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Insights of ion mobility spectrometry and its application on food safety and authenticity: A review

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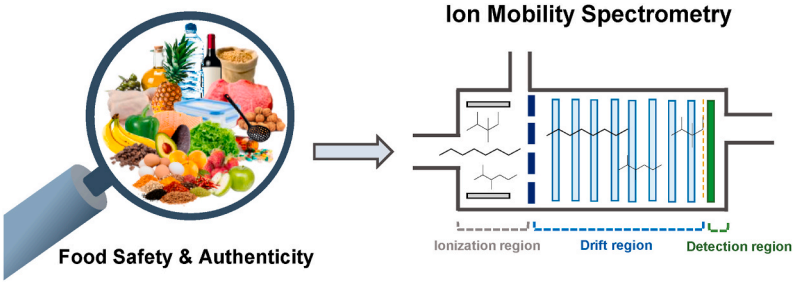
HIGHLIGHTS

- Insights of Ion Mobility Spectrometry (IMS) in food safety and authenticity.
- Developments of IMS in terms of sensitivity and resolution.
- Recent advances in collision cross section reproducibility and prediction.
- Applications of IMS for food safety and authenticity are reviewed.
- Target, On-site, Imaging, High-throughput, and fingerprinting IMS approaches.

GRAPHICAL ABSTRACT



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ABSTRACT

Ion mobility spectrometry (IMS) is gaining importance in the field of food safety and authenticity in recent years due to its main potential to overcome the challenges that arise from the complexity of food matrices. For many years, IMS has been used as a stand-alone analytical detector due to its quick response, high sensitivity, and portability, and stand-alone applications in food analysis have been explored in recent years. At the same time, IMS hyphenation to mass spectrometry (MS) techniques, usually combined with liquid or gas chromatography (LC/GC), provides an additional dimension to separate isobaric compounds and thus improves method selectivity. Besides, with such ion mobility – mass spectrometry (IM−MS) methods, background noise decreases, increasing method sensitivity, and it provides complementary information to mass spectra and retention time with the collision cross section (CCS). The development of CCS databases within the food safety field would even permit the identification of compounds in non-targeted approaches. Furthermore, it would increase the confidence of control laboratories when determining a sample as non-compliant. Therefore, the number of applications by IMS on food safety and authenticity has increased remarkably in recent years. This review provides the general insights of IMS with the current state and recent approaches for its performance improvement and a general outlook of its applicability in food safety and authenticity.

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Abbreviations

CCS	Collision Cross Section
DESI	Desorption Electrospray Ionization
DIMS	Differential Ion Mobility Spectrometry
DTIMS	Drift Tube Ion Mobility Spectrometry
ESI	Electrospray Ionization
FAIMS	Field Asymmetric Waveform Ion Mobility Spectrometry
FTICR	Fourier Transform Ion Cyclotron Resonance
GC−MS	Gas Chromatography−Mass Spectrometry
GC × GC	Comprehensive Two-Dimensional Gas Chromatography
IM−MS	Ion Mobility−Mass Spectrometry
LAESI	Laser Ablation Electrospray Ionization
LC−MS	Liquid Chromatography−Mass Spectrometry
LC × LC	Comprehensive Two-Dimensional Liquid Chromatography
LESA	Liquid Extraction Surface Analysis
LMJ−SSP	Liquid Micro Junction Surface Sampling
MSI	Mass Spectrometry Imaging
MALDI	Matrix-Assisted Laser Desorption Ionization
QuEChERS	Quick, Easy, Cheap, Effective, Rugged and Safe
SUPER	Serpentine Ultralong Path with Extended Routing
SPME	Solid-Phase Microextraction
SLIM	Structures for Lossless Ion Manipulation
TIMS	Trapped Ion Mobility Spectrometry
TWIMS	Traveling Wave Ion Mobility Spectrometry

1. Introduction

Food safety has always been part of the food supply chain. However, it has never been more relevant than today since increasing numbers of potentially harmful compounds are known or even used in agriculture and could end up in food products. Food products are complex mixtures constituted by a great variability of endogenous organic nutrients, such as proteins, fats, carbohydrates, vitamins, and volatile organic compounds. However, food products can also contain exogenous (xenobiotic) substances due to the use of agrochemicals and technological processes in the food industry, or they can even include contaminants that have migrated from materials that could have come in contact with food [1,2]. Thereby, the differences in the chemical structure and polarity of compounds of interest and the complexity of food matrices lead to a wide range of challenges in both sample preparation and analytical techniques used for their determination. Furthermore, the low concentration levels in which some analytes are usually found (μg kg^{-1}, or ng kg^{-1}) make their analysis even more difficult.

