Plasmonic nanoshells enhanced laser desorption/ionization mass spectrometry for detection of serum metabolites

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Abstract

Laser desorption/ionization mass spectrometry (LDI MS)-based small metabolites detection is fundamentally important for the clinic prognoses and diagnoses. Plasmonic materials have been applied as efficient substrates for LDI MS of these molecules. However, there is no clear understanding of the mechanism of using plasmonic materials for enhanced LDI MS of small metabolites, thus restricting their application for real case serum samples. In this work, we report the use of plasmonic nanoshells for enhanced LDI MS detection of small analytes. The antibonding modes of Au nanoshells provided unique opportunity for the generation of hot carriers in the ultra-violet (UV) optical range. This effect of the Au nanoshells displayed desirable analytical sensitivity and endurance towards small metabolites (e.g. amino acids) in complex protein/mixtures as compared to Au nanorods/nanospheres and conventional organic matrix. Further we achieved LDI MS profiling and detection of small metabolites from complex serum samples by Au nanoshells. Our work not only shed light on the enhancement mechanism of LDI MS detection using plasmonic nanoparticles with hot carriers, but also contributed to the real case application of LDI MS in clinical study.

1. Introduction

Detection and profiling of small metabolites (e.g., amino acids) are instrumental for clinical molecular diagnostics towards diverse physiological and pathological process [1,2]. Conventional analytical techniques based on spectroscopic [3–5], chromatographic
and electrochemical [10–12] approaches require tedious sample pre-treatment or expensive labeling reagents, but provide moderate throughput and little structural information of molecules. For comparison, inorganic particles assisted laser desorption/ionization mass spectrometry (LDI MS) represents a simple, fast, and accurate analytical technique for simultaneous detection of various molecules within a wide mass range [13–18]. Particularly, plasmonic metallic (e.g., Au) nanoparticles (NPs) have been utilized to enhance the LDI MS detection of small analytes [19], mainly due to four aspects: (1) avoiding the strong interferences in the low mass range (m/z < 500) and sweet spots effects by traditional organic matrices; (2) high absorption coefficient in the UV–Vis optical range (e.g., >108 mol−1 cm−1 at 518 nm for 14 nm Au NPs); (3) cost-friendly and facile preparation method for large scale application; (4) mature surface modification protocol based on the gold-thiol (Au–S) interaction for capturing analytes [20]. Even though different types of metallic plasmonic particles have been developed with promising detection limits of analytes (−nmol-pmol) for LDI MS [18,21], their working mechanism is yet to be explored limiting their application with real case biological samples.

Another important feature of plasmonic metallic NPs is the localized surface plasmon resonance, which originates from the collective oscillation of quasi-free electrons on the metal surface under the excitation of incident light [22,23]. Recently, theoretical and experimental breakthrough has demonstrated that plasmonic NPs can also directly convert the collected light into hot carriers for the great potential application in photochemical reactions, photo-detectors and solar cells [24–33]. For example, the plasmon hot electrons excited by low-intensity visible light can effectively drive catalytic oxidation reactions of ethylene epoxidation, CO oxidation, and NH3 oxidation at relatively lower temperatures than most commercial heterogeneous catalytic reactions, which improves the energy efficiency and the long-term stability of the catalyst [34]. Plasmonic antennas are capable of improving efficiency of photo-detectors by concentrating the light absorption and generation of hot electrons near metal/semiconductor interfaces with additional highly intense, wavelength-tunable, and polarization specific features [27]. Therefore, plasmon-induced hot carriers are often involved in the process of photoemission, local heating, photo-chemistry, and photo-desorption [35].

