Review

Ion Mobility–Mass Spectrometry for Bioanalysis

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Abstract: This paper aims to cover the main strategies based on ion mobility spectrometry (IMS) for the analysis of biological samples. The determination of endogenous and exogenous compounds in such samples is important for the understanding of the health status of individuals. For this reason, the development of new approaches that can be complementary to the ones already established (mainly based on liquid chromatography coupled to mass spectrometry) is welcomed. In this regard, ion mobility spectrometry has appeared in the analytical scenario as a powerful technique for the separation and characterization of compounds based on their mobility. IMS has been used in several areas taking advantage of its orthogonality with other analytical separation techniques, such as liquid chromatography, gas chromatography, capillary electrophoresis, or supercritical fluid chromatography. Bioanalysis is not one of the areas where IMS has been more extensively applied. However, over the last years, the interest in using this approach for the analysis of biological samples has clearly increased. This paper introduces the reader to the principles controlling the separation in IMS and reviews recent applications using this technique in the field of bioanalysis.

1. Introduction

Methods and technologies for the determination of endogenous and exogenous compounds in biological matrices such as plasma, urine, saliva, sweat, infected tissues, infected exudates, feces, breath, and breast milk [1–12] are under continuous development as a consequence of society's growing interest in improving the knowledge of individuals' health conditions. In this regard, the research on proper biomarkers or biological indicators of a medical state observed from outside the patient, which can be accurately and reproducibly measured, has gained special interest in the pharmaceutical and biomedical fields [13]. In addition, in the bioanalysis area, the determination of drugs and related compounds in biological samples is essential not only for correlating drug exposure to efficacy but also for predicting adverse effects related to the drug or its metabolites. In bioanalysis, samples are analyzed for qualitative or quantitative purposes, i.e., for the identification and structural elucidation or the quantitation of exogenous or endogenous molecules [14–16]. Due to the inherent complexity of biological matrices, samples are usually subjected to clean-up or preconcentration procedures to enrich the sample and to eliminate possible interferences that can hinder the determination of the compound(s) of interest. The complexity of such procedures ranges from simple dilution of the sample (dilute and shoot (DAS)) [17–19] or protein precipitation (PPT) [20,21] to intricate procedures dealing with solid-phase (SPE) [22–24] or liquid–liquid (LLE) [25] extractions [26,27]. It is clear that the sample treatment procedure is determined by the information available regarding the structural and the physicochemical properties of the analytes, the matrix, and the purpose of the analysis. Thus, for metabolomic fingerprinting, nonspecific methods

(such as DAS or PPT) are preferred to prevent the loss of compounds that can result in important features [28]. On the contrary, the quantitative determination of drugs and/or known metabolites often requires high sensitivity, which means that specific methods developed considering the physicochemical properties of the analyte(s) should be used. Extracts obtained after sample treatment are then analyzed using several instrumental platforms. In metabolomics, analytical techniques, such as NMR, which can provide a huge amount of data that can be analyzed using mathematical models are commonly used for the analysis of the biological matrices [29–32]. However, in bioanalysis in general, high-performance separation techniques are usually welcomed to improve the efficiency of the analysis. In this regard, liquid chromatography (LC) has been the most extensively exploited technique. While first LC was used mostly with UV detection (LC-UV), nowadays, LC coupled with mass spectrometry has become the gold standard in bioanalysis combining high (compound) resolution, sensitivity, and specificity with a high sample throughput [33–35]. In addition, mass spectrometry provides structural information that is essential for identification purposes. Other separation techniques such as gas chromatography (GC), capillary electrophoresis (CE), or supercritical fluid chromatography (SFC) have also been considered as an alternative because of their complementary selectivity to LC [36–41]. However, the application of these techniques is by far less extended because of instrumental or methodological drawbacks.