In recent years, the fast response, portability, and low cost of stand-alone ion mobility spectrometry (IMS) have shown a great advantage in detecting contaminants in foodstuff [3–7]. IMS is an analytical technique based on the separation of ionized compounds in the gas phase at atmospheric pressure. Separation depends on the velocity of ions in an electric field in the presence of a so-called drift gas (also called buffer gas), and this speed is related to the size and shape of the ion and, if applicable, different ion conformations. In general, heavier ions are larger and will collide with the drift gas more often and therefore move more slowly in the direction of the electric field. But also, there can be differences in velocity between ions of the same mass because their conformations can differ in compactness, such that isomers, at high enough resolution even stereoisomers and isotopologues, can be separated in the IMS instrument [8,9]. Stand-alone IMS can be very powerful in, for example, fingerprinting approaches, but it is challenging to sensitively detect and identify compounds, especially in complex matrices like food matrices, if no specialized detection method is hyphenated to IMS.

Under this scenario, in the field of food analysis, mass spectrometry (MS) has become an essential analytical technique for many control laboratories. This is due to the ability of MS to identify and characterize a great variety of compounds unequivocally, detecting them with great sensitivity and selectivity and overcoming most of the main drawbacks observed with traditional detection systems for the analysis of food samples [10–12]. In this way, in the field of food safety and authenticity, multiclass methods where a high number of compounds are analyzed in a single method are becoming increasingly necessary to improve control laboratory workloads [13,14]. However, although liquid chromatography (LC) and gas chromatography (GC) coupled to mass spectrometry (LC−MS, GC−MS) techniques reach high selectivity and sensitivity, the separation of certain compounds in complex matrices is not possible. The development of two different chromatographic separation steps (LC × LC and GC × GC), using columns with different selectivity permitted to increase the peak capacity of the conventional chromatographic analysis [15–17], allowed to separate analytes by two different sequential retention mechanisms from other components in a very complex matrix. Nevertheless, these techniques require long analysis time and data treatment and show difficulties when separating isobaric compounds. In this context, IMS coupled to MS has shown great potential permitting the separation of isomers as well as reducing the background noise, which improves the signal-to-noise ratio (S/N) [18,19]. This separation step provides an additional identification step when incorporated in LC−MS or GC−MS workflows and leads to a two-to threefold higher total number of compounds that can be separated and identified in a single run, the so-called peak capacity [20,21]. Overall, IMS is a technique that has become more and more popular in the field of food analysis during the last decade, both stand-alone and in combination with LC−MS and GC−MS workflows. To the best of our knowledge, few studies have been focused on reviewing IMS and its application in the food safety and authenticity field [5,22,23].

Accordingly, the present review aims to emphasize the insights of IMS technology and highlight all recent developments in resolution, sensitivity, CCS reproducibility and prediction, and imaging studies. Additionally, this study presents the main applications that have been developed in food safety and authenticity during the last 5 years (2017–2021). In this review we aimed to give a complete overview of the vast number of recent papers covering very different aspects of IMS, including both stand-alone IMS detection and IM−MS, that are all relevant to the future of food analysis.

2. Current state of IMS and recent approaches to improve its performance

Due to the great potential shown by IMS, to date, three types of dispersive IMS platforms are commercially available: time-dispersive, trapped, and space-dispersive IMS [23]. Until 2019, the main time-dispersive techniques were drift tube IMS (DTIMS) and traveling wave IMS (TWIMS). Both techniques measure ion mobility as a function of the time spent in a drift tube, but in DTIMS the electric field in the drift tube is linear and constant over time, while in TWIMS an electric field wave travels through the drift tube to propel ions (Fig. 1a and b). In the latter case, the resolution is not linearly dependent on mobility as in DTIMS. It can therefore be optimized for a certain mobility range by choosing wave amplitude and gas pressure [24]. In trapped IMS (TIMS), the electric field increases over the length of the instrument such that ions will be trapped at a certain location in the tube depending on their mobility, in equilibrium between the drift gas that pushes them to the detector side and the electric field that pulls them back to the entrance (Fig. 1c). The ions can be released at any desired moment by decreasing the field. Finally, high-field asymmetric waveform IMS (FAIMS), also

