

Mass Spectrometry & Purification Techniques

Review Article

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Ionic Liquids Matrices Assisted Laser Desorption/Ionization Mass Spectrometry (ILMALDI-MS)

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Abstract

This review article discussed application of ionic liquids as matrices (ILMs) for mass spectrometry (MS). ILMs were applied for matrix assisted laser desorption/ionization, (ILMALDI-MS), electrospray ionization (ILMs-ESI-MS) and desorption corona beam ionization (DCBI-MS). Ionic liquids matrices provided several advantages such as low vapor pressure, have high stability for storage and under vacuum, extremely high sensitivity and showed low background or interferences. They are non-explosive, non-flammable and are thermally stable. The materials are promising for real measurements and require further investigations to improve the current performance. The combination between the conventional matrices and organic bases leaded to high ionization performance. The proton transfer efficiency of ILMs is higher than conventional matrices as the proton take place from the salt form. They were applied for many analytes such as biomarker, protein, peptides, polymers (synthetic and nature), small organic compounds and pharmaceuticals drugs.

Keywords: Ionic liquids; Mass spectrometry; Proteomics; Pathogenic bacteria; Quantification; Carbohydrate

Introduction

Room-temperature ionic liquids (RTIL) are molten salts with melting point below 100 °C [1]. They have distinctive properties and thus they were used for catalysis [1-6], separations [7], mass spectrometry [8], and other [9]. They have been applied as ion pairing reagent for electrospray ionization mass spectrometry (ESI-MS) [10], solvent for liquid-liquid extraction [11], stationary phases for chromatography [12] and as solvents in electrochemistry [13]. The materials have many properties that enhanced and improved the analysis using mass spectrometry. In general, the typical mass spectrometer is consist of five parts; inlet for the sample, ion source, analyzer, detector and vacuum [14-21]. The main roles of ionic liquids in mass spectrometry are mainly focused in the improvement of the analyte ionization, as solvent [22] and as ion-pairing reagent for ESI-MS [10].

The present review is a tutorial article for researchers who seek about the application of ionic liquids for mass spectrometry. The article focus mainly on electrospray ionization mass spectrometry (ESI-MS), matrix assisted laser desorption/ionization mass spectrometry (MALDI-MS) and desorption corona beam ionization (DCBI-MS).

Principle of Mass Spectrometry

Mass spectrometry is analytical technique that is based on the ionization of the investigated target. The ionization could take place by electron with high energy (Electron impact mass spectrometry, EI-MS), fast atom (fast atom bombardment mass spectrometry, FAB-MS), secondary ion (secondary ion mass spectrometry, SIMS), electrospray ionization (ESI-MS), laser desorption/ionization (LDI-MS), plasma desorption (PDMS) and matrix assisted laser desorption/ionization (MALDI-MS). The hard ionization methods such as EI-MS provided useful information for the compound structure elucidation. In contrast, soft ionization methods provided better ionization for thermal labile compounds such as protein, peptides, biomolecules, DNA, etc. (no fragmentations).

Laser desorption/ionization mass spectrometry is promising for many aspects. This technique can be used for solid material and for the analysis of surface. The latter application is important for direct analysis of biochips, thin film and thin liquid chromatography (TLC). The direct desorption/ionization using the laser (laser desorption/ ionization mass spectrometry, LDI-MS) produces many drawbacks; it is limited to the analyte that have high absorption of the laser energy. It caused also fragmentation of the analytes and consumes high laser energy. Thus, a small organic molecule (matrix) absorbs the laser energy and assist desorption/ionization process were used. The matrices offered a proton transfer with the analyte under investigation. Thus, the general prerequisites of effective matrices for MALDI are; 1) they must dissolve and co-crystallize with the target, 2) have suitable chromophoric groups that strongly absorb the laser radiation, 3) are stable for storage, 4) are stable under high-vacuum conditions, 5) suppress both chemical and thermal degradation of the analyte, and 6) assist the ionization/desorption process of the sample [22]. The ions after ionization were separated based on m/z in gas phase [23,24]. Thus, desorption/ionization process depends on the laser wavelength. The most common laser is UV-MALDI (255 or 337 nm) [25]. It is important to mention that most of these requirements are absent for nanoparticles applications (surface assisted laser desorption/ionization mass spectrometry (SALDI-MS) [26-44]. The organic matrices showed often low spectra quality due to the number of unwanted adducts. They produced poor homogeneous sample spots [45]. Furthermore, some of these matrices are unstable under vacuum. Benzoic acids matrices were sublimed and leaved the sample before laser shots. This drawback showed variation in the sample analysis with the time. Because of these drawbacks, a number of ILs was applied [46,47].

Ionic Liquids Matrices

In 2001, Armstrong et al. reported the first ILMs [22]. Almost all the requirements of conventional matrices were fulfilled in the ionic liquids because these materials were the salts of the common organic matrices such as 2,5-dihydroxy benzoic acid (DHB), 3,5-dimethoxy-4-hydroxy-cinnamic acid (SA) or α -cyano-4-hydroxy cinnamic acid

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(Figure 1). First, they have a significant absorbance of the laser energy. Second, they are able to undergo proton transfer with the investigated analyte. Third, they have low vapor pressure. Last but not least, they should not cause any fragmentation or form cluster formation. Thus, they served as effective matrices for MALDI-MS [22]. However, ILMs offered new advantages that absent in conventional matrices; First, the pH can be controlled by the selection of suitable organic base (Figure 1). The acidity of conventional matrices, 2,5-DHB (pK = 3.0) or α-cyano-4hydroxy cinnamnic acid (CHCA, pK =1.2), may cause protein denature and cause fragmentation of the acid labile biomolecules. Absence of the acidic groups in ILMs may explain the absence of fragmentation using ionic liquid matrices. Second, the absorption of laser energy can be also tuned by the base type or concentrations. The addition of base to the organic acids caused bathochromic or hypsochromic shifts. These shifts depend on the base strength and its concentration [48]. Third, the ionic liquids matrices have low vapor pressure and thus they are green solvents (green analytical technologies). Fourth, the ion pair of ionic liquids matrices implies strong interaction with the desired analytes. The main interactions may be electrostatic or hydrogen bonds. These interactions offered good ionization of the mixture that contains analytes with different ionizability.