In the last decades, ion mobility spectrometry (IMS), which separates gas ions according to their size-to-charge ratio, has gained interest as a powerful separation method. Ion mobility studies were already conducted in the early 20th century [42–45]; however, it was not until the 1970s that IMS was introduced as an analytical tool by Cohen and Karasek [46,47]. Since then, IMS has been extensively used in a wide range of research areas from environmental and security fields to biomedical and pharmaceutical applications [48–57]. For instance, IMS has been used for the detection of illegal drugs and their precursors (such as acetic anhydride or pyridine) [58,59], environmental analysis [60], the diagnosis of bacterial infections [61], forensic examination [62], military and chemical weapons monitoring [63,64], and aerospace applications [65]. The use of ion mobility has also gained relevance in bioanalysis in recent years owing to the potential improvement of the sensitivity and the capacity of the technique to separate strongly related compounds based on their conformational differences. In addition, ion mobility can provide some structural information by means of CCS determination (see below), which can be considerably helpful for the identification of unknown compounds. Initially, IMS was mainly used as a standalone technique; however, in recent years the coupling of IMS with mass spectrometry has spectacularly gained in importance [66]. This fact responds to the improvement in the analysis of complex samples that can be obtained taking advantage of (1) the separation based on the different mobility of the ions and (2) the structural information that mass spectrometry provides. Besides, the addition of a third separation dimension that is obtained with the coupling of an orthogonal technique, mainly liquid chromatography, has also shown a high potential for the analysis of complex samples [67,68]. In this case, the separation of the compounds of interest from other matrix components is driven by their lipophilicity (LC), shape (IMS), mass (MS), and charge (IMS and MS).

Bioanalysis has remarkable relevance in the analytical field owing to the necessity of linking human health conditions with objective indicators or descriptors. In this regard, the development of new analytical approaches for the characterization of biological samples is fundamental to increase the understanding of human health status. Hence, this paper is an overview of the use of ion mobility mainly coupled with mass spectrometry in the bioanalytical field. A brief introduction to the theoretical background of the technique is given, followed by a description of the different ion mobility techniques used in bioanalysis. Recent applications are described to provide insights into the current landscape of this field. However, an exhaustive coverage of applications is beyond the scope of the present contribution, and therefore, this paper focuses on some relevant applications published over the last few years. The main search was done using SciFinder, considering publications from

2015 to the present time and using concepts such as ion mobility, bioanalysis, metabolism, and drugs as the general search inputs. However, to cover other more specific points, keywords such as different ion mobility types, mass spectrometry, and liquid chromatography and a more extended period were also considered. Besides, relevant papers from a historical perspective that deal with fundamentals and background are also included.

2. Theoretical Background

In this section, a brief introduction to the technique is given. However, for a more comprehensive description of the principles governing IMS separations as well as the instrumental characteristics, readers are referred to more specific publications [69–75].

Ion mobility spectrometry is an analytical technique that allows the separation of ions in the gas phase based on their mobility, which depends on their charge, size, and shape. Thus, the velocity of the ions, or drift velocity (v_d), in the gas-phase medium is proportional to the strength of the electric field (E) applied, with the ion mobility (K) being the proportionality coefficient:

$$v_d = K\,E \tag{1}$$

According to the Mason–Schamp equation [76], the mobility of the ions in the gas phase can be related to the compound properties as follows:

$$K = \frac{3}{16}\left(\frac{2\pi}{K_B T}\right)^{\frac{1}{2}}\left(\frac{1}{m} + \frac{1}{M}\right)^{\frac{1}{2}}\frac{q}{\Omega} \tag{2}$$

where K_B is the Boltzmann constant (1.38065×10^{-23} J·K^{-1}), T is the gas temperature, m and M are the mass of the buffer gas and the ion, respectively, q is the ionic charge ($q = ze$, with z being the number of elemental charges and e being the elementary charge), and Ω is the collision cross-section (CCS).