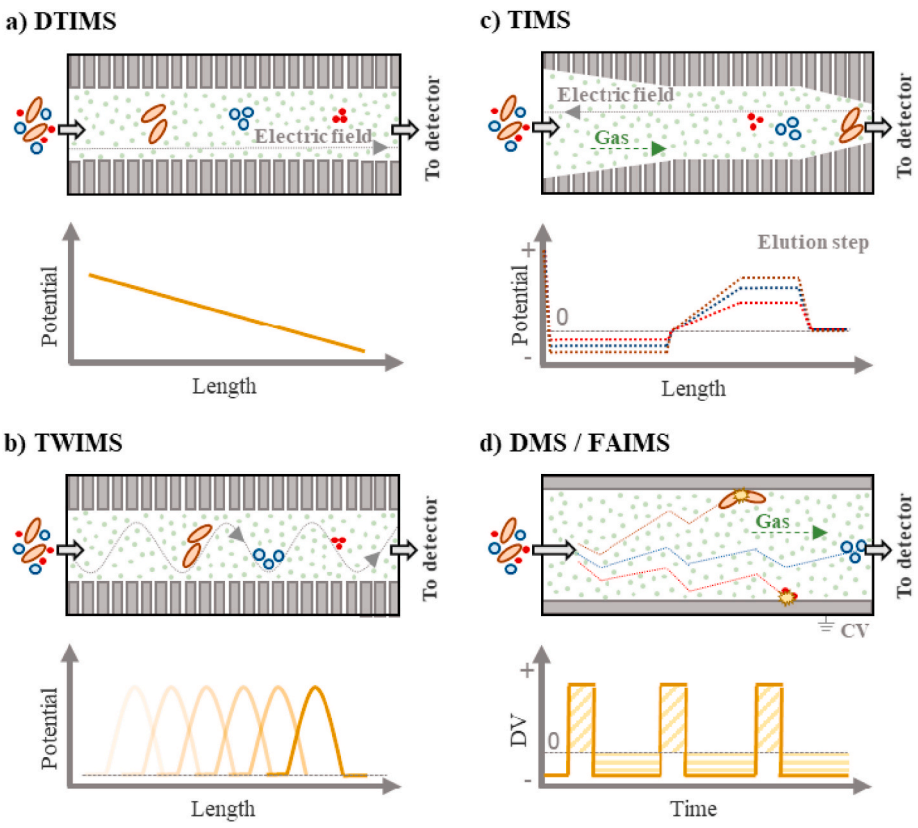

Fig. 1. Commercially available IMS platforms until 2019. Adjusted from Ref. [23], Copyright (2019), with permission from MPDI. Gas particles are depicted in light green and different ions in red, blue and orange. For TIMS, the potential profile that is used to elute and detect a certain ion type is depicted in the corresponding color. In DMS/FAIMS, DV stands for dispersive voltage, and is applied perpendicular to the gas flow. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

called differential IMS (DIMS) or differential mobility spectrometry (DMS), sometimes even ion mobility increment spectrometry (IMIS), is a selective IMS technique. In such platforms, electric fields of alternating strength and polarity are applied between the two sides of the instrument while a gas flow propels ions towards the exit, such that only ions with very specific mobility will follow the right trajectory to reach the detector (Fig. 1d) [25]. According to Gabelica et al., FAIMS, DIMS, DMS, and IMIS are only distinguished for historical reasons, and the use of FAIMS in all cases would be sufficient [26].

In the case of DTIMS, TWIMS, and TIMS, an obtained arrival time in the tube can be converted to a collision cross-section (CCS). The CCS is a single descriptor for the size of an ion in the gas phase as a function of its charge [23]. It is derived from the ion mobility and corrected for the strength of the electric field applied, the drift gas pressure, and the temperature. Analysis with the three different platforms or different instrument settings should theoretically result in the same CCS for each compound, or, if a compound has different conformations or adducts, for each conformation and each adduct. Therefore, it can be used as a characteristic value for analyte confirmation and identification. However, in practice, the CCS depends on the drift gas [21] and minor differences are often found depending on the IMS platform and instrument settings. For TWIMS and TIMS, the mathematics behind CCS calculation is very complex, leading to deviations [27,28]. Moreover, certain circumstances in different instruments might lead to slightly different ion conformations. Therefore, to specify how CCS values are obtained, CCS is sometimes annotated as $^{\text{IMS platform}}\text{CCS}_{\text{drift gas}}$, for example, $^{\text{TW}}\text{CCS}_{\text{N}_2}$ for CCS values obtained by TWIMS in nitrogen gas. For FAIMS, no CCS can be calculated because this method delivers relative ion mobilities between high and low electric fields instead of absolute ion mobilities. Moreover, conformational changes might occur when the field strength is switched, or even ion clustering and declustering, because in FAIMS much stronger electric fields are used than for time-dispersive and trapped ion mobility [25].