Understand the ionic liquids properties are very important and further characterization are highly required. The characterization of these materials may take place using different analytical tools included ultraviolet-visible absorption (UV-vis absorption), Fourier transform infrared (FTIR), nuclear magnetic resonance (NMR) and mass spectrometry included fast atom bombardment mass spectrometry (FAB-MS), laser desorption/ionization mass spectrometry (LDI-MS), matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS), electrospray ionization mass spectrometry (ESI-MS), and field desorption mass spectrometry (FD-MS) [49-52]. These techniques are useful and may be used in the future to monitor the synthesis procedure [48]. UV-vis absorption characterization is important for MALDI-MS applications. The measurement may be used as pre-experiment to judge the performance of the ionic liquids before the MALDI-MS measurement. The UV-vis absorption may be tuned by the base properties (pK_b) and its concentrations. The changes of UV absorption may be due to the polarization of the carboxylic moieties. It is important to keep in our mind that the proton transfer occurs from the salt and not from the carboxylic group of the conventional organic matrices.

Application of ionic liquids for mass spectrometry

Ionic liquids are used as ion pairing reagents for ESI-MS [10,53] and matrices for matrix assisted laser desorption/ionization mass spectrometry.

Application of ionic liquids for MALDI-MS

Ionic liquids were used as effective matrices for MALDI-MS. They were applied for wide number of analytes such as lipids [49,54], proteins [55], peptides [7], sterols [54], oligonucleotides [56,57], polymers [22,23,58], carbohydrates [55], oligosaccharides and glycoconjugates [58] intact bacteria [47], and DNA oligomers [57].

Application of ionic liquids for proteomics

Analysis of protein is very important for clinical studies, medicine, biotechnology, etc. Mass spectrometry shows the fingerprinting (PMF) of the protein and offers simple and clear identifications. The protein analysis is aimed to achieve high sensitivity (low limit of detection, LOD), high signal-to-noise ratios, and prevention of unwanted adducts of the analyte proteins/peptides with matrix compounds or alkali ions







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[58]. Armstrong et al. [22] reported the first application of ionic liquids application for bradykinin. ILMs were applied for the identification of tryptic digests of six model proteins and for identification of a protein extracted from a two-dimensional gel with the proteome of the bacterium Corynebacterium glutamicum [59,60]. ILMs were applied for wide mass detection range 1000 Da to 270,000 Da. The material offered high S/N, low limit of detection, and are soft ionization compared to traditional organic matrices. Thus, they are promising for the noncovalent interactions between the monomers without disruption. The signal to noise ratio was varied based on the ionic liquids composition. The material offered homogeneous spots that is absent in conventional matrices. The formation of sweet spots in conventional matrices caused time consumption and cannot used for quantification analysis. Thus, ILMs severed for quantitative or semi-quantitative analysis. These analyses take place without the need of internal standards [61]. Ionic liquids matrices offered high sensitivity compared to the conventional matrices. For instance the analysis of sequence coverage of bovine serum albumin (BSA digests) explained clearly the high sensitivity of ILMs based on CHCA compared to the traditional CHCA crystalline matrix. Data showed high performance down to 1 fmol of BSA [62]. The main drawbacks of quantitative analysis of conventional matrices are due to the lack of homogenous spots that showed variation in the area under investigations (Figure 2). These challenges makes the quantitative analysis is difficult. However, quantitative or semi-quantitative analyses were achieved using ionic liquids. The quantitative analysis of peptide and protein were reported by Li and Gross [56] and by Bungert et al. for the screening of enzymatic reactions [63].

Ionic liquids matrices offered dual functions; solvent and matrices. They were used to improve the sample preparation for microfluidic deposition device [64]. Authors observed no solidification of ionic liquids matrices that provided a homogenous spots and small fluctuation of laser shots-shots (Figure 2). The homogeneous spots are not required only for semi-quantitative or quantitative analysis, but it is also important for the analysis of mixture. The analysis of protein using MALDI-MS is varied based on the molecular weights and the ionizability. Mixtures contain high ionizability molecules cause ion-suppression for molecules with low ionizability.

Ionic liquids matrices based on two different conventional matrices (called sinapinic acid (SA) and DHB) were used to analysis a set of intact glycoproteins with several degrees of glycosylation [65]. Glycoproteins are very sensitive for the analysis using conventional matrices and showed fragmentation of these analytes. In contrast, ionic liquids showed no fragmentation and improved the reproducibility [65]. The efficiency of ionic liquids matrices as solvent improve the protein dispersion. The analysis of protein usually takes place from mixture. The mixture contains different protein/peptides with different miscibility. The conventional matrices (organic acids) usually are dissolved in aqueous mixture of acetonitrile or methanol. The difference in miscibility among these species showed different interaction and leaded to variation in the co-crystallization process. However, the ion pair of the ionic liquids and their solvation performance provided better homogeneity and produced strong interaction with almost all the species.

Ionic liquids for carbohydrates and oligonucleotides

Carbohydrates have the same challenges of MALDI-MS analysis. The analysis of carbohydrate is very sensitive compared to proteins. The functional groups in carbohydrate are mainly hydroxyl groups. These groups could undergo dehydration using the conventional acids. The carbohydrates mainly associate with other biomolecules such as proteins, peptides, lipids, etc. For instance, the analysis of sulfated and sialylated

oligosaccharides showed dissociation of sulfate groups and sialic acids, thus ion species of intact molecules are hardly detected [66,67]. Ionic liquids such as 3-aminoquinoline (3-AQ)/a-cyano-4-hydroxycinnamic acid (CHCA) (3-AQ/CHCA), 1,1,3,3-tetramethylguanidium (TMG, G) salt of p-coumaric acid, and 3-AQ /2,5-dihydroxybenzoic acid (2,5-DHB) were reported. The materials have been used for the analysis of carbohydrates or phosphopeptides. Among the different ionic liquids matrices, 1,1,3,3-tetramethylguanidium (TMG, G) salt of p-coumaric acid (CA) (G3CA) suppressed dissociation of sulfated and sialylated oligosaccharides (Figure 3) [68]. Another types of ionic liquids such as 2,5-dihydroxybenzoic acid butylamine (DHBB), α-cyano-4hydroxycinnamic acid butylamine (CHCAB), 3,5-dimethoxycinnamic acid triethylamine (SinTri) were also reported [58]. The material showed no ion fragmentation (soft ionization), improved the shotshot reproducibility, and showed high stability. ILMs showed no fragmentation of labile groups [69]. Furthermore, they showed higher sensitivity in the positive and negative ion mode and offered high sensitivity (10 pmol). It was reported that ILMs (G2CHCA) and ILM: TMG salts of p-coumaric acid (G₂CA) are promising for the analysis of sulfated/sialylated/neutral oligosaccharides in both positive and negative ion modes with low limit of detection [70,71].