Equation (2) clearly shows the dependence of the ion mobility on the charge (q) and the mass (M) of the ion but also on the ion CCS, which is related to its size and shape and reflects its chemical structure and its three-dimensional conformation. In fact, for small molecules, CCS is characteristic of each ion and then can be used for structural identification purposes [77–80]. However, from a practical point of view, not all the IM instruments enable CCS calculation. As we will see in the following section, drift tube ion mobility spectrometry (DTIMS) allows the direct determination of CCS. On the contrary, its determination can only be accomplished upon calibration with other IM modes, such as traveling wave ion mobility spectrometry (TWIMS), differential mobility analysis (DMA), and trapped ion mobility spectrometry (TIMS), but not with field asymmetric waveform ion mobility spectrometry (FAIMS).

IMS can be classified into three different categories according to the mechanism of separation of the ions [81]. In time-dispersive methods, the separation occurs based on the different times that ions require to go through the same pathway, as happens in DTIMS and TWIMS (Figure 1a). In a different way, the separation in FAIMS and DMA is governed by space-dispersive methods, where ions describe different trajectories according to their mobility (Figure 1b). Note that in this type of technique, the mobility spectrum is obtained from a voltage scan, and each ion will reach the end of the path at a specific voltage value. Finally, in the case of ion trapping with selective release methods, such as in TIMS, ions are trapped in a pressurized region and are selectively ejected based on their mobilities (Figure 1c).
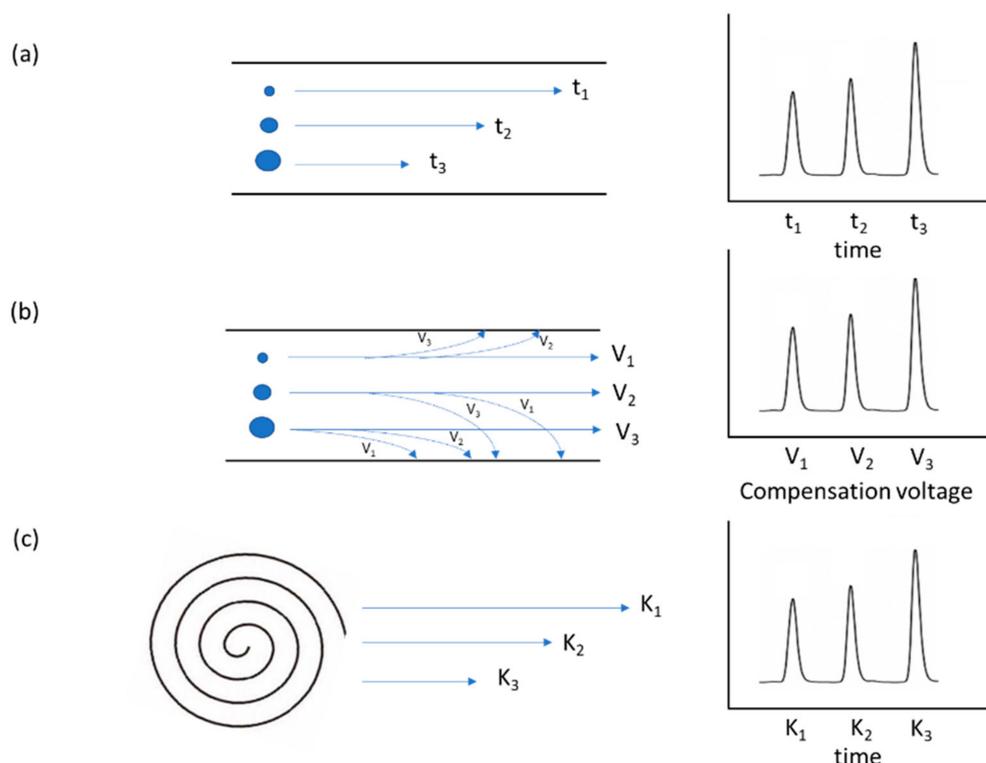
Figure 1. Classification of IMS based on the mechanisms of separation. (**a**) Time-dispersive methods, (**b**) space-dispersive methods, and (**c**) ion trapping with selective release methods.