Several factors have been studied to improve the separation and detection capability of chemicals in food samples using analytical platforms that include IMS. Thus, in recent years, the improvement of the resolution and sensitivity of IMS platforms has been sought through the evaluation of different parameters as well as the development of new IMS instruments. In addition, the latest advances in IMS have aimed to improve CCS reproducibility by optimizing both instruments and software, to allow the creation of reliable CCS databases that will aid in identifying food safety hazards.

2.1. *Resolution, sensitivity and selectivity*

In IMS, the resolution is often expressed as resolving power, as a measure for the number of peaks that can be distinguished in a single spectrum, which is for IMS usually defined as drift time divided by peak width at half height [8]. While by mass spectrometry very high resolving powers of thousands to over one million are achieved, the resolving powers of TWIMS, DTIMS, and TIMS platforms are 20–350, 50–350, and 200–400, respectively [8]. However, these resolving powers are not fixed as continuous improvements are going on regarding the resolution and sensitivity of IMS instruments. This involves both upgrades in hardware and optimization of instrument settings. Before entering the drift tube, for example, ions pass a gate, shutter, grid electrode, or trapping funnel that determines the size of the ion packages that are let in. Developments to increase compression of ion packages or to reduce the gate's opening time lead to higher and narrower peaks in IMS spectra, thus improving sensitivity and resolution [29,30]. Nevertheless, peak width in IMS does not only reflect instrument resolution. It also provides information about the flexibility and rearrangements of ions as they move through the drift tube [31]. Moreover, Kirk et al. calculated that ideal drift conditions in DTIMS are almost reached with current techniques [9]. A significant further decrease in peak widths thus should not be expected for DTIMS. On the other hand, Larriba-Andaluz et al. reasoned that there are still theoretical possibilities to confine ions in the radial direction in TIMS to improve sensitivity and resolution [32].

Sensitivity can also be improved by optimizing the ionization process and reducing ion loss during acquisition. Son and Choi showed that the ionization efficiency could highly depend on the solvent [33]. Schneider et al. optimized arrival time, electrode spacing, gas flow rate, and waveform frequency to reduce ion loss in DMS [34]. Pfammatter et al. reached 80% ion transmission for FAIMS using heated electrodes [35]. A very important manner to reduce ion loss is optimizing the ion beam use. This is possible by multiplexing, which for IMS involves the injection of ion packages in the drift region in much shorter time intervals than usual, such that ions from different ion packages are in the drift region simultaneously. In this case, the generated datasets need to be deconvoluted afterward. For DTIMS, multiplexing can improve the ion utilization efficiency from around 1 to almost 50% [36]. Alternatively, ion loss can be prevented by the accumulation of ions at the IMS entrance, such that all of the ion beam can be used. However, for longer trapping events the ion package becomes so dense that undesired space-charge effects occur that affect the ion behaviour. Therefore, multiplexing is still desired in some cases as it reduces the ion accumulation time [37]. Agilent Technologies developed a new post-acquisition data reconstruction technique named high resolution demultiplexing (HRdm), aiming to enhance resolution in the IMS dimension [38]. This technique is a resolution enhancement technology based on IMS data files acquired using multiplexing and combines standard techniques to perform simultaneous demultiplexing and deconvolution on current DTIMS−MS (Fig. 2). In this way, HRdm can increase the IMS resolving power up to 200 in full scan mode. Moreover, May et al. proved that the overall analysis times and drift time measurement precision, when using the HRdm processed data sets, did not influence the obtained CCS values for biologically relevant lipids and carbohydrates [39]. Although to the best of our knowledge, HRdm software has not been tested for food-related applications, it could have great potential in the food safety field to detect and separate isomers at low concentration levels.

