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MoS_2/Ag nanohybrid: A novel matrix with synergistic effect for small molecule drugs analysis by negative-ion matrix-assisted laser desorption/ionization time-of-flight mass spectrometry

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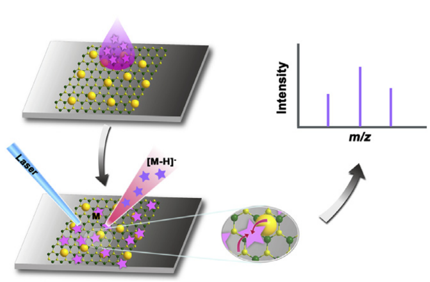
HIGHLIGHTS

- MoS_2/Ag nanohybrid was applied as a novel matrix in negative-ion MALDI-TOF MS.
- The MoS_2/Ag nanohybrid exerted synergistic effect on the detection of small molecules.
- The MoS_2/Ag nanohybrid showed good signal reproducibility and low background interferences comparing to organic matrices.
- MoS_2/Ag allows simultaneous analysis of multiple drugs and quantification of acetylsalicylic acid in spiked serum samples.

GRAPHICAL ABSTRACT



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ABSTRACT

This paper reports a facile synthesis of molybdenum disulfide nanosheets/silver nanoparticles (MoS_2/Ag) hybrid and its use as an effective matrix in negative ion matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS). The nanohybrid exerts a strong synergistic effect, leading to high performance detection of small molecule analytes including amino acids, peptides, fatty acids and drugs. The enhancement of laser desorption/ionization (LDI) efficiency is largely attributed to the high surface roughness and large surface area for analyte adsorption, better dispersibility, increased thermal conductivity and enhanced UV energy absorption as compared to pure MoS_2. Moreover, both Ag nanoparticles and the edge of the MoS_2 layers function as deprotonation sites for proton capture, facilitating the charging process in negative ion mode and promoting formation of negative ions. As a result, the MoS_2/Ag nanohybrid proves to be a highly attractive matrix in MALDI-TOF MS, with desired features such as high desorption/ionization efficiency, low fragmentation interference, high salt tolerance, and no sweet-spots for mass signal. These characteristic properties allowed for simultaneous analysis of eight different drugs and quantification of acetylsalicylic acid in the spiked human serum. This

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work demonstrates for the first time the fabrication and application of a novel MoS_2/Ag hybrid, and provides a new platform for use in the rapid and high throughput analysis of small molecules by mass spectrometry.

1. Introduction

Nowadays, matrix-assisted laser desorption/ionization (MALDI) time-of-flight mass spectrometry (MALDI-TOF MS) has been served as a powerful tool for the analysis of biomolecules such as peptides [1], proteins [2], and oligosaccharides [3]. However, while it is applied in the analysis of small molecules, it often meets challenges, largely due to interference of conventional organic matrix-related ions (e.g., α-cyano-4-hydroxycinnamic acid, CHCA) in low-mass regions (<500 Da) [4] and poor reproducibility originating from the heterogeneity of the matrix-analyte crystals [5]. To overcome these drawbacks, great efforts have been made to develop nanomaterials as alternative matrices, especially for small molecule analysis. This technique is also known as surface-assisted laser desorption/ionization (SALDI) [6]. Up to now, a variety of inorganic nanomaterials with different compositions and morphologies, including silicon [7,8], metal/metal oxide [9–11], and carbon-based materials [12–14], have been utilized as MALDI matrices. These nanomaterial-based matrices minimized the background interferences, increased sensitivity, and simplified the sample preparation. However, the need for elaborate nanofabrication process can limit their application. In addition, most of the metal oxide and carbon-based materials display poor dispersibility in solution that often yields inhomogeneous distribution of nanomaterials on the sample target. This usually results in poor shot-to-shot and sample-to-sample reproducibility and decreases sensitivity of MALDI-TOF MS [15]. Thus, exploration of better matrices with simple preparation approach, good dispersibility, and high laser desorption/ionization (LDI) efficiency is still very necessary and highly relevant for MS analysis.

