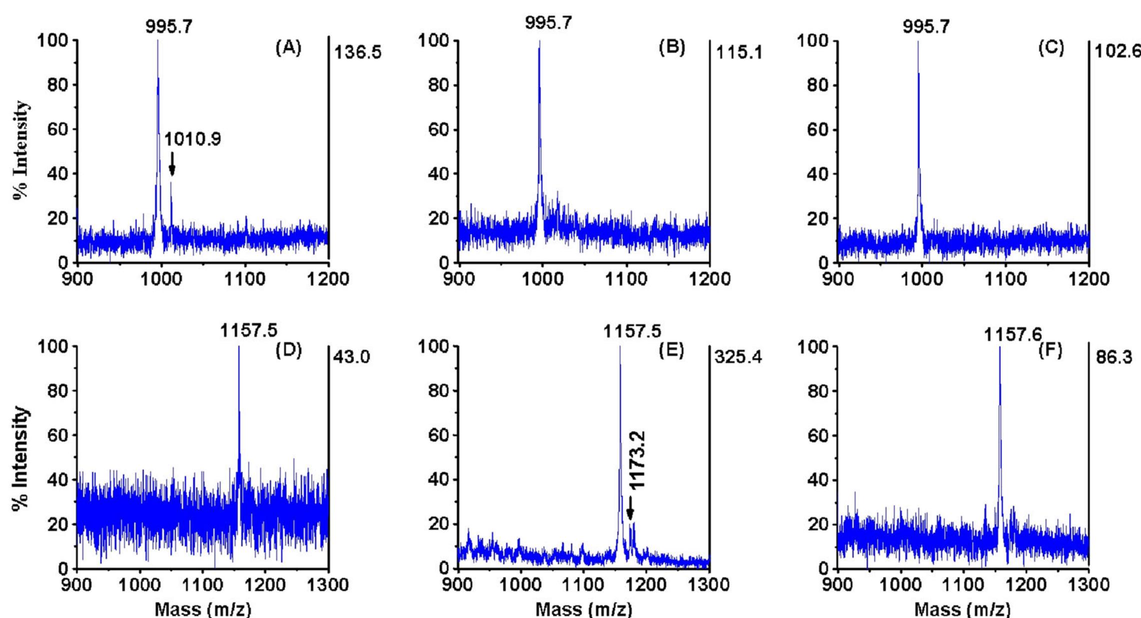

Figure 5. QDA-LDI mass spectra of (A) 1 pM and (B,C) 1-nM α-CD, and (D) 1 pM and (E,F) 1-nM β-CD with (A,D) DSP-CdTe, (B,E) DMSA-CdTe and (C,F) MPA-CdS QDs as matrix. The peaks correspond to the adducts of $[\alpha\text{-CD} + Na]^+$ at *m/z* 995.7, $[\alpha\text{-CD} + K]^+$ at *m/z* 1010.9, $[\beta\text{-CD} + Na]^+$ at *m/z* 1157.5, $[\beta\text{-CD} + K]^+$ at *m/z* 1173.2.

Table 1. Analytical performances of the previously reported technique using nanomaterials for the detection of various analytes

Technique	Analyte	Nanoparticles	LOD	Ref
SALDI-MS	Aminothiols, glutathione, cysteine and homocysteine	Nile red-adsorbed gold nanoparticles	25–54 nM	22
SALDI-MS	α-CD, β-CD and ϒ-CD	Gold nanoparticles	250–500 nM	23
MALDI-MS	Dextran[$H(C_6H_{10}O_5)_nOH$] (average M.wt. 1500), and β-CD	Diamond nanoparticles	1–5 μM	24
SALDI-MS	Sucrose, α-CD, β-CD, ϒ-CD, PL-6 k and PL-10 k	HgTe nanostructures	8.5–100 nM	25
SALDI-MS	Maltoheptaose, palatinose, D-panose, N-acetyllactosamine and β-gentiobiose	Magnesium oxide nano particles	4.0–10 nM	27
MALDI-TOF-MS	Amino acids, peptides, fatty acids, β-agonists and neutral oligosaccharides	Carbon nanodots	10–50 μM	28
SALDI-MS	Testosterone, polypropylene glycol (average M.wt. 400), α-CD, β-CD and synthetic polymers	Zinc oxide	1.600–500 μM	29
SALDI-MS	Small biomolecules	Lithium-rich composite metal oxide	5 pM	43
QDA-LDI-MS	α-CD and β-CD	DSP-CdTe QDs DMSA-CdTe MPA-CdS QDs	1 pM 1 nM 1 nM	This work