3. Ion Mobility Techniques

As mentioned before, different ion mobility technologies have been developed, with the mobility of gas ions being the common driving force for their separation. However, the design and thus, the specific principle of separation is characteristic of each of the different technologies. Note that new variants are being developed, but the lack of commercial instrumentation makes them unfeasible from a practical point of view. In the following paragraphs, the specificities of ion mobility modes mostly used in bioanalysis are described, illustrating their applicability by reviewing some examples. In addition, in Table 1, manufacturers of each type of IMS are given.

Table 1. Manufacturers of the different ion mobility analyzers.

Technology	Manufacturer
DTIMS	AgilentTOFwerk
TWIMS	Waters
DMA	SEADM
FAIMS	ThermoFisherOwlstone
DMS	Sciex
TIMS	Bruker

3.1. Drift Tube Ion Mobility Spectrometry (DTIMS)

In this case, the ion mobility analyzer is a tube (drift tube) consisting of a series of stacked-ring electrodes with a current of an inert gas flowing through the tube (mostly nitrogen or helium) (Figure 2A). The application of a uniform electric field along the drift tube makes the ions move towards the detection region. The collisions of the ions with the drift gas, which moves in the opposite direction than the ions do, determine their mobility; more compact ions, which suffer fewer collisions, move faster than extended

ones. Thus, the time that ions need to reach the detector (drift time) depends on their shape, which is related to the CCS value [69,70]. In fact, DTIMS is the only analyzer that, if conditions are well controlled, allows one to directly determine CCS values with high accuracy without the need to use calibrators. For instance, CCS values in combination with mass spectrometry information were used for the identification of antiepileptic drugs in human serum [78]. DTIMS provides an orthogonal dimension to the LC separation, and furthermore, CCS measurements increase the confidence in the identification [78]. A clear example of the utility of CCS values for differentiating isobaric compounds is the case of carbamazepine epoxy, oxacarbazepine, and phenytoin with CCS values of 154.0, 155.8, and 166.6 Å^2, respectively [78]. The relevance of measuring CCS is also pointed out by Nichols et al., who created a CCS library based on the analytical standards in the Mass Spectrometry Metabolite Library of Standards [82]. The addition of these values in the analysis of human serum extracts has been shown to be advantageous as a molecular descriptor [82]. Apart from the use of DTIMS for obtaining structural information, the technique has been exploited for the separation of isomers. This is the case for bile acids, for which separation by liquid chromatography is long and offers poor resolution for some isomeric compounds. After the application of ion mobility, good resolution outcomes were obtained for small bile acids (BAs), but BAs with high m/z values still remained unresolved. The addition of metal ions such as copper and zinc to the sample resulted in complexes that had differentiated mobilities and, thus, were separable by DTIMS [83]. Ion mobility has also shown to be an interesting option for the analysis of metabolites in biological samples for metabolite profiling, the so-called metabolomics [84–87]. As an example, Zhang and coworkers compared three different operation modes, namely FIA/IM-MS, LC-MS, and LC-IM-MS for metabolomics analyses of human plasma and HaCaT cells using DTIMS [85]. A clear benefit was observed by the addition of the third dimension (ion mobility) to the LC-MS analyses. In this regard, a reduction of chemical noise, an accurate measurement of isotope ratios, an increased peak capacity, and additional structural information were achieved by LC-IM-MS [85]. CCS determination has also been demonstrated to be useful in metabolomics since it can aid in the small molecule identification for both targeted and untargeted metabolite screening [87]. Reisdorph and coworkers described a typical DTIMS metabolomics workflow as a proposal to investigators who are interested in using IM-MS in their metabolomic studies [84].
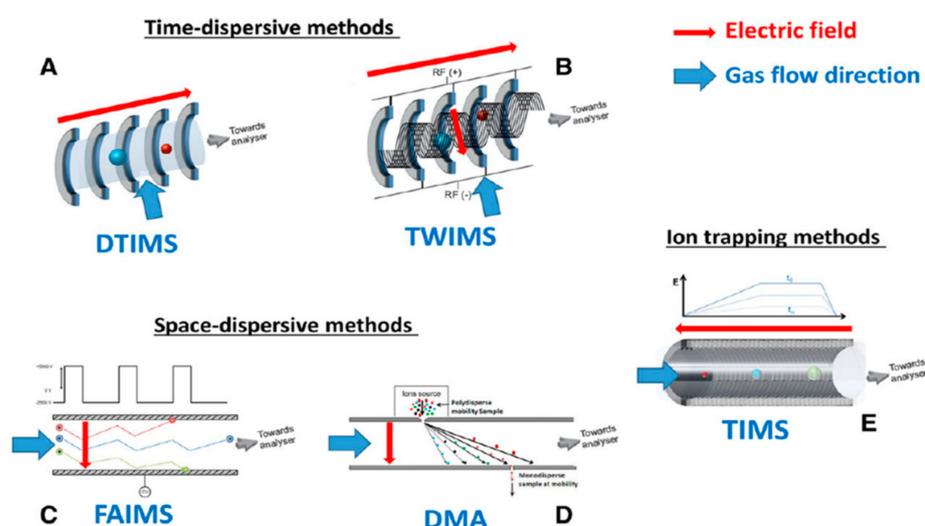