Carbohydrates are poor ionized analyte compared to proteins. For instance, polyanionic oligosaccharides (dermatan sulfate (DS) and chondroitin sulfate (CS)) exhibited very poor ionization. Furthermore, they undergo thermal fragmentation through the loss of SO₃ groups [69]. The proton transfer efficiency of the conventional matrices is week compared to the proton transfer in ionic liquids matrices. Guanidinium salt of a-cyano-4-hydroxycinnamic acid enhanced ionizability of these species without loss of its labile groups (SO₂). Because the poor ionizability, these species are undetectable in mixture contains high ionizability species using conventional organic matrices. In contrast, ionic liquids matrices enhanced the ionizability and improved the detection in mixture (Figure 4) [69]. It was reported that N,N-diisopropylethyl ammonium a-cyano-4-hydroxycinnamate and N,N diisopropylethyl ammonium ferulate were the best matrices for carbohydrates [55]. Two ILMs matrices, 2-(4-hydroxyphenylazo) benzoate-1,1,3,3-tetramethylguanidinium and sperminium were evaluated for the analysis of heparin oligosaccharides and results showed no fragmentation [72].

ILMs were also used for ESI-MS as ion pairing for polysaccharides analysis [73]. Ionic liquids matrices assisted electrospray ionization mass spectrometry (ILMs-ESI-MS) provided high spectra quality compared to the conventional ESI-MS. The improvement is mainly due to the powerful solvation of ionic liquids compared to the traditional solvent such as methanol, ethanol, etc. The use of these new materials as solvent is eco-friendly. Furthermore, the ionic liquids matrices are a proton donor/acceptor. The analysis of polysaccharide using ILMs-ESI-MS is detected as alkali-adducts and not protonated species. However, the spectra are very simple and multi-alkali peaks are absent. The analysis showed no fragmentation of labile groups and may be useful for non-covalent interaction of the carbohydrate and other biomolecules such as lipids, protein, etc. Ionic liquids-assisted ESI (ILA-ESI) mass spectrometry has significantly improved the detection sensitivity of large neutral polysaccharide compounds [73].

The applications of ionic liquids have been extended for other species such as oligodeoxynucleotides [57]. Ionic liquids matrices of 3-hydroxypicolinic acids (3-HPA) and 2,5-dihydroxybenzoic acids (2,5-DHB) were used for the analysis of oligodeoxynucleotides (ODNs). ILMs (butyl ammonium 2,5-dihydroxybenzoate (DHBB), butyl ammonium α -cyano-4-hydroxycinnamate (CHCAB), and triethyl

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Figure 4: Positive-ion reflector MALDI mass spectra of purified dermatan sulfate tetrasaccharide (DS dp4) acquired with DHB, DHBB and G₂CHCA under the same experimental conditions. The peak, corresponding to the DS dp4, sodium salt ([M + Na]⁺, m/z 1029) is accompanied by Na/H exchange peaks, denoted by closed circles. Peaks corresponding to the SO₃ loss fragments are denoted by open circles; matrix clusters are denoted by diamonds. Figure reprinted with permission from Ref. [69].

ammonium sinapinate (SinTri)) were investigated for the analysis of oligonucleotides [58]. The analysis provided high spectra quality, showed no fragmentation, offered signal-to-noise ratio 10 times higher than the conventional matrix and showed small variation in intensity (Figure 5) [58].

Ionic liquids for lipids and phospholipids

Analysis of lipids using matrix assisted laser desorption/ionization mass spectrometry is very promising for clinical studied. Lipids and phospholipids were served as biomarkers for many diseases. These species suffer from the previous drawbacks of conventional matrices that have been reported for protein, peptides, carbohydrates, or oligonucleotides. Furthermore, lipids have small molecular weight. The conventional matrices have molecular weight 500 Da and can be detected in mass spectrometry. The ions peaks of conventional matrices cause ion-suppression of the analyte ions and may cause peak submerge with the ion peaks of target analyte. The applications of ILMs for phospholipids (PLs) are promising as they provided many advantages compared to the traditional matrices. ILMs showed high ionization performance, produced no alkali-metal ions adducts, and decreased the fragmentation [49]. The adulteration of extra virgin olive oil (EVOO) with hazelnut oil (HO) was evaluated using ILMs by the analysis of phospholipids (PLs) [74]. Phospholipids (PLs) are usually present in seed oils at a concentration range of 10-20 g/kg. In other side, PLs in VOOs are 300-400 times lower. Thus, high sensitivity is required in order to monitor these adulterations. Phospholipids (PLs) were extracted selectively then were analysed using TBA (tributylamine)/ CHCA (a-Cyano-4-hydroxycinnamic acid). Ionic liquids matrices were served as dual function (extraction solvent and matrices). These extractions improved and increased the phospholipids signal

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Figure 5: (A) Plot of normalized [M + Na]⁺ ion intensities yielded from 90 different positions on a MALDI-MS preparation of the oligosaccharide maltoheptaose with ionic liquid matrix DHBB (black squares) in comparison to traditional DHB matrix (grey circles). (B) Resulting [M+H]⁺ ion intensities from 90 positions on a human angiotensin II preparation with ionic liquid matrix CHCAB (black triangles) and alternatively with traditional CHCA matrix (grey squares). The relative standard deviations (RSD) of the data series are given as bar graphs beneath the normalized ion intensity distribution diagrams. Black bars indicate RSD values found using ionic liquid matrixes, and gray bars indicate RSD values of the data series yielded by the respective traditional MALDI matrixes. Figure reprinted with permission from Ref. [58].

from EVOO and HO samples. At the same time, the pretreatment increased the phospholipids signals and decreased the signal of triacylglycerols and diacylglycerols. They offered high sensitivity (at 1% contamination level) [74]. Direct analysis of PLs using ionic liquids (2,4-dihydroxybenzoic acid butylamine, α -cyano-4-hydroxycinnamic acid butylamine and 3,5-dimethoxycinnamic acid triethylamine, 2,4-dihydroxybenzoic acid butylamine) were successfully applied and showed high sensitivity and low limit of detection [49,58]. The analyses of complicated samples were reported. For instance, analysis of a complex lipid mixture (i.e., a raw extract of a milk sample) using ILs showed high S/N ratio, reduced chemical noise and limited formation of matrix-clusters [50]. The reports showed mainly dual function for ILMs, i.e., solvent for extraction and matrices. The low percentage of PLs is critical and requires further efforts to achieve high sensitivity.