Quantitative analysis of human serum glucose

The quantitative QDA-LDI-MS analysis of carbohydrates was demonstrated with glucose as a model target analyte, considering its significant clinical indicator for diabetes. After removing the high-abundance molecules greater than 10 kDa, the mass spectra of human serum and 5-mM glucose spiked serum samples were shown in Fig. 6A and 6B. They showed a clear peak of $[\text{glucose} + Na^+]$ at *m/z* of 203 with good signal-to-noise ratio. At high glucose concentration, the peak for $[\text{glucose} + K^+]$ was also observed at *m/z* of 209. Their peak intensities linearly increased with the increasing concentration of glucose. Considering the signal-to-noise ratio, the peak of $[\text{glucose} + Na^+]$ was used for glucose detection, which showed a linear regression equation of $y = 164.7904x - 662.5698$ with a R^2 value of 0.9945 (Fig. 6C). Thus the standard addition method could be used for QDA-LDI-MS detection of glucose in untreated serum sample. The concentration of glucose in the sample was measured to be 4.02 mM. The linear range was appropriate for its application in serum analysis. The relative error for eight individual measurements was found to be less than 4%, which demonstrated the acceptable precision of the QDA-LDI-MS method for

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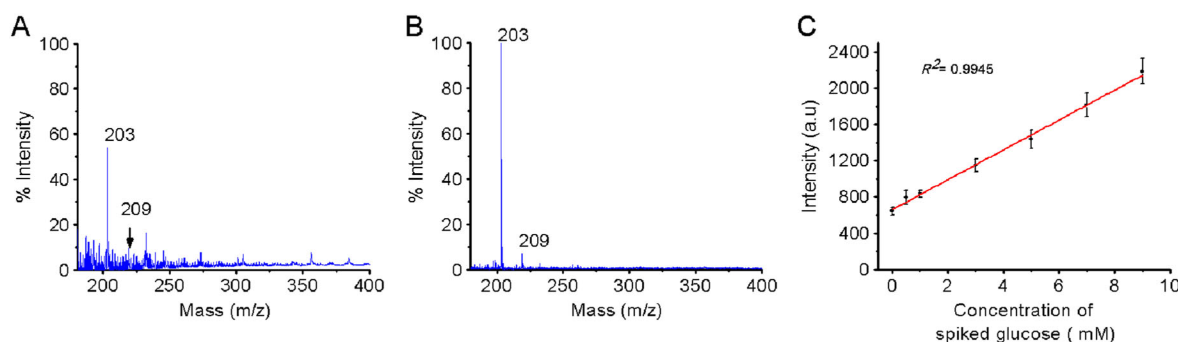

Figure 6. QDA-LDI mass spectra of (A) human serum and (B) 5 mM of glucose spiked in the human serum with DSP-CdTe QDs as matrix, and (C) plot of intensity of [glucose + Na^+] at *m/z* 203 *versus* concentration of glucose spiked inhuman serum (eight individual measurements).

practical application. In addition, the result was close to the reference value of 4.16 mM provided by the hospital, indicating good accuracy. These results clearly demonstrated the potentiality of QDs as the matrix to develop a QDA-LDI-MS approach for the analysis of carbohydrates with good reproducibility. Therefore, the proposed QDA-LDI-MS strategy was suitable for the quantitative analysis of carbohydrates in complex biological samples.

Conclusions

The efficacy of various QDs as SALDI matrices has been explored for the detection of wide range of carbohydrates and oligosaccharides/cyclic-oligosaccharides, which show typical Na^+ or K^+ adducts and higher MS intensity than those with conventional organic matrix. These functionalized QDs have an ability to interact strongly with carbohydrates for selective ionization. The present approach offers a new dimension of QDs to the application in MALDI-MS detection of carbohydrates. Furthermore, QDs as a matrix possess some advantages, such as ease of operation, low background with less matrix interference, excellent stability, high adsorption capacity and high sensitivity. The quantitative MS analysis of glucose in human serum samples also shows good performance. QDA-LDI-MS approach has promising potential for application to the analysis of carbohydrates in complex biological samples.

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