In the case of IM−MS, the coupling between IM and MS also needs to be improved to reduce ion loss and increase resolving power by adjusting IM output such that the timing is optimal for MS; either by physically adjusting the interface [40] or by different instrument settings such as scan functions [41]. Poltash et al. developed a Fourier-transform DTIMS suitable for coupling to an orbitrap MS [42]. The Fourier-transform DTIMS operates in pulsing mode at increasing frequency, such that ions of different mobility are released from the DTIMS over an elongated timescale. This provides compatibility with the acquisition times of orbitrap MS, which are significantly longer than most other MS platforms. In particular, the instrument is designed to prevent conformational changes of protein and protein complexes during analysis, which could be interesting as well in food analysis. A similar approach of elongating TIMS timescales is necessary to couple TIMS to Fourier-transform ion cyclotron resonance (FTICR) −MS. This can be achieved by accumulating ions during TIMS, but long ion residence in the TIMS tube leads to ion heating and thus undesired side effects. Gated TIMS significantly decreases the accumulation time in the TIMS tube by delivering multiple small ion packages to the collision cell for final accumulation before entering the FTICR−MS [43]. To make FAIMS compatible with orbitrap-MS, the common drift gas (H_2 or He) was replaced with N_2 [44]. Such progress improves the versatility of IM−MS and thus the applicability in different fields such as food analysis.

Other approaches to increase sensitivity and resolution aim to better separate different ion types. Theoretically, this is possible in multiple ways, such as increasing the electric field or drift length or decreasing drift gas temperature [45]. In practice, there are certain limitations, such as ion heating and fragmentation in high electric fields. However, there are several tricks to reach a better separation. For example, ion arrival distribution can be optimized by ramping the traveling wave velocity in TWIMS instead of keeping it constant. As a result, less peaks overlap, and peak capacity significantly increases [21].

In more specific cases where the separation of two or more compounds of interest is difficult, the formation of adducts, usually metal adducts, can be beneficial to accomplish baseline separation. Such adducts can be formed during the ionization process when metal salt or another adduct is added to the sample, and they can have several effects. Metal adducts are heavier; therefore, their drift time is longer, enhancing peak separation [46,47]. But also, the ion conformation can be influenced by adducts; this again leads to changes in mobility [48]. For example, only one of two isomers may have a special conformation in the adduct form, such that both isomers can be easily distinguished only when metal salt is applied [49]. Moreover, dimer formation is possible in the presence of metal ions. Whether or not such dimers are formed might depend on ion conformation [48]. As well, the conformation and mobility of the dimer might depend on the isomer [50]. Sometimes more than one metal ion coordinates to the compound of

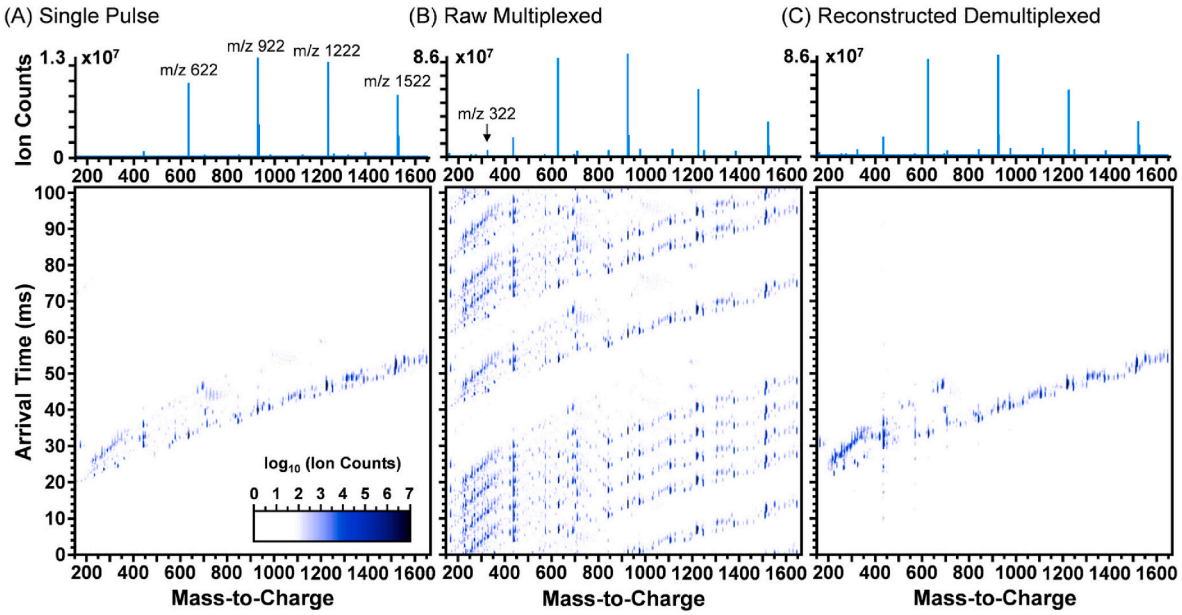

Fig. 2. Example 2D IM−MS spectra of tuning mixture obtained from (A) conventional single pulse IM operation, (B) 4-bit multiplexing, and (C) the IM−MS spectrum reconstructed (demultiplexed) from the multiplexed spectrum. Reprinted from Ref. [39], Copyright (2020) with permission from ACS Publications.