Analysis of Analytes with Small Molecular Weight

Analysis of small molecules such as organic compounds, drugs and pharmaceutical is difficult for matrix assisted laser desorption/ ionization mass spectrometry (MALDI-MS). The small molecular weight of these species suffer from ion suppression, peak submerge and adducts formations with the ions of matrices species. In general, the molecular weights of these species are mainly below than 1000 Da. Ionic liquids matrices showed no interference and offered clear backgrounds. Thus, they are promising for the analysis of the analytes with small molecular weight. The analysis of small molecular weight species is important for organic chemistry, pharmaceutical analysis, forensic science and industrial interests. MALDI-MS offered direct analysis of the surface samples such as TLC, thin films, etc. Lovejoy et al. reported the application of tetraalkylphosphonium-based ILs of conventional matrices, such as DHB, CHCA and feluric acid, as extraction solvent and matrix for the analysis of different dyes [75]. N,N-diisopropylethylammonium α -cyanohydroxy cinnamate was used for the analysis of cocaine, lysergic acid diethylamide, levamisole and papaverine with low limit detection and excellent correlation coefficients ranging from 0.95 to 0.99 [76].

Mass Spectrometry Imaging (MSI)

Analysis of biomolecules using mass spectrometry imaging (MSI) is simple, sensitive, are applicable for organs and biological important [77]. The image offers clear and useful information about the biomolecules distribution in the investigated tissues. MSI was used to investigate the analysis of endogenous and exogenous. Homogenous formation and well distribution of the matrices over the investigated area is very critical and is common limitation for conventional organic matrices. The heterogonous distribution of the organic matrices of the investigated area showed mis-distribution of the molecules in the tissue. The interactions of the matrices with the molecules may cause diffusion of the biomolecules on the surface of the organs. This phenomenon may lead to misunderstand of MSI. Thus, the sample must be carefully prepared to maintain the spatial distribution of the biological biomolecules [78].

Room temperature ionic liquids (RTILs) offered many advantages that improved the analysis of MSI. They form a homogenous spots on the investigated area and co-crystallize faster than conventional matrices. These features limit the lateral and spatial distribution. ILMs derived from α -cyano-4-hydroxycinnamic acid (CHCA) were synthesized and tested for SIMS and MS imaging [54]. In contrast to solid matrices such as CHCA and 2,5-DHB, the data showed that the ion intensities are uniform across the sample surface. The mass spectrometry imaging of onion skin membranes were imaged. ILMs offered the ions characteristic peaks of the cell nuclei [54].

Analysis of lipids using an automatic microspotter coupled to specific ILMs based on 2,5-DHB matrix (2,5-DHB/ANI, 2,5-DHB/ Pyr, and 2,5-DHB/3-AP) was reported (Figure 6) [79]. Automatic microspotter method decrease the time of the sample preparation and offered a homogenous layer over the investigated area. The method was also validated on human ovarian cancer biopsies [79]. Li et al. reported the application of 1-methylimidazolium α-cyano-4-hydroxycinnamate ILMs for the MALDI imaging of gangliosides in mouse brain [80]. Three different ILMs were prepared and were characterized for synthetic polymer [81]. MALDI-MSI using ILMs showed superior sample spot homogeneity, small variations in the mass spectra, offered high stability under vacuum, and showed negligible fragmentation (soft ionizations) (Figure 7) [82]. The properties of CHCA/aniline compared to conventional matrices (CHCA, DHB) offered many merits such as; 1) produced high spectral quality i.e., high resolution, high sensitivity, high S/N ratio, 2) are applicable for a wide number of different analytes, 3) are high tolerance for contaminants, 4) offered high crystallization on tissues (coverage capacity, homogenous spots, and decrease the time of crystallization), 5) high vacuum stability, thus there is no signals variation with the time, 6) high ions yield in negative mode, and 7) showed low fragmentation [80,82] (Figures 6 and 7).

Polymers Analysis

The analyses of polymer using matrix assisted laser desorption/

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spectrometry imaging. In this context 5 zones have been detected. Inset of microscopic images of each zone (X5) have been presented as well as the molecula images distribution of ions present in each zone. Figure reprinted with permission from Ref. [79].



and negative modes (b). MALDI imaging can be compared with rat brain anatomy (c). Image reprinted with permission from Ref. [82]. ionization mass spectrometry (MALDI-MS) is promising for industrial and environmental interests. The analysis using MALDI-MS is simple.

and environmental interests. The analysis using MALDI-MS is simple, requires small amount of the sample, sensitive, can be used for surface analysis and to monitor the polymerization process and is sensitive to observe the changes of the polymer structure under stimuli effect such as temperature, etc. It is very important to differentiate between the synthetic polymer and nature polymer. The polymer showed fragmentation by the organic acids. The laser irradiation could also cause changes of the polymer properties after the interaction and may be lead to ion suppression. Ionic liquids matrices (ILMs) for the analysis of polymer are promising compared to traditional MALDI-MS. The characterization of polar biodegradable polymers using N,N- diisopropyl ethyl ammonium α -cyano-4-hydroxycinnamate (DEA-CHCA) were reported [83]. DEA-CHCA offered maximum signal with minimum laser intensity (small polymer degradation). Ionic liquids called N,N-diisopropyl ethyl ammonium 3-oxocoumarate and N,N-diisopropyl ethyl ammonium dihydroxymonooxo acetophenoate, were used for the analysis of aliphatic biodegradable polymers [84]. The ability to identify and differentiate the polymers and additives in lubricant residues of condoms were investigated (Figure 8) [85]. The data is very useful for condoms analysis in sexual assault cases [85].

Pathogenic Bacteria Analysis

Analysis of cells such as pathogenic bacteria is very important for biotechnologies and clinical aspects. The advances of the cell analysis lead to improvement of the detection of bacterial infections at early stage. The advances in MALDI-MS analysis may lead to better treatment and increase the change for remediation. The bacterial cells are very complicated and contain several biomolecules with different molecular weight. Thus, ion suppression is an observable phenomenon. Bacteria analysis is quite often to observe very few peaks however there are several millions of biomolecules in the cell. Abdelhamid el al. reported the first application of ILMs for bacterial analysis [47,48]. The data revealed high potential of these materials in bacterial analysis. Authors also reported novel ionic matrices based on a new organic matrix called mefenamic acid. They proposed a simple method for the analysis of the endotoxin 'lipopolysaccharide' of the pathogenic bacteria [18]. This method is simple, sensitive, accurate and selective method for the bacteria identification. The reported approach is very useful to detect the pathogenic bacteria without direct analysis of the bacteria cells. The analysis of the bacteria cell may be direct (intact cell) [47] or by targeting one of the cell biomolecules (Figure 9) [48]. These two approaches were reported using ILMs.