Figure 2. Schematic representation of the commercially available IMS technology: DTIMS (**A**), TWIMS (**B**), FAIMS (**C**), DMA (**D**) and TIMS (**E**) Reproduced from [70] with permission.

3.2. Travelling Wave Ion Mobility Spectrometry (TWIMS)

Traveling wave ion mobility spectrometry (TWIMS), like DTIMS, is a time-dispersive technique. The separation cell also consists of a series of stacked-ring electrodes. However, in TWIMS, the separation is obtained by a dynamic application of the electric field rather than a linear one. This is obtained through the alternative application of positive and negative radio frequency voltages to adjacent electrodes. In this way, a traveling wave is created, in which magnitude and speed govern the ion separation. As in the case of DTIMS, more compact ions suffer less friction with the buffer gas, and as a result, they move faster than extended ones [69,70]. Figure 2B shows a scheme of the technique.

In general, TWIMS has been extensively applied as a separation technique; however, the possibility of determining CCS offers the potential of using it for characterization purposes. Nevertheless, unlike in DTIMS, in TWIMS, a calibration with reference standards is needed for CCS calculation. In the bioanalytical field, one can find CCS libraries that are generated for a specific set of compounds, such as steroids [88] or rat metabolites [89]. More specifically, CCS values were also used for the structural elucidation of small molecules. In this regard, several publications using TWIMS have been found to deal with the identification of metabolites of drugs or specific compounds [90–92]. For instance, Ross et al. developed a workflow for the structural elucidation of drug metabolites using TWIMS [91]. After in vitro metabolite generation, the samples were analyzed by FIA-IM-MS. The analysis of the obtained data (CCS values and MS information) allowed them to characterize drug metabolites from a diverse panel of drugs. They found that CCS changes depend not only on the type and position of the modification but also on the structural characteristics of the parent drug. As mentioned before, a previous calibration was needed for CCS determination. They used a mixture of polyalanines and drug-like compounds with known ^{DTIM}CCS values to calibrate ^{TWIM}CCS values (Figure 3). Regarding the use of this technique for separation purposes in bioanalysis, some applications can be found in combination with LC as an orthogonal separation dimension [93–95] or as a standalone separation technique [96]. In the latter case, a rapid and sensitive method was developed for the quantification of drugs in tissue sections using matrix-assisted laser desorption ionization (MALDI) as an ionization source. Isomer separations can also be accomplished with TWIMS. As an example, the separation of bile acid isomers was successfully achieved [97]. As has been pointed out before, the small differences in the mobility of some of these isomeric compounds are not enough for a baseline separation. In this case, Chouinard and coworkers used cyclodextrin adduct formation to increase ion mobility resolution [97]. Finally, it is worth mentioning the use of TWIMS in metabolomic studies, which has been reviewed elsewhere [98]. Following a metabolomic approach, Poland and coworkers were able to profile changes in the gut metabolome after biliary diversion surgery. For such a purpose, an untargeted UPLC-IM-MS method was optimized for fecal samples obtained from mice that have undergone bile diversion surgery [99]. Urinary metabolic phenotyping can also be mentioned as an example of metabolomics studies performed using TWIMS [100,101].
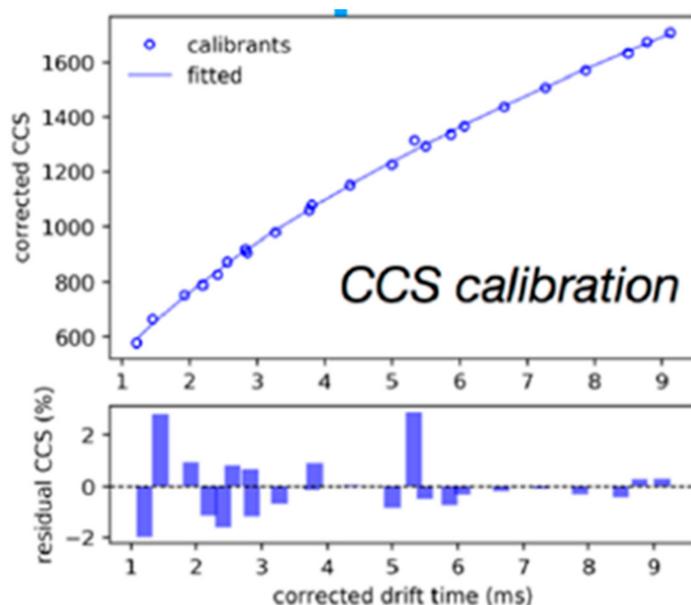
Figure 3. Calibration of ^{TWIM}CCS values using known ^{DTIM}CCS values from a mixture of polyalanines and drug-like compounds. This figure was adapted from [91] with the permission of the publisher.