However, the investigation of plasmon-induced hot carriers in the field of LDI MS is rather limited to the best of our knowledge most likely because the pulsed laser wavelength employed in the LDI MS is commonly in the ultraviolet (UV) optical range (e.g., Nd:YAG laser at 355 nm) [20] while plasmon resonances of Au NPs typically locate in the visible-near infrared (NIR) range. Previously we have employed Au nanoshells for LDI MS detection of standard small molecules [18], but the enhancing mechanism has not been investigated regarding the surface plasmon resonance. In this work, we report the generation of hot carriers in plasmonic Au nanoshells for the enhanced LDI MS detection of amino acids in serum (Scheme 1). Au nanoshells were chosen as the LDI MS enhancement substrate due to the following reasons: (1) it has been demonstrated that the nanoshell may present a larger generation rate per unit of volume than the solid spherical nanoparticle [36]; (2) plasmon resonances of Au nanoshells are highly tunable from visible to NIR range by changing the inner and outer diameters and their corresponding dark antibonding modes typically in the UV range may promote the generation of hot carriers [37–39]; (3) electrons from the d-band in Au can also contribute to the hot carrier generation process [29,36]. As a result, we achieved lower detection-limits of various amino acids (3–30 pmol) by Au nanoshells much superior to Au nanorods and nanospheres. Furthermore, there are very few reports for LDI MS based detection of metabolites in human blood/serum samples [40,41], whereas plasmonic nanoparticles have not been used as matrix and the mechanism for enhanced LDI MS detection performance remains to be investigated. Therefore, we first time achieved LDI MS profiling and detection of small metabolites from native serum samples by Au nanoshells, due to the desirable analytical sensitivity and endurance towards small metabolites (e.g., amino acids) in complex mixtures. Our work not only shed light on the enhancement mechanism of LDI MS detection using plasmonic NPs with hot carriers, but also contributed to the real case application of LDI MS in clinical study.

2. Experimental section

2.1. Materials

All materials were used as received without any further purification. Chloroauric acid tetrahydrate (HAuCl4·4H2O), trisodium citrate dehydrate (99%), tetraethyl orthosilicate (TEOS, 98%), ethanol, ammonium hydroxide aqueous solution (25–28 wt%), sodium chloride, sodium hydroxide, potassium carbonate, formaldehyde aqueous solution (37–40%), cetyltrimethylammonium bromide (CTAB, 97%) and ascorbic acid (AA) were purchased from Sinopharm Chemical Reagent Co. Ltd (Shanghai, China). Sodium borohydride (NaBH4, 98%) and cetyltrimethylammonium chloride (CTAC, 97%) were obtained from J&K Chemical Ltd (Shanghai, China). and tetrakis[(hydroxymethyl)-phosphonium chloride (THPC, 80%) were received from TCI (Tokyo, Japan). 3-aminopropyltriethoxysilane (APTES, 99%) was purchased from Aladdin (China). Deionized water (18.2 MΩ) was provided by a CascadatM system.

Scheme 1. Illustration of LDI MS analysis based on plasmonic Au nanoshells. The schematic of a nanoshell on the left showed a SiO2 core coated with an Au shell.
2.2. Synthesis of NPs

Au nanoshells NPs were fabricated by following previous reports [42,43]. Briefly, silica particles were synthesized following a Stöber process by mixing ammonia and absolute ethanol, followed by adding TEOS dropwise. Then 10 mL of silica colloids was directly functionalized with 50 μL of APTES without purification overnight. Next, these functionalized silica colloids were further decorated with some tiny Au colloids (1−2 nm) and then were purified by repeated centrifugations. A subsequent 10 min reduction in an overnight-aged mixture of HAuCl₄ (3 mL, 1%) and K₂CO₃ (100 mL, 3.6 mM) in the presence of formaldehyde (5 mL) resulted in a continuous Au shell on the silica surface. The nanoparticles were centrifuged after reaction and re-dispersed in water to form a stable suspension [18,43]. The averaged dimension of obtained Au nanoshells was a 100 nm core in diameter and a 33 nm Au shell in thickness (an outer diameter of 166 nm).

Au nanorods were prepared by following a method previously reported [44]. The seed solution was synthesized as follows: 5 mL HAuCl₄ (0.5 mM) was mixed with 5 mL CTAB (0.2 M) solution in a 25 mL vial. 0.5 mL of fresh NaBH₄ (6 mM) solution was then injected to the above mixture solution under vigorous stirring (1200 rpm). The solution color changed from yellow to brownish yellow and the stirring was stopped after 5 min. The seed solution was aged at 30°C for 90 min before use. To prepare the growth solution, 1.4 g of CTAB and 146.8 mg of NaOH were dissolved in 50 mL of warm water (−50°C) in a 250 mL flask. The solution was allowed to cool down to 30°C and 3.6 mL AgNO₃ solution (4 mM) was added. The mixture was kept undisturbed at 30°C for 15 min after which 50 mL of HAuCl₄ solution (1 mM) was added. The solution became colorless after 90 min of stirring (700 rpm) and 0.42 mL of HCl (37 wt % in water) was then introduced to adjust the pH value. After another 15 min of slow stirring at 400 rpm, 0.25 mL of ascorbic acid (0.064 M) was added and the solution was vigorously stirred for 30 s. Finally, 0.08 mL of seed solution was injected into the growth solution. The resultant mixture was stirred for 30 s and left undisturbed at 30°C for 12 h for particle growth. The final products were isolated by centrifugation at 7000 rpm for 30 min followed by removal of the supernatant. The average size of obtained nanorods was 120 nm in length and 47 nm in width.