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Figure 8: 3D PCA score plot of seven different condom lubricant types, four of which are easily distinguished. Figure reprinted with permission from Ref. [85].



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Figure 10: Thermal imaging of the liquid drop and ion chronograms of sibutramine (80 mg L⁻¹) in different liquid matrices: (a) water; (b) [BMIM]BF₄. Image reprinted with permission from Ref. [86].

Summary and Prospective

Ionic liquids matrices (ILMs) showed a promising and brilliant future for wide applications using mass spectrometry. ILMs were used as extraction solvent, matrices and for semi-quantitative or quantitative analysis. The materials could be used for almost all the molecules without any exception. They were applied for many techniques such as matrix assisted laser desorption/ionization mass spectrometry, electrospray ionization mass spectrometry (ESI-MS), and desorption corona beam ionization mass spectrometry (DCBI-MS) [86]. Ionic liquids assisted desorption corona beam ionization mass spectrometry (ILsA-DCBI-MS) were used for quantitative and analysis of 21 small low-polar molecules. The analysis required no internal standards and showed a clear discrimination between the different analytes. Ionic liquids matrices were applied for small and large molecules. ILsA-DCBI-MS were recorded by thermal imaging and mass spectrometry simultaneously as shown in Figure 10. They have strong solvation power of the species with different miscibility [87,88]. They offered higher sensitivity to a maximum of 1000-fold [68] with lower limit of detection compared to the conventional solid matrices [54]. Ionic liquids matrices have higher stability for storage and under vacuum [80,89]. They offered homogeneous spots that improved the reproducibility of laser shots-shots and decreased the time consuming [50]. The ion-pairing charge of ionic liquids implies strong interaction with the analytes [90]. Authors observed no background (low interferences) and noticed no adduct formation. ILMs have low vapor pressure that improved the sample detection and showed no variation with the time under vacuum [91,92]. Further efforts should be taken to improve the performance of ionic liquids. For instance, additives such as acetic acids derivatives may increase the performance of ionic liquids matrices [93]. New sample preparation and systematic studies of the effect of base are required.

Organic acid, ILMs and nanoparticles were applied for mass spectrometry. ILMs are biocompatible compared to nanoparticles [94,95]. However, nanoparticles offered many new functions [96,97], and offered soft ionization for noncovalent interactions [98]. ILMs assisted MALDI-MS is promising compared to ESI-MS [99,100]. ILA-MALDI-MS can facilitate the biological activities of pathogenic cells [101]. To shorten the whole story, conjugate ionic liquids with mass spectrometry is true marriage and showed promising future for analytical chemistry, proteomics, biotechnology, biomedicine, etc. [102].

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References

- 1. Wasserscheid P (2006) Chemistry: volatile times for ionic liquids. Nature 439: 797.
- Welton T (1999) Room-Temperature Ionic Liquids. Solvents for Synthesis and Catalysis. Chem Rev 99: 2071-2084.
- Dupont J, de Souza RF, Suarez PA (2002) Ionic liquid (molten salt) phase organometallic catalysis. Chem Rev 102: 3667-3692.
- van Rantwijk F, Madeira Lau R, Sheldon RA (2003) Biocatalytic transformations in ionic liquids. Trends Biotechnol 21: 131-138.
- Rooney DW, Seddon KR (2001) Ionic liquids, in Handbook of Solvents, ed. Wypych G (Toronto: ChemTech Publishing). 1459-1484.
- Ohno H (2003) Ionic Liquids: The Front and Future of Material Development. Tokyo: CMC Press.
- Han X, Armstrong DW (2007) Ionic liquids in separations. Acc Chem Res 40: 1079-1086.
- Joshi MKD, Anderson JL (2012) Recent advances of ionic liquids in separation science and mass spectrometry. RSC Advances 2: 5470-5484.
- 9. Pandey S (2006) Analytical applications of room-temperature ionic liquids: a review of recent efforts. Anal Chim Acta 556: 38-45.
- Soukup-Hein RJ, Remsburg JW, Breitbach ZS, Sharma PS, Payagala T, et al. (2008) Evaluating the use of tricationic reagents for the detection of doubly charged anions in the positive mode by ESI-MS. Anal Chem 80: 2612-2616.
- Carda-Broch S, Berthod A, Armstrong DW (2003) Solvent properties of the 1-butyl-3-methylimidazolium hexafluorophosphate ionic liquid. Anal Bioanal Chem 375: 191-199.
- Armstrong DW, He L, Liu YS (1999) Examination of ionic liquids and their interaction with molecules, when used as stationary phases in gas chromatography. Anal Chem 71: 3873-3876.
- He L, Zhang W, Zhao L, Liu X, Jiang S (2003) Effect of 1-alkyl-3methylimidazolium-based ionic liquids as the eluent on the separation of ephedrines by liquid chromatography. J Chromatogr A 1007: 39-45.
- Abdelhamid HN (2013) Applications of Nanomaterials and Organic Semiconductors for Bacteria and Biomolecules analysis/ biosensing using Laser Analytical Spectroscopy. National Sun-Yat Sen University, ROC.
- 15. Gross, Jürgen H (2011) Mass Spectrometry. 2nd edn. Springer.
- 16. Edmond de Hoffmann, Stroobant V (2001) Mass Spectrometry: Principles and Applications. 3rd edn. John Wiley and Sons, New York, USA.