3.3. Differential Mobility Analysis (DMA)

Differential mobility analysis (DMA) is a space-dispersive technique in which the ions are separated based on their capacity to reach the ion mobility cell exit so that a scan is needed for the detection of different ions. In this approach, a constant electric field is applied between two cylindrical and concentric metal electrodes. Ions are introduced between the two electrodes where they are pushed towards the exit by means of an orthogonal flow of sheath gas. Only those ions with the appropriate mobility will reach the cell exit. The other ions will collide with the electrode, thus preventing their detection. By scanning the electric field, an ion spectrum based on the different ion mobilities can be recorded (Figure 2D). In general, DMA is mainly used for the determination of large analytes such as aerosol particles or macromolecules and is less applied for small molecules [72]. In fact, very few bioanalytical applications for DMA have been found. Even so, the potential of the technique has been proven in several cases. As an example, the isomers sarcosine and L-alanine were partially resolved in urine, and for such a purpose, a minimal sample preparation consisting of a simple dilution step was required [102]. It is also worth mentioning that the technique has also been applied in metabolomic studies. Thus, the urinary metabolic fingerprint obtained by DMA–quadrupole time-of-flight (QTOF) allowed Martinez-Lozano and coworkers to differentiate between prostate cancer patients and healthy individuals [103].

3.4. Field Asymmetric Waveform Ion Mobility Spectrometry (FAIMS) and Differential Mobility Spectrometry (DMS)

Field asymmetric waveform ion mobility spectrometry (FAIMS), like DMA, is a space-dispersive technique in which separation occurs on a spatial scale rather than in a temporal one (Figure 2C). This technique is often equally named differential mobility spectrometry (DMS); however, although the principle of operation is the same, some small differences exist between both techniques due to the geometry of their electrodes. Devices with cylindrical electrodes are referred to as field asymmetric waveform ion mobility spectrometers, whereas planar electrodes are used in DMS [104]. Here, we will use the term FAIMS when describing the principles of operation. In FAIMS, a high asymmetric electric field is applied between two electrodes. The motion of ions is then driven not only by the changing electric field but also because of the carrier gas, which is injected in the same direction as the ions.

