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Review Article

Nanoparticle-based laser desorption/ionization mass spectrometric analysis of drugs and metabolites

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ABSTRACT

Nanoparticle-assisted laser desorption/ionization mass spectrometry (LDI-MS) is a powerful tool for the analysis of a wide range of molecules. Many of the drawbacks in the matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS) can be avoided with the application of nanomaterials as matrices as well as substrates for the LDI-MS to achieve a low background noise in low *m/z* region and high reproducibility. Surface-assisted LDI (SALDI)-MS, especially the nanoparticle-based LDI-MS, has emerged as a promising technique for the analysis of trace amounts of substances in various biological samples due to their high surface area for analyte enrichment, efficient desorption/ionization, and homogeneous crystallization of sample. Therefore, it is highly useful in clinical, forensic, medical, food and drug analyses, disease diagnosis, and various other fields. In this review, we briefly discuss the application of various nanomaterials, which include metal-based, carbon-based, silicon-based nanomaterials and nanocomposites, as matrices and substrates for LDI-MS based drug and metabolite analyses and possible detection strategies. Also, we discuss the idea of using "mass tag" for signal amplification for drug and metabolite detection using nanoparticle assisted LDI-MS.

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1. Introduction

Laser desorption/ionization (LDI) is an ionization technique that desorbs and ionizes substances through heating them by pulse laser irradiation. LDI is the one of the most prevalent ionization techniques; only second to electrospray-based ionization (ESI), due to its high speed of analysis, simple spectra and its capacity to analyze wide category of substances. Early LDI-mass spectrometry (LDI-MS) techniques had limitations in the type of substances due to low laser absorption and ionization efficiencies, easy fragmentation and thermal degradation of analytes. Organic molecule (nicotinic acid) as matrix to assist the LDI process of the analyte was introduced in the 1980's by Hillenkamp and Karas [1]. The matrix enhances the desorption and ionization of the analytes by absorbing laser energy and transferring it to analytes while preventing their direct fragmentation. This technique, named matrix-assisted laser desorption/ionization (MALDI), has greatly expanded the category of analytes, especially large molecules, that can be analyzed by LDI-MS [2–4]. In a typical process, both the matrix and the analyte molecule are desorbed and ionized by protonation or deprotonation. Although MALDI improves the signal of large biomolecules by preventing fragmentation to an extent and increases ionization efficiency, the matrices create intense fragmentation signals in the <700 m/z region of the mass spectrum [5]. Thus, matrix fragmentation results in poor analysis of smaller molecules even though matrices can be modified to reduce matrix effects [6]. In addition, the uneven crystallization of the matrix and the analyte molecules may cause heterogeneous sample distribution on the MALDI plate and affect the shot-to-shot and sample-to-sample reproducibilities. Another variation of the LDI-MS, the surface assisted laser desorption/ionization (SALDI), has emerged as the technique of choice for the analysis of small molecules, such as drugs and metabolites [7–11]. SALDI is an ionization technique that utilizes inorganic substances, nanomaterials or composites to assist in the ionization of target analyte [12]. SALDI has significantly lower matrix interferences in the low *m/z* region with more homogeneous analyte distribution and higher salt tolerance in comparison with MALDI [13–15].

Many nanostructured inorganic materials such as silica, metal and metal oxide nanoparticles, semiconductor nanoparticles and some carbon-based nanomaterials like graphene oxide are efficient substrates in SALDI-MS analysis for drug and metabolite analysis due to their excellent photoabsorption coefficient and heat transfer efficiency [7,16–22]. In a SALDI process, the applied laser beam heats up the substrate instead of the analyte. The substrate then transfers heat to the analyte, leading to the desorption and ionization of the latter. Thus, the desorption and ionization of the analyte highly depend on the photothermal conversion and heat transfer efficiencies of the substrate [23]. The mechanism of SALDI process is illustrated in Fig. 1. Recently, Picca et al. have reported a concise review on the mechanism of nanophase induced LDI in nanoparticle assisted LDI-MS [24]. Since there is very low fragmentation of nanostructure-based substrates in SALDI process, the interference due to the fragments is highly reduced. As a result, the low background noises of

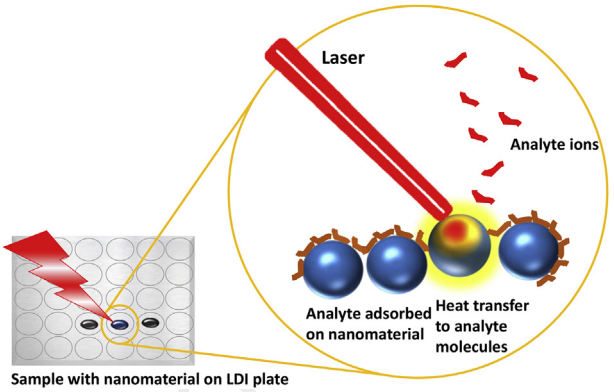

Fig. 1 – Schematic representation of a SALDI process mechanism.

SALDI-MS at low *m/z* region allow for the analysis of a large category of small molecules. Common pollutants, illegal or medicinal drugs and their metabolites tend to have small molecular sizes, which can be analyzed by SALDI-MS. Another important aspects in mass spectrometry based detection of metabolite is the metabolomics profiling and targeted approach [25–28]. For selective ionization of the analytes, SALDI matrices are engineered through structural and surface modification, which has the advantages of maximizing the specificity and sensitivity of MS methods. The nanoparticle surfaces modified with specific molecules, such as antibodies, proteins, and aptamers, highly reduce the background noise and interference from the undesired molecules from the biological samples. Therefore, combination of separation or enrichment of analytes and efficient SALDI is critical in nanoparticle-based LDI-MS for drugs and metabolites analysis.

In this review, we mainly discuss the detection of drugs and metabolites using nanomaterial-assisted LDI-MS. A summary of the various types of naomaterial substrates and analytes discussed in this review is presented in Table 1. Based on the category of nanomaterials employed as substrate, different names have been coined to the LDI processes for convenience, by various authors. For example, nano-assisted LDI (NALDI) [16], desorption/ionization on silicon (DIOS) [17], silicon nanopost arrays-assisted LDI (NAPA-LDI) [29], colloidal graphite-assisted LDI (GALDI) [30], carbon dot assisted LDI (CALDI) [31], etc. However, the role of these substrates in the LDI application is almost the same. We briefly discuss the type of nanomaterial substrates and their important properties which improve the LDI process and application of "mass tag" for LDI-MS signal amplification, in drug and metabolite analysis.

2. Nanomaterials as a matrix for SALDI-MS

The major role of nanomaterial in nanomaterial-based LDI-MS is the enrichment of the analyte molecules and their efficient desorption and ionization. Therefore, nanomaterials with large surface area, porous structure, easy functionalization, high photoabsorption properties and heat transfer efficiency are highly favored. Metal nanoparticles, especially gold

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