- 17. Karas M, Krüger R (2003) lon formation in MALDI: the cluster ionization mechanism. Chem Rev 103: 427-440.
- Knochenmuss R, Zenobi R (2003) MALDI ionization: the role of in-plume processes. Chem Rev 103: 441-452.
- 19. Dreisewerd K (2003) The desorption process in MALDI. Chem Rev 103: 395-426.
- Horneffer V, Dreisewerd K, Ludemann HC, Hillenkamp F, Lage M, et al. (1999) Is the incorporation of analytes into matrix crystals a prerequisite for matrix-assisted laser desorption/ionization mass spectrometry? A study of five positional isomers of dihydroxybenzoic acid. Int J Mass Spectrom 187: 859-870.
- 21. Krüger R, Pfenninger A, Fournier I, Gluckmann M, Karas M (2001) Analyte incorporation and ionization in matrix-assisted laser desorption/ionization visualized by pH indicator molecular probes. Anal Chem 73: 5812-5821.
- Armstrong DW, Zhang LK, He L, Gross ML (2001) Ionic liquids as matrixes for matrix-assisted laser desorption/ionization mass spectrometry. Anal Chem 73: 3679-3686.
- Benninghoven A, Sichtermann WK (1978) Detection, identification and structural investigation of biologically important compounds by secondary ion mass spectrometry. Anal Chem 50: 1180-1184.
- Barber M, Bordoli RS, Garner GV, Gordon DB, Sedgwick RD, et al. (1981) Fastatom-bombardment mass spectra of enkephalins. Biochem J 197: 401-404.
- Abdelhamid HN, Wu HF (2013) Furoic and mefenamic acids as new matrices for matrix assisted laser desorption/ionization-(MALDI)-mass spectrometry. Talanta 115: 442-450.
- Wu HF, Gopal J, Abdelhamid HN, Hasan N (2012) Quantum dot applications endowing novelty to analytical proteomics. Proteomics 12: 2959-2961.
- Ugarov MV, Egan T, Khabashesku DV, Schultz JA, Peng H, et al. (2004) MALDI matrices for biomolecular analysis based on functionalized carbon nanomaterials. Anal Chem 76: 6734-6742.
- Sunner J, Dratz E, Chen YC (1995) Graphite surface-assisted laser desorption/ ionization time-of-flight mass spectrometry of peptides and proteins from liquid solutions. Anal Chem 67: 4335-4342.
- Wei J, Buriak JM, Siuzdak G (1999) Desorption-ionization mass spectrometry on porous silicon. Nature 399: 243-246.
- 30. Abdelhamid HN, Wu HF (2015) Synthesis of a highly dispersive sinapinic acid@ graphene oxide (SA@GO) and its applications as a novel surface assisted laser desorption/ionization mass spectrometry for proteomics and pathogenic bacteria biosensing. Analyst 140: 1555-1565.
- Khan MS, Abdelhamid HN, Wu HF (2015) Near infrared (NIR) laser mediated surface activation of graphene oxide nanoflakes for efficient antibacterial, antifungal and wound healing treatment. Colloids and Surfaces B: Biointerfaces 127: 281-291.
- Abdelhamid HN, Talib A, Wu HF (2015) Facile synthesis of water soluble silver ferrite (AgFeO2) nanoparticles and their biological evaluation as antibacterial agents. RSC Advances 5: 34594-34602.
- 33. Shastri L, Abdelhamid HN, Nawaz M, Wu HF (2015) Bidentate nanoparticlesingle drop microextraction as a sensitive preconcentrating probes: Synthesis, characterization and application of the silver nanoparticles modified with binary functional groups for highly sensitive protein analysis in MALDI-TOF MS. RSC Adv. 5: 41595-41603.
- Abdelhamid HN (2015) Delafossite Nanoparticle as New Functional Materials: Advances in Energy, Nanomedicine and Environmental Applications. Materials Science Forum 832: 28-53.
- 35. Abdelhamid HN, Wu HF (2015) Synthesis and characterization of quantum dots for application in laser soft desorption/ionization mass spectrometry to detect labile metal–drug interactions and their antibacterial activity. RSC advances 5: 76107-76115.
- Wu BS, Abdelhamid HN, Wu HF (2014) Synthesis and Antibacterial activity of graphene decorated stannous dioxide (SnO2). RSC advances 4: 3722-3731.
- Abdelhamid HN, Wu HF (2014) Polymer dots for quantifying the total hydrophobic pathogenic lysates in a single drop. Colloids and Surfaces B: Biointerfaces 115: 51-60.
- Abdelhamid HN, Bhaisare ML, Wu HF (2014) Ceria nanocubic-ultrasonication assisted dispersive liquid-liquid microextraction coupled with matrix assisted laser desorption/ionization mass spectrometry for pathogenic bacteria analysis. Talanta 120: 208-217.

- of mercury using graphene assisted laser desorption/ionization mass spectrometry. J Am Soc Mass Spectrom 25: 861-868. 40. Nasser Abdelhamid H, Wu BS, Wu HF (2014) Graphene coated silica applied for high ionization matrix assisted laser desorption/ionization mass
 - applied for high ionization matrix assisted laser desorption/ionization mass spectrometry: A novel approach for environmental and biomolecule analysis. Talanta 126: 27-37.