Under these conditions, only those ions with the proper mobility will reach the detector. However, a compensation voltage is superposed to the dispersion field, which corrects the trajectory of the ions of interest. Again, those ions whose trajectory is not properly corrected will migrate away. The compensation voltage (CV) can be scanned to generate a CV spectrum. In FAIMS, the ions are separated based not directly on their mobility, but on changes in mobility. This implies that the mechanism of separation in FAIMS is more different from MS when compared to the mechanisms of the other ion mobility techniques [70,104].

Among all the ion mobility techniques, DMS-MS is the most widely used in the bioanalytical field. DMS coupled with MS is mainly used as a filtering process both in combination with liquid chromatography (LC) [105–109] or as a stand-alone separation [110,111]. The filtering capacity of the technique provides clear benefits in terms of eliminating interferences and reducing background noise, which can entail an increase in sensitivity. In Figure 4, the improvement in sensitivity obtained in the determination of eptifibatide in rat plasma with LC-DMS–multiple ion monitoring (LC-DMS-MIM) with respect to LC-MIM or LC–multiple reaction monitoring (LC-MRM) is shown. The results suggest that LC-DMS-MIM can be considered as a proper bioanalytical alternative for compounds with poor CID efficiency [108]. Kayleigh and coworkers reported also an increase in signal-to-noise ratios by eliminating interferences for the determination of anabolic–androgenic steroid metabolites in urine using LC-FAIMS-MS. Furthermore, the separation capacity of FAIMS added to the LC separation allows a substantial reduction in chromatographic run time [106]. Going further, LC can be totally avoided in some cases by using the separation obtained by DMS. This is the case of the determination of cocaine and its metabolites in human serum. The DMS-MS/MS method demonstrated the potential of the technique for high-throughput analysis of these compounds [110]. The separation of isomers was also achieved with DMS [112,113]. However, the scarce structural differences between isomers, above all for small molecules, make the separation challenging. In these cases, but also as a general strategy for improving the separation, gas modifiers can be added. Hence, Ruskic and Hopfgartner studied the effect of using different modifiers on the separation of several isomeric drugs in human plasma [112]. DMS has also been combined with gas chromatography (GC), as proposed by Criado-García and coworkers, who developed a rapid noninvasive method for the determination of toxic levels of alcohols in saliva [114].
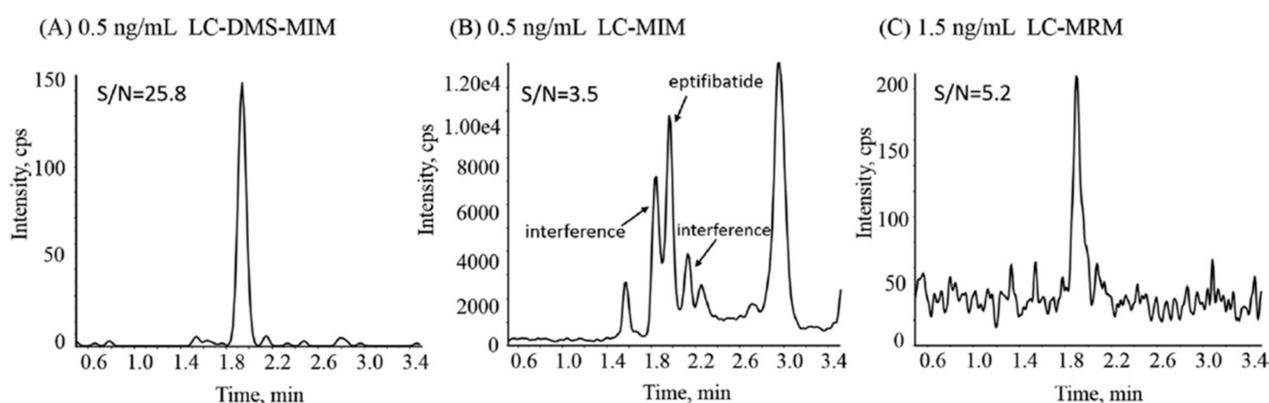

Figure 4. Comparison of the performance of the LC-DMS-MIM assay for eptifibatide in rat plasma with that of similar assays without DMS. Reproduced from [108] with permission.