Surfactant coated Au nanospheres were synthesized using a seed-mediated process [45,46]. Typically, seed solution was firstly prepared by vigorous mixing of 10 mL of aqueous CTAC solution (0.1 M) and 515 μL of HAuCl₄ (4.86 mM) with 450 μL of NaBH₄ solution. The seed solution was aged for at least 1 h in a hot bath and then was diluted for 10 times. Next, 10 mL of CTAC solution (0.1 M) was mixed with 515 μL of HAuCl₄ (4.86 mM) and 75 μL of ascorbic acid (0.04 M). 100 μL of diluted seed solution was added into the above mixed solution under sonication and kept in darkness for at least two days. The average size of the Au nanospheres obtained was around 20 nm from the TEM measurement.

Surfactant-free Au nanoparticles were synthesized using the reported Frens method [47]. Briefly, 100 mL of 0.25 mM HAuCl₄ aqueous solution was heated in a conical flask and boiled. 3 mL of 1%(w/v) sodium citrate aqueous solution was added to the boiling solution and continued heating until formation of deep ruby red color, indicating the formation of gold nanoparticles with an average size of 12.2 ± 1.4 nm.

2.3. Characterization

TEM images of Au nanoparticles were obtained using a JEOL-2010 transmission electron microscope (JEOL, Japan) operating at 300 kV. SEM images of Au nanoshells were taken on an S-4800 field emission scanning electron microscope (SEM, Hatzchi, Japan) operating at 1 kV. The experimental extinction spectra of Au nanoparticles were collected on a UV1900 UV−Vis spectrometer (Aucybest, China).

2.4. Numerical simulations

Calculated far field spectra, electric field enhancement maps and surface charge density distribution were obtained from the finite-difference time-domain (FDTD) method with the program of FDTD Solutions (Lumerical Solutions, Inc., Canada). All the simulations incident illumination was set with a total-field scattering-field (TFSF) source. For the dielectric function of Au, we used the Drude model [48] or the empirical data provided by Johnson and Christy [49]. The empirical data were further fitted by the Lumerical’s multi-coefficient model.

2.5. LDI MS detection

In LDI MS detection of amino acids, valine, lysine, methionine, arginine, tryptophan, phenylalanine, and their mixture of 100 ng μL⁻¹ concentration were used to investigate the performance of plasmonic NPs (e.g. Au nanoshells, nanorods, and nanospheres) as the matrix. The stand solutions were prepared by a stepwise dilution method. In order to investigate the influence of sample complexity on LDI MS detection, a mixture of valine, lysine, methionine, arginine, tryptophan, and phenylalanine was spiked in to the bovine serum albumin (BSA) solution (10 mg mL⁻¹) and salts solutions (0.5 M NaCl or KCl) at a concentration of 100 ng μL⁻¹. For serum detection, serum samples donated by three healthy volunteers were harvested and saved in tubes according to the standard protocol as reported [50]. The serum samples were processed by a simple filtration treatment using the Nanosep Centrifugal devices with a microporous membrane filter from PALL Corporation. All the samples were stored at −20°C before use.

In all LDI MS analysis, 0.5 μL of analytes solutions or serum samples were spotted on the plain steel MALDI plate and dried in air at the room temperature, followed by adding 0.5 μL of plasmonic NPs suspension or organic matrix solution (p-cyano-4-hydroxycinnamic acid, CHCA). Mass spectra were acquired in the reflection mode on 5800 Proteomics Analyzer (Applied Biosystems, Framingham, MA, USA) with the Nd:YAG laser at 355 nm, a repetition rate of 200 Hz and an acceleration voltage of 20 kV. LDI MS analyses were performed employing delayed extraction in the positive ion mode with pre-calibrations by standard molecules. The delay time for this experiment was optimized to 300 ns and accurate mass measurement was employed for the peak assignments. All spectra were directly used without any smoothing procedures.