39. Abdelhamid HN, Wu HF (2014) Ultrasensitive, rapid, and selective detection

- Bhaisare ML, Abdelhamid HN, Wu BS, Wu HF (2014) Ionic magnetic for pathogenic bacteria separation. J Mater Chem B 2: 4671-4683.
- 42. Hua PY, Manikandan M, Abdelhamid HN, Wu HF (2014) Graphene nanoflakes as efficient ionizing matrix for MALDI MS based lipodomics of cancer cells and cancer stem cells. J Mater Chem B 2: 7334-7343.
- 43. Gedd G, Abdelhamid HN, Schanwaz K, Wu HF (2014) ZnO nanoparticle modified polymethyl methacrylate assisted dispersive liquid-liquid micro extraction coupled MALDI-MS for rapid pathogenic bacteria analysis. RSC advances 4: 45973-45983.
- 44. Abdelhamid HN, Wu HF (2014) Facile synthesis of nano silver ferrite (AgFeO2) modified with chitosan applied for biothiol separation. Mater Sci Eng C Mater Biol Appl 45: 438-445.
- 45. Mirgorodskaya E, Braeuer C, Fucini P, Lehrach H, Gobom J (2005) Nanoflow liquid chromatography coupled to matrix-assisted laser desorption/ionization mass spectrometry: sample preparation, data analysis, and application to the analysis of complex peptide mixtures. Proteomics 5: 399-408.
- Abdelhamid HN, Gopal J, Wu HF (2013) Synthesis and application of ionic liquid matrices (ILMs) for effective pathogenic bacteria analysis in matrix assisted laser desorption/ionization (MALDI-MS). Analy.Chim.Acta. 767: 104-111.
- 47. Abdelhamid HN, Khan MS, Wu HF (2014) Design, characterization and applications of new ionic liquid matrices for multifunctional analysis of biomolecules: a novel strategy for pathogenic bacteria biosensing. Anal Chim Acta 823: 51-60.
- Li YL, Gross ML, Hsu FF (2005) lonic-liquid matrices for improved analysis of phospholipids by MALDI-TOF mass spectrometry. J Am Soc Mass Spectrom 16: 679-682.
- Calvano CD, Carulli S, Palmisano F (2009) Aniline/alpha-cyano-4hydroxycinnamic acid is a highly versatile ionic liquid for matrix-assisted laser desorption/ionization mass spectrometry. Rapid Commun Mass Spectrom 23: 1659-1668.
- Milman B L, Alfassi ZB (2005) Detection and Identification of Cations and Anions of Ionic Liquids by Means of Electrospray Ionization Mass Spectrometry and Tandem Mass Spectrometry. Eur. J. Mass Spectrom 11: 35-42.
- Gross JH (2007) Liquid injection field desorption/ionization-mass spectrometry of ionic liquids. J Am Soc Mass Spectrom 18: 2254-2262.
- Remsburg JW, Soukup-Hein RJ, Crank JA, Breitbach ZS, Payagala T, et al. (2008) Evaluation of dicationic reagents for their use in detection of anions using positive ion mode ESI-MS via gas phase ion association. J. Am. Soc. Mass Spectrom 19: 261-269.
- Fitzgerald JJ, Kunnath P, Walker AV (2010) Matrix-enhanced secondary ion mass spectrometry (ME SIMS) using room temperature ionic liquid matrices. Anal Chem 82: 4413-4419.
- 54. Crank JA, Armstrong DW (2009) Towards a second generation of ionic liquid matrices (ILMs) for MALDI-MS of peptides, proteins, and carbohydrates. J Am Soc Mass Spectrom 20: 1790-1800.
- 55. Li YL, Gross ML (2004) Ionic-liquid matrices for quantitative analysis by MALDI-TOF mass spectrometry. J Am Soc Mass Spectrom 15: 1833-1837.
- Carda-Broch S, Berthod A, Armstrong DW (2003) lonic matrices for matrixassisted laser desorption/ionization time-of-flight detection of DNA oligomers. Rapid Commun Mass Spectrom 17: 553-560.
- Mank M, Stahl B, Boehm G (2004) 2,5-Dihydroxybenzoic acid butylamine and other ionic liquid matrixes for enhanced MALDI-MS analysis of biomolecules. Anal Chem 76: 2938-2950.
- Smirnov IP, Zhu X, Taylor T, Huang Y, Ross P, et al. (2004) Suppression of alpha-cyano-4-hydroxycinnamic acid matrix clusters and reduction of chemical noise in MALDI-TOF mass spectrometry. Anal Chem 76: 2958-2965.
- 59. Zabet-Moghaddam M, Heinzle E, Lasaosa M, Tholey A (2006) Pyridiniumbased ionic liquid matrices can improve the identification of proteins by peptide mass-fingerprint analysis with matrix-assisted laser desorption/ionization mass spectrometry. Anal Bioanal Chem 384: 215-224.

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- Tholey A, Zabet-Moghaddam M, Heinzle E (2006) Quantification of peptides for the monitoring of protease-catalyzed reactions by matrix-assisted laser desorption/ionization mass spectrometry using ionic liquid matrixes. Anal Chem 78: 291-297.
- Towers MW, McKendrick JE, Cramer R (2010) Introduction of 4-chloro-alphacyanocinnamic acid liquid matrices for high sensitivity UV-MALDI MS. J Proteome Res 9: 1931-1940.
- Bungert D, Bastian S, Heckmann-Pohl DM, Giffhorn F, Heinzle E, et al. (2004) Screening of sugar converting enzymes using quantitative MALDI-ToF mass spectrometry. Biotechnol Lett 26: 1025-1030.
- Weidmann S, Kemmerling S, M\u00e4dler S, Stahlberg H, Braun T, et al. (2012) Ionic liquids as matrices in microfluidic sample deposition for high-mass matrixassisted laser desorption/ionization mass spectrometry. Eur J Mass Spectrom (Chichester, Eng) 18: 279-286.
- Giménez E, Benavente F, Barbosa J, Sanz-Nebot V (2010) Ionic liquid matrices for MALDI-TOF-MS analysis of intact glycoproteins. Anal Bioanal Chem 398: 357-365.
- Sekiya S, Wada Y, Tanaka K (2005) Derivatization for stabilizing sialic acids in MALDI-MS. Anal Chem 77: 4962-4968.
- Zhang J, Lamotte L, Dodds ED, Lebrilla CB (2005) Atmospheric pressure MALDI Fourier transform mass spectrometry of labile oligosaccharides. Anal Chem 77: 4429-4438.
- Fukuyama Y, Funakoshi N, Takeyama K, Hioki Y, Nishikaze T, et al. (2014) 3-Aminoquinoline/p-coumaric acid as a MALDI matrix for glycopeptides, carbohydrates, and phosphopeptides. Anal Chem 86: 1937-1942.
- Laremore TN, Zhang F, Linhardt RJ (2007) Ionic liquid matrix for direct UV-MALDI-TOF-MS analysis of dermatan sulfate and chondroitin sulfate oligosaccharides. Anal Chem 79: 1604-1610.
- Fukuyama Y, Nakaya S, Yamazaki Y, Tanaka K (2008) Ionic liquid matrixes optimized for MALDI-MS of sulfated/sialylated/neutral oligosaccharides and glycopeptides. Anal Chem 80: 2171-2179.
- Tissot B, Gasiunas N, Powell AK, Ahmed Y, Zhi ZL, et al. (2007) Towards GAG glycomics: analysis of highly sulfated heparins by MALDI-TOF mass spectrometry. Glycobiology 17: 972-982.
- Przybylski C, Gonnet F, Bonnaffé D, Hersant Y, Lortat-Jacob H, et al. (2010) HABA-based ionic liquid matrices for UV-MALDI-MS analysis of heparin and heparan sulfate oligosaccharides. Glycobiology 20: 224-234.
- 72. Chang YL, Lee YC, Yang WB, Chen CH (2011) lonic liquid-assisted electrospray ionization of polysaccharides. J Mass Spectrom 46: 367-375.
- 73. Calvano CD, Ceglie CD, D'Accolti L, Zambonin CG (2012) MALDI-TOF mass spectrometry detection of extra-virgin olive oil adulteration with hazelnut oil by analysis of phospholipids using an ionic liquid as matrix and extraction solvent. Food Chem 134: 1192-1198.
- 74. Lovejoy KS, Purdy GM, Iyer S, Sanchez TC, Robertson A, et al. (2011) Tetraalkylphosphonium-based ionic liquids for a single-step dye extraction/ MALDI MS analysis platform. Anal Chem 83: 2921-2930.
- Ostermann KM, Luf A, Lutsch NM, Dieplinger R, Mechtler TP et al. (2014) MALDI Orbitrap mass spectrometry for fast and simplified analysis of novel street and designer drugs. Clinica. Chimica. Acta 433: 254-258.
- Caprioli RM, Farmer TB, Gile J (1997) Molecular imaging of biological samples: localization of peptides and proteins using MALDI-TOF MS. Anal Chem 69: 4751-4760.
- Schwartz SA, Reyzer ML, Caprioli RM (2003) Direct tissue analysis using matrix-assisted laser desorption/ionization mass spectrometry: practical aspects of sample preparation. J Mass Spectrom 38: 699-708.
- Meriaux C, Franck J, Wisztorski M, Salzet M, Fournier I (2010) Liquid ionic matrixes for MALDI mass spectrometry imaging of lipids. J Proteomics 73: 1204-1218.
- Chan K, Lanthier P, Liu X, Sandhu JK, Stanimirovic D, et al. (2009) MALDI mass spectrometry imaging of gangliosides in mouse brain using ionic liquid matrix. Anal Chim Acta 639: 57-61.
- Gabriel SJ, Pfeifer D, Schwarzinger C, Panne U, Weidner SM (2014) Matrixassisted laser desorption/ionization time-of-flight mass spectrometric imaging of synthetic polymer sample spots prepared using ionic liquid matrices. Rapid Commun Mass Spectrom 28: 489-498.
- Lemaire R, Tabet JC, Ducoroy P, Hendra JB, Salzet M, et al. (2006) Solid ionic matrixes for direct tissue analysis and MALDI imaging. Anal Chem 78: 809-819.