interest, leading to even more separation possibilities [51,52]. Zhou et al. applied ionization in the presence of acetone to create $(Ac)_2H^+$ adducts on pesticides in a selective manner [53]. For small isomers and enantiomers, cyclodextrins can be used as adducts to form non-covalent complexes to achieve separation [54–56]. Also, compound modification can be used to improve the separation between compounds of interest. Maddox et al. used the Paterni-Bücher reaction to create unique IMS profiles for difficult to distinguish steroids [57] while Will et al. used derivatization with S-naproxen chloride to separate amino acid stereoisomers via TIMS [58]. However, it needs to be mentioned that a full separation of compounds was not always achieved in the above studies or depended on the IMS platform. Full separation is essential for quantifying different compounds of interest in mixtures.

2.2. High-resolution IMS

Several successful and less successful attempts have been made to improve the resolution of IMS by developing new platforms. Theoretically, the highest resolving powers can be achieved by increasing the effective drift length [59]. However, as there are practical limits to the size of IMS instruments, new solutions are needed to carry this out. High-resolution ion cyclotron mobility spectrometry was one of the first attempts to increase the path length by introducing a nonlinear drift tube, but this platform seems to stay behind since no developments have been reported since 2016. In contrast, cyclic IMS was commercialized in 2019 (Waters Inc., Massachusetts), and Structures for Lossless Ion Manipulation (SLIM) in 2021 (MOBILion Systems Inc., Pennsylvania).

The cyclic IMS is a circular instead of a linear TWIMS device, such that the ends are connected, and the path length can be vastly increased by passing ions through the device multiple times in a row (Fig. 3) [60]. TWIMS is suitable for this approach because the traveling electric field in the tube changes over time rather than space. Increasing the potential is therefore not necessary for longer ion pathways. Moreover, the traveling wave can be easily programmed to continue when passing the connected ends of the IMS, thereby allowing, theoretically, an infinite number of cycles. Elongating the ion pathway by multiple passages leads to a better ion separation and, thus, better resolving power. Giles et al. achieved a maximum resolving power of 750 at 100 cycles [45], which is a vast improvement compared with DTIMS, TWIMS, or TIMS. Interestingly, the entrance of the cyclic IMS is at the same time its exit as well as the mass spectrometer entrance, which makes it an excellent location to perform additional manipulations. For example, ion selection or fragmentation could then be performed between two IMS cycles but also just before ions enter the MS. This increases the number of possibilities for compound confirmation or identification significantly. No additional improvements on the concept of Giles et al. which Waters Inc. Commercialized, have been reported so far. The platform was successfully used to distinguish pentasaccharide anomers [61]; however, this involved a prototype for fundamental research and not the commercial instrument, so whether similar results can be obtained with the Waters instrument is unclear.

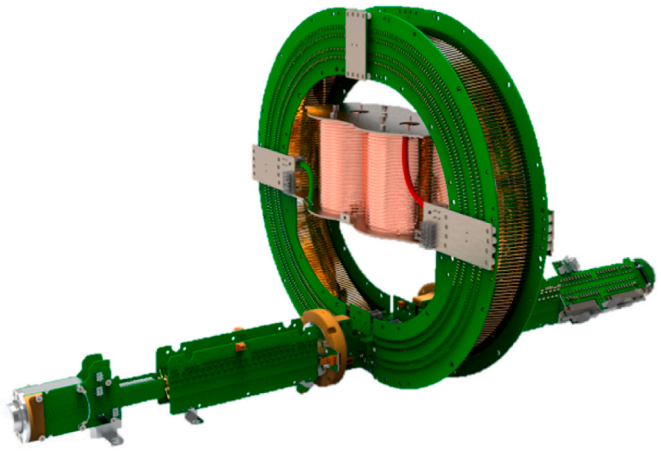

Fig. 3. Cyclic IMS. Reprinted from Ref. [60]. Copyright (2021), with permission from Waters corporation.