3. Results and discussion

We investigated the enhancement performance of plasmonic materials including Au nanoshells, nanorods, and nanospheres in LDI MS detection of amino acid mixtures containing valine, lysine, methionine, arginine, tryptophan, and phenylalanine. Au nanoshells used here have an inner diameter of 100 nm and an outer diameter of 166 nm, according to the TEM image (Fig. 1). The SEM image showed uniform particle size and a complete outer Au shell with a rough surface (Fig. 1a-i). The extinction spectrum of Au nanoshells shows two resonance peaks roughly at 620 nm and 537 nm, which most likely correspond to the dipolar and quadrupolar resonance modes of Au nanoshells (Fig. 1b-i). More detailed spectra incident illumination were set with a total-field scattering-field (TFSF) source. For the dielectric function of Au, we used the Drude model [48] or the empirical data provided by Johnson and Christy [49]. The empirical data were further fitted by the Lumerical’s multi-coefficient model.
mass assignment) with signal strength up to 40000. In contrast to Au nanoshells, no signals can be obtained without any matrix (Fig. S2a) or using the bulk silicon oxide particles with an average diameter of ~120 nm as matrix (Fig. S2b) suggesting the poor LDI efficiency, whereas strong background noises were produced using conventional organic matrix (Fig. S2c) due to unwanted fragmentation. This clearly confirms the strong enhancement of LDI MS detection of amino acids using Au nanoshells.

For further understanding the enhancement effect in LDI MS measurement on Au nanoshells, Au nanorods and nanospheres were prepared and employed as the enhancement matrix in the LDI MS. Au nanorods used have an averaged size of 120 nm length and 47 nm width, and Au nanospheres have an averaged 20 nm diameter (Fig. 1a-ii & iii). We have also measured the extinction spectrum of nanorods in Fig. 1b-ii showing resonance peaks at 525 and 740 nm, which can be assigned to the nanorod’s transverse and longitudinal mode, respectively. In contrast, Au nanospheres show only one resonance peak at 536 nm owing to their dipolar plasmon mode (Fig. 1b-iii). Surprisingly, no detectable signals from the amino acids can be found in the LDI MS measurement based on the Au nanorods and nanospheres (Fig. 1c-ii & iii). Considering the potential influence of cationic surfactants on the LDI process [51–53], we prepared surfactant-free gold nanoparticles as control to validate the performance of gold nanoshells. As shown in Fig. S3, we observed enhanced signals of amino acids (arginine and phenylalanine) from gold nanoshells compared to gold nanoparticles, which excluded the influence from cationic surfactants and demonstrated the better analytical performance of gold nanoshells.

The generation of plasmon-induced hot carriers has been reported to promote the desorption of molecules [35]. By simply comparing all extinction spectra of Au nanoparticles and the pulse laser wavelength (355 nm), it is difficult to figure out the explanation why only Au nanoshells can boost the signals of amino acids in the LDI MS measurement. The nanoshell may own a larger generation rate of plasmonic hot carriers per unit of volume than the solid rod-like or spherical nanoparticle [36], however, no resonance modes are excited at 355 nm from all experimental extinction spectra of Au nanoparticles since the interband transition occurs below 500 nm for Au [54,55]. Typically the rate of hot carrier generation essentially follows the spectral profile of the plasmons [24,36]. Moreover, the Au absorption coefficient should be the same at this wavelength for nanoshells, nanorods, and nanospheres. Therefore, it is quite needed to find a possible mechanism to explain the significant enhancement effect of Au nanoshells in LDI MS.

In the framework of the plasmon hybridization model, plasmon behaviors of a nanoshell can be decomposed into the plasmon interaction between a nanosphere and a nanocavity, resulting in the formation of a low-energy symmetric bonding mode and a high-energy asymmetric antibonding mode [38]. The antibonding mode of the Au nanoshell has been calculated to be in the UV range [37,39]. Although the antibonding mode is damped due to the interband transition of Au in the experimental spectral measurement [54,55], but the generation of hot carriers by the antibonding mode is not forbidden. We have performed FDTD method to calculate the extinction spectrum of a Au nanoshell. Fig. 2-i displayed the extinction spectrum of an Au nanoshell calculated with a dielectric function from empirical data, where no plasmon mode can be observed in the wavelength range below 500 nm (the shaded area) due to electron interband transitions of Au. The difference between experimental data and simulated data in this work is similar to previous references regarding the plasmonic stimulations [56–58]. But two resonance modes (1 and 2) can be easily found in the wavelength of 560 and 710 nm, well replicate the
Fig. 2. FDTD simulated extinction spectra of Au nanoshells with the dielectric function from (i) empirical data and (ii and iii) the Drude model in (i, ii) water and (iii) air. The shaded area indicates the wavelength regions where interband transitions of Au occur. The corresponding electric field and surface charge distributions of mode 1–6 are plotted on the right. The dashed line indicates the wavelength of the Nd:YAG laser at 355 nm.