- Berthod A, Crank JA, Rundlett KL, Armstrong DW (2009) A second-generation ionic liquid matrix-assisted laser desorption/ionization matrix for effective mass spectrometric analysis of biodegradable polymers. Rapid Commun Mass Spectrom 23: 3409-3422.
- Serrano CA, Zhang Y, Yang J, Schug KA (2011) Matrix-assisted laser desorption/ionization mass spectrometric analysis of aliphatic biodegradable photoluminescent polymers using new ionic liquid matrices. Rapid Commun Mass Spectrom 25: 1152-1158.
- 84. Spencer SE, Kim SY, Kim SB, Schug KA (2011) Matrix-assisted laser desorption/ionization-time of flight-mass spectrometry profiling of trace constituents of condom lubricants in the presence of biological fluids. Forensic Sci Int 207: 19-26.
- Wang H, Wu Y, Guo B, Sun W, Ding L, et al. (2012) Quantification of lowpolar small molecules using room temperature ionic liquids matrix-assisted desorption corona beam ionization. Analyst 137: 3982-3988.
- Alfassi ZB, Huie RE, Milman BL, Neta P (2003) Electrospray ionization mass spectrometry of ionic liquids and determination of their solubility in water. Anal Bioanal Chem 377: 159-164.
- Mihkel Koel M (2005) Ionic Liquids in Chemical Analysis. Critical Reviews in Analytical Chemistry. 35: 177-192.
- 88. Hao Y, Peng J, Hu S, Li J, Zhai M (2010) Thermal decomposition of allylimidazolium-based ionic liquid studied by TGA–MS analysis and DFT calculations. Thermochimica Acta 501: 78-83.
- Anderson JL, Ding J, Welton T, Armstrong DW (2002) Characterizing ionic liquids on the basis of multiple solvation interactions. J Am Chem Soc 124: 14247-14254.
- Emelyanenko VN, Verevkin SP, Heintz A, Corfield JA, Deyko A et al. (2008) Pyrrolidinium-based ionic liquids. 1-Butyl-1-methyl pyrrolidinium dicyanoamide: thermochemical measurement, mass spectrometry, and ab initio calculations. J Phys Chem B 112: 11734-11742.
- Leal JP, Esperança JM, da Piedade ME, Lopes JN, Rebelo LP, et al. (2007) The nature of ionic liquids in the gas phase. J Phys Chem A 111: 6176-6182.
- 92. Tholey A (2006) lonic liquid matrices with phosphoric acid as matrix additive for the facilitated analysis of phosphopeptides by matrix-assisted laser desorption/ ionization mass spectrometry. Rapid Commun Mass Spectrom 20: 1761-1768.
- Abdelhamid HN, Wu HF (2015) Proteomic analysis of the mode of antibacterial action of nanoparticles and their interactions with proteins. Trends in Analytical Chemistry 65: 30-46.
- 94. Abdelhamid HN, Wu HF (2013) Probing the Interaction Between Chitosan Capped CdS Quantum Dots and Pathogenic Bacteria and their Biosensing Application. J Mater Chem B 1: 6094-6106.
- 95. Gopal J, Abdelhamid HN, Hua PY, Hui-Fen Wu HF (2013) Chitosan nanomagnets for effective extraction and sensitive mass spectrometric detection of pathogenic bacterial endotoxin from human urine. J Mater Chem B 1: 2463-2475.
- Abdelhamid HN, Wu HF (2013) Multifunction of graphene magnetic particles coated with chitosan for bacterial analysis using MALDI-MS and fluorescence spectroscopy. Journal of material chemistry B1: 3950-3961.
- Abdelhamid HN, Wu HF (2014) Monitoring the metallofulfenamic bovine serum albumin interactions: A novel method for metallodrug analysis. RSC Advances 4: 53768-53776.
- 98. Khan N, Abdelhamid HN, Wang JC, Yan JY, Chung FT, et al. (2015) High order tandem mass spectrometry (MS4) for flutamide structural analysis from pharmaceutical formulations in Electrospray ion trap mass spectrometry. Analytical Chemistry Research 3: 89-97.
- Abdelhamid HN, Wu HF (2015) Soft lonization of Metallo-Mefenamic using Electrospray Ionization Mass Spectrometry. Mass Spectrometry Letter 6: 43-47.
- 100. Sekar R, Kailasa S, Abdelhamid HN, Chen YC, Wu HF (2013) Probing the metal complexation reaction of tobramycin with copper (II) and iron (III) ions by electrospray ionization mass spectrometry. International Journal of Mass Spectrometry 338: 23-29.
- 101.Abdelhamid HN, Khan MS, Wu HF (2014) Graphene oxide as a nanocarrier for gramicidin (GOGD) for high antibacterial performance. RSC Advances 4: 50035-50046.
- 102. Abdelhamid HN (2016) Ionic Liquids for Mass Spectrometry: Matrices, Separation and Microextraction. Trends in Analytical Chemistry 77:122–138.