To achieve sensitive and reproducible MALDI-TOF MS, great endeavors have been devoted to the combined functionalization of nanomaterials [16–19]. Shi et al. prepared highly water-dispersible polydopamine-modified carbon nanotubes to overcome the poor dispersibility of pristine multi-walled carbon nanotubes (MWCNTs) and demonstrated that the composites have improved the performance of the analysis of various water soluble small molecules [16]. Apart from the increased dispersibility, some hybrid nanocomposites can exhibit synergistic effect in the enhancement of the LDI efficiency of analytes. Xu et al. developed a hybrid nanocomposite with a large graphitized inner surface area, strong UV adsorption and excellent dispersibility, which have improved the LDI efficiency and prevented inhomogeneous distribution [17]. Kim et al. designed a graphene oxide/multi-walled carbon nanotube double layer and applied it as a MALDI substrate. The design showed enhanced surface roughness and surface area for analyte adsorption, and improved wettability in water because of the charged surface [18]. Although these methods have achieved some success, most of the nanomaterial-based matrices were based on the MS detection platform in positive ion mode. This often results in multiple alkali metal adducts in the mass spectrum, which is difficult to identify [12,17]. In contrast, the negative ion spectrum is much clearer and easier to interpret with one deprotonated ion peak present [20,21]. Furthermore, recent studies have showed that better sensitivity can be obtained in negative mode than positive mode for analytes [20,22]. Given the advantages of negative ion mode for small molecule analysis, exploring negative ion mode-compatible matrices with improved LDI efficiency is highly desirable.

As a two-dimensional (2D) single atomic layer of carbon atoms, graphene exhibits large surface area of its nanosheet structure, excellent optical and electrical properties, and has proved to be a useful matrix in the analysis of small molecules in negative ion mode [22]. Min et al. further prepared the N-doped graphene as a matrix and demonstrated it has higher LDI efficiency than other graphene-based matrices in negative ion mode [20]. Recently, considerable attention has been given to graphitic carbon nitride because of its 2D layer structure analogous to graphene [21]. The pyridinic nitrogen atoms in g-C_3N_4 nanosheets possess sp^2 electrons in the π-conjugated system, thus can promote the charging process in the negative ion mode [21]. Another graphene analogue, MoS_2 nanosheet, has similar features including 2D ultrathin atomic layer structure and high surface area, and has showed great potential in nanoelectronics, optoelectronics, and energy harvesting [23]. Especially, MoS_2 sheet edges have been identified as the active sites to dissociate H_2 and associate H for hydrogen evolution [24,25]. MoS_2 nanosheets can be easily synthesized in large quantities and directly dispersed in solutions without surfactants or oxidation treatment comparing to graphene [26]. In addition, MoS_2 nanosheet has high absorption in the UV–visible range, and thus is suitable for MALDI experiments. Furthermore, MoS_2 is a promising supporting material to stabilize metal-nanoparticles such as gold and silver nanoparticles, forming hybrid composites. Berry's group has reported the increased thermal conductivity of MoS_2 after metal-nanoparticle incorporation [27], which is propitious to the LDI process [17]. Additionally, AgNPs have been successfully utilized as an effective matrix for the determination of estrogens by negative ion MALDI-TOF MS where AgNPs have shown extremely high absorption coefficients in the near UV–vis region, a large heat capacity and high heat conductivity [28,29]. Therefore, we anticipate that the combination of MoS_2 nanosheets with AgNPs would be very beneficial for enhancing the sample signal and reproducibility in negative ion MALDI-TOF MS.

Herein, we report the development of a facile method to prepare water-dispersible MoS_2/Ag hybrid and its application for the first time to negative ion MALDI-TOF MS analysis of small molecules (Scheme 1). The modification of Ag on the surface of MoS_2 nanosheet is expected to yield larger surface roughness and surface area for analyte adsorption, better dispersibility, increased thermal conductivity and enhanced UV energy absorption. Compared with single component MoS_2 or Ag, the hybrid nanocomposites lead to the synergistic effect in the enhancement of the LDI efficiency for a range of analytes including amino acids, peptides, fatty acids, and drugs. In comparison with organic matrices in both positive and negative ion mode, the MoS_2/Ag hybrid matrix in negative ion mode exhibits significant advantages, such as high sensitivity, free matrix background, good salt tolerance, and excellent reproducibility. These characteristic properties allow it for simultaneous analysis of eight different drugs and further quantification of acetylsalicylic acid in the spiked human serum, making it a promising, generic platform for negative ion MALDI-TOF MS analysis of small molecules in complex, real world samples. The mechanism study of