As stated above, CCS values could not be determined by FAIMS; however, in some cases, compensation voltage, which is characteristic of each analyte at given conditions, could be used for application in metabolite identification [115]. Finally, it is worth pointing out that, although FAIMS (or DMS) has normally been used for targeted analysis, several applications can be found using this technique for metabolomic analysis. As an example, an LC-FAIMS-MS method, which has been demonstrated to be able to resolve co-eluting

isomeric species, was applied for the untargeted metabolomic analysis of human urine, allowing the differentiation between fresh and aged urine [116]. Regarding DMS, a novel untargeted metabolomics method, based solely on DMS, was applied in a clinically relevant chronic kidney disease patient population [117].

3.5. Trapped Ion Mobility Spectrometry (TIMS)

Trapped ion mobility spectrometry (TIMS) is a relatively recent technique. Briefly, ions are trapped into the drift cell by means of an electric field that keeps ions static against a circulating gas. Under these conditions, following the same separation principles as those in DTIMS (ions are pushed through a gas using an electric field), the ions are separated based on their size-to-charge ratio. After the separation step, the electric field is decreased gradually, allowing ions to be eluted from high to low size-to-charge ratios [69,70,118]. Few applications in the bioanalytical area have been found using TIMS; among them, publications by Adams and coworkers can be highlighted [119,120]. Their works involving LC-TIMS-MS include the determination of isomeric drugs of abuse and their metabolites in human urine [119] or the targeted monitoring of polychlorinated biphenyl metabolites in human plasma [120]. TIMS has also been used, combined with MALDI, for spatial metabolomics [121,122].

4. Conclusions and Future Perspectives

The determination of endogenous and exogenous compounds in biological matrices such as plasma and urine is essential in increasing the knowledge of the health status of individuals. Sample analysis deals with the first step of sample treatment followed by the analysis of extracts with the appropriate instrumental technique to determine, qualitatively or quantitatively, the compounds of interest. Among the different approaches, LC-MS stands out as the most extensively used technique in bioanalysis. However, the consideration of alternative separation techniques has been shown to be important in exploring different separation mechanisms and, thus, obtaining complementary selectivity. Among these alternatives, a clear interest exists in exploiting the orthogonality of IMS, in which the separation is driven by the mobility of ions in the gas phase. However, several IMS modalities can be differentiated according to their specific separation mechanism. Three categories can be highlighted: (i) time-dispersive, (ii) space-dispersive, and (iii) ion trapping with selective release methods. Differences between these three modalities have been introduced in this work, but for rapid understanding, one can compare the mode of separation for each category with different analyzers in mass spectrometry. Thus, time-dispersive methods can be compared to time-of-flight analyzers, space-dispersive methods can be compared with quadrupole separations, and ion trapping can be compared with ion trap instruments.

As has been pointed out, IMS has been shown to be a powerful approach not only as a separation technique but also for identification purposes. By evaluating the published bioanalytical applications, one can realize that FAIMS or DMS are the techniques of choice when the separation of the compound of interest from other matrix components is the main objective of the analysis, as they achieve a clear improvement in the sensitivity by reducing background noise. The separation of closely related compounds such as isomers is also the main focus of space-dispersive categories. On the contrary, time-dispersive methods, which allow the determination of CCS, are more directed to those applications that look for structural characterization of the molecules of interest. Finally, nowadays, TIMS has been scarcely applied in the bioanalytical field.

Looking ahead, we think that future technical improvements will imply a substantial increase in the application of IMS in the bioanalytical field. In fact, we have commented here on only those modalities that are fully developed and commercially available. However, new modalities are currently being developed that can also eventually be advantageous for the analysis of complex matrices, such as biological matrices.

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