Fig. 3. LDH MS spectra of 2 nmol a) valine, b) lysine, c) methionine, d) arginine, e) tryptophan, f) phenylalanine in 0.5 μL of purified water (18.2 MΩ cm) and g) the detect limits using plasmonic nanoshells as matrix in positive ion mode.
experimental optical spectrum (Fig. 1b–i). These two modes can be assigned to the dipolar and quadrupolar mode of the nanoshell, confirmed by the maps of electric field distributions (Fig. 4). When the Drude model was applied in the calculation, which ignores the interband transition of Au, we can clearly see the pronounced multiple plasmon modes from the UV to NIR range of the extinction spectrum of the Au nanoshell in water (Fig. 2-ii). Since the LDI MS measurements were performed in air, the calculated extinction spectrum of the Au nanoshells in air was also obtained from the FDTD simulations (Fig. 2-iii). We have found four pronounce plasmon modes (3–6) in the extinction spectrum the Au nanoshells in air, which are blueshifted compared to those in water mainly due to the change of the refractive index of the media. From the calculations of surface charge distributions, we have confirmed that the mode 3–5 corresponds to the bonding dipolar, bonding quadrupolar, antibonding quadrupolar plasmon mode, respectively. Mode 6 exhibits the mixed features of antibonding quadrupolar and antibonding dipolar mode to some extent. The Nd:YAG laser employed in this work is at 355 nm, which can excite the resonance mode 6 and consequently generates hot carriers. For plasmon energies above the interband transition threshold, the dominant portion of the hot carriers will be hot holes formed at the upper edge of the metal d band with the electrons locates just above the Fermi level [35]. Therefore, we concluded that nanoshells would be superior to nanospheres or nanorods because of the boost of the hot carriers by the excitation of antibonding mode of the nanoshells.

Notably, considering the large amounts of salts and water molecules in the analyte solutions, after the drying process (see Experimental Section for details) Au nanoshells are coated with a layer of ions and water molecules on surface [20,41]. Consequently, Au nanoshells may allow desirable generation of hot carriers to promote the photo-production of complexes of metal ions (Na\(^+\) and K\(^+\)) and small metabolites. From electrochemical aspects, the formation of ion layer on Au nanoshells surface facilitates the LDI process to produce metal ions adducted molecular species (Fig. 1c) for subsequent MS detection in the positive ion mode.

In the following application tests, we recorded the standard spectra of the amino acids and tested the corresponding detection limits using Au nanoshells. Mass spectra of 2 nmol analytes were shown in Fig. 3a–f using Au nanoshells. Typical peaks with sodium and potassium adduction can be obtained in the positive model yielding m/z 140.06 [M+Na]\(^+\) and m/z 156.04 [M+K]\(^+\) for valine (Fig. 3a), m/z 169.09 [M+Na]\(^+\) and m/z 185.06 [M+K]\(^+\) for lysine (Fig. 3b), m/z 172.04 [M+Na]\(^+\) and m/z 188.01 [M+K]\(^+\) for methionine (Fig. 3c), m/z 197.10 [M+Na]\(^+\) and m/z 213.07 [M+K]\(^+\) for arginine (Fig. 3d), m/z 227.07 [M+Na]\(^+\) and m/z 243.05 [M+K]\(^+\) for tryptophan (Fig. 3e), m/z 188.06 [M+Na]\(^+\) and m/z 204.04 [M+K]\(^+\) for phenylalanine (Fig. 3f). No fragment ion signals of the analytes were observed indicating the desirable soft ionization process and
Au composites produced little background signals due to the stable structure. The detection limits of amino acid in LDI MS summarized in Fig. 3g are in the range of 3–30 pmol, which is comparable to the best results from current reports [41,59,60] and essential for detection of molecules with low abundance in real case.