In SLIM, two stacked printed circuit boards for the application of both direct current and radiofrequency electric fields create a custom-made ion pathway (Fig. 4) with essentially no loss of ions and resolution even in switches and sharp turns [62,63]. The direct current electrodes propel the ions along the chosen path, while at the same time radiofrequency confines the ion packages to prevent ion loss. Thus, uniform fields can be applied in SLIM, but traveling waves over the direct current electrodes allow the introduction of extremely curved pathways (SUPER, Serpentine Ultralong Path with Extended Routing) such as in Fig. 4c [64]. May et al. showed that for a broad range of compounds, resolving powers of at least 200 can be obtained with a prototype commercial SLIM SUPER platform [65]. The instrument was able to resolve several isomeric and isobaric compounds that cannot be distinguished by MS: reversed-sequence peptides, triglyceride double-bond positional isomers, trisaccharides, and ganglioside lipids. These results show that high-resolution IMS might become a very important technique in analyzing isomeric compounds in the near future.

In the meantime, in non-commercial SLIM SUPER platforms, a switch was introduced that can guide ions either into the SLIM−IMS again or to MS detection, aided in creating extended ion pathways with a total length over 0.5 km, resulting in a resolving power of ~1860 [64]. This specific platform showed that there is a potential for separating glycans [66], amino acid enantiomers [55], stereoisomeric peptides [67] and antibody-drug conjugates [68]. Interestingly, it was even demonstrated that isotopologues and some isotopomers, molecules with stable isotopes in different positions on the same molecule, have different mobilities, although they are far from fully separated [69]. Such results can probably not be obtained with the commercial instrument that lacks the abovementioned switch. However, the vastly extended pathway in SLIM SUPER, especially the platform with a switch, also has a disadvantage: the long residence of ions in the IMS. This limits the frequency of injecting ion packages and, therefore, the throughput. Ibrahim et al. built an escalator system to lift ions to different SLIM levels [70]. Later on, this system was combined with four SLIM SUPER levels to prevent overlap between slower and faster ions originating from different ion packages [71]. Clowers et al. took a different approach and recently developed deconvolution strategies to allow interpretation of data from the commercial prototype when such overlap occurs [72]. Moreover, when reaching ultrahigh resolving power, measurements become sensitive for small time shifts and thus peak shifts. Hollerbach et al. found a data processing method to correct these shifts [73].

The ability to print custom electrode and ion pathway designs on a printed circuit board and incorporate sharp turns in any direction provides a very high versatility when using SLIM technology. This is what makes SLIM an up-and-coming technique. Furthermore, new designs can add all kinds of features, as we have seen earlier regarding the ion elevators. Other examples of new designs developed non-commercially are the incorporation of both constant and oscillatory electric fields for continuous ion selection [74], tandem SLIM by trapping of selected ions [75,76] and the application of oppositely charged potential minima on each plate to allow simultaneous IMS of both positively and negatively charged ions [77], including a specially designed dual polarity ion switch [78]. The optimization of the electrode design and waveform can be performed both theoretically and practically [79,80]; resolution depends primarily on electrode dimensions in combination with plate distance (inter-surface gap) and traveling wave amplitude.

Importantly, ion accumulation is another feature that can be incorporated in SLIM−IMS. In general, a drawback of TWIMS is that ion packages, while ‘surfing’ on the potential waves, likely get dispersed over neighboring potential waves, especially when larger ion packages

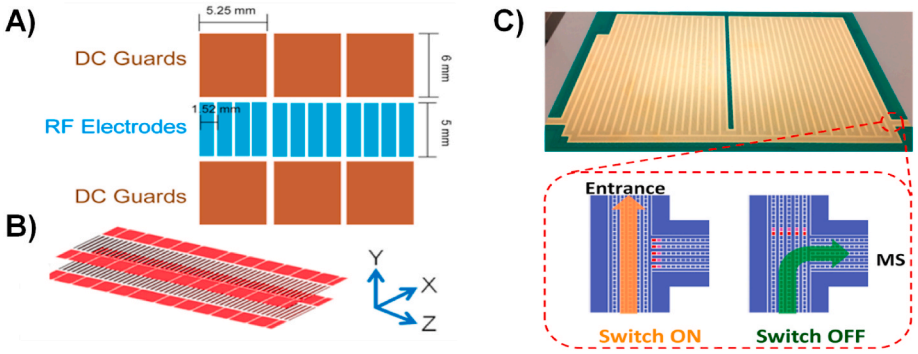

Fig. 4. SLIM electrodes; (A) design of the ion pathway, (B) stacking of plates to create a three-dimensional pathway and (C) extended routing design of 13.5 m in length with a switch that facilitates multiple ion passages through the device. Reprinted from Refs. [62,63], Copyright (2014,2019) with permission from ACS Publications and Elsevier, respectively.