Considering the high concentration of proteins and salts in biological samples, we also examined the performance of Au nanoshells in complex protein/salt mixtures over control experiments without any matrix or using organic matrix. As shown in Fig. 4a-i & ii & iii, no signals from spiked amino acids can be recognized without any matrix in BSA (10 mg mL⁻¹, Fig. 4a-i), KCl (0.5 M, Fig. 4a-ii) and NaCl (0.5 M, Fig. 4a-iii) solutions, whereas only background signals were produced by the use of CHCA (Fig. 4b-i & ii & iii). For comparison, six amino acids can be detected using Au nanoshells in all cases (Fig. 4c), yielding both sodium and potassium ions adducted peaks mixing with BSA (valine at \( m/z \) of 140.06 [M+Na]⁺ and 156.04 [M+K]⁺, lysine at \( m/z \) of 169.09 [M+Na]⁺ and 185.06 [M+K]⁺, methionine at \( m/z \) of 172.04 [M+Na]⁺, arginine at \( m/z \) of 197.10 [M+Na]⁺, tryptophan at \( m/z \) of 227.07 [M+Na]⁺ and 243.05 [M+K]⁺) in Fig. 4c-i, only potassium ions adducted peaks mixing with KCl in Fig. 4c-ii, and only sodium ions adducted peaks mixing with NaCl in Fig. 4c-iii. The absence of other metal ions adduction in Fig. 4c-ii & iii can be caused by the presence of highly concentrated specific ions in solution. The above data demonstrated the desirable performance of Au nanoshells for LDI MS in complex mixtures towards practical applications.

In the final stage, we applied Au nanoshells for detection of real case human serum samples. In analysis of serum samples, we observed no signals from 500 nL of serum samples by LDI MS without any matrix (Fig. 5a) and background noises using CHCA (Fig. 5b). In contrast, typical small molecules can be identified using Au nanoshells in Fig. 5c at \( m/z \) of 159.98 [M+K]⁺ for cysteine in the range of 120–180, \( m/z \) of 185.06 [M+K]⁺ for lysine and 197.10 [M+Na]⁺ for arginine in the range of 180–200, \( m/z \) of 203.05 [M+Na]⁺ and 219.02 [M+K]⁺ for glucose and 205.06 [M+Na]⁺ for mannitol in the range of 200–220, \( m/z \) of 243.05 [M+K]⁺ for tryptophan in the range of 220–280. We zoomed the spectrum to show the signals of molecules in the \( m/z \) ranges of 120–180, 180–200, 200–220, and 220–280 in Fig. 5c. Notably, other small carbohydrates can also be detected by Au nanoshells indicating the capability for profiling of small metabolites in serum. We detected another two human serum samples and obtained similar results (Fig. S4 & S5), demonstrating the universal application of Au nanoshells in real case. This is the first demonstration using plasmonic NPs for successful LDI MS detection of small metabolites in native serum with relatively low molecular abundance and high sample complexity, which relied on the improved sensitivity and protein/salt endurance as validated by our previous assays.

**Fig. 5.** LDI MS spectra from 500 nL of native serum (from volunteer 1) as filtered using a) no matrix, b) CHCA and c) plasmonic particles, the spectra from plasmonic nanoshells are zoomed to show typical molecules identified. The four specific zooming ranges of spectrum are \( m/z \) of 120–180, 180–200, 200–220, and 220–280, as displayed in the horizontal axis of c).
4. Conclusion

In summary, we reported the generation of hot carriers in plasmonic nanoshells for enhanced LDI MS detection of small analytes. Compared to Au nanorods and nanospheres, the antibonding modes of Au nanoshells provide unique opportunity for the generation of hot carriers in the UV optical range, and consequently the Au nanoshells displayed desirable analytical sensitivity endurance in complex protein/mixtures towards amino acids. The performance of Au nanoshells was additionally demonstrated to be superior over traditional organic matrix, which can be further applied in detection and profiling of small metabolites in serum samples for clinical use. This work not only makes solid contributions to a better understanding of enhanced LDI MS detection by Au nanoshells with hot carriers, but also starts the practical application of plasmonic particles assisted LDI MS for serum analysis in clinical study.

Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.anca.2016.11.017.

References