enter the IMS. This impairs resolution and sensitivity. A solution to this was presented in non-commercial SLIM devices [62,81], where a sudden transition to a lower wave frequency is built into the drift region to accumulate ions between a lower number of waves: several waves will 'arrive' in the time that one low-frequency wave 'departs'. Subsequently, the frequency is gradually increased again. Such accumulation leads to narrower and higher peaks and even facilitates compression of larger initial ion packages, further enhancing sensitivity. Enhanced peak capacity in combination with LC was also demonstrated [56]. Moreover, more recently, an improved ion accumulation design was introduced non-commercially. After injection, ions are first accumulated in the SLIM−IMS behind a small region with a blocking voltage before being released in the separation region [82]. In this design, 98% of produced ions at the electrospray ionization source are injected and accumulated, leading to up to 625 times higher signal intensities. For multipass applications, ions are sent back directly to the beginning of the separation region; the accumulation region and blocking voltage are thus only used directly after injection. This shows the versatility of SLIM−IMS again.

A potential problem with high-resolution IMS such as cyclic IMS and SLIM is that conformations of molecules might change during >30 ms arrival times, as was demonstrated by trapping ions for a certain time in a quadrupole before analyzing their mobility [83]. Back then, this effect was attributed to differences in optimal conformation in solution and in the gas phase. However, recent more detailed investigations using SLIM [75] and cyclic IMS [84] concluded that conformational changes could be largely prevented in the first hundreds of milliseconds by preventing ion heating and collision-induced unfolding. Nevertheless, the possibility of small changes in CCS has to be taken into account for high arrival times.

2.3. CCS reproducibility

The incorporation of IMS in LC− or GC−MS workflows can be of great help for the characterization of complex samples with unknown chemical composition (non-targeted analysis) since it is not possible to determine the CCS of an unknown ion using stand-alone IMS. The combination of retention time and mass spectra is not always enough to distinguish a single compound, for example, in isomers with very small structural differences. IMS can add a dimension to this, such that the chance of incorrectly identifying a certain compound as another one significantly decreases. However, in non-targeted approaches, this is only possible if CCS values are highly reliable and reproducible between laboratories and preferentially also between IMS platforms. For instance, some experiments have been carried out for mycotoxins, and at the moment, a maximum relative error of 2% is used as a rule of thumb [85]. High reproducibility would allow molecule identification from CCS databases that contain experimentally obtained or predicted CCS values for large numbers of compounds. However, to date, CCSs are not yet accepted as an identification point for confirmatory analysis [86] despite many research groups have already started to build CCS databases, amongst others for drugs [87–89], contaminants [90], steroids [91], mycotoxins [92], pesticides [93,94] or a combination of them [95]. Several CCS databases can be found online, e.g. CCSbase (experimental and predicted) [96,97], unified CCS compendium (DTIMS only) [98] and the Bush lab CCS database [99–101].

Groups assessing inter-laboratory reproducibility have done so only for a single IMS platform. Stow et al. found good reproducibility for DTIMS of metabolites, lipids, peptides, and proteins, with average relative standard deviations of 0.29% for stepped field measurements and a relative bias of 0.54% comparing single field to stepped field [102]. For $^{TW}CCS_{N_2}$ of human and veterinary drugs, however, errors up to 5% were found between laboratories, although for most compounds, the difference was below 2% [88]. For steroids, relative standard deviations mostly below 1.5% were found using the same platform, also in a calf urine matrix [103]. As might be expected, generating a cross-laboratory database as a reference instead of a single-laboratory database improved overall deviations between measurements and reference values; some deviations were higher than 2%, but none were higher than 2.5%. Relative $^{TW}CCS_{N_2}$ standard deviations of mycotoxins were found to be mostly below 2% using different commercially available TWIMS systems, but values up to 5.5% were found [85]. Apparently, in some cases, the relative error between CCS values from different laboratories is still much larger than 2%, and the reproducibility between different platforms is likely worse. Causon and Hann estimated the uncertainties that are related to CCS determination in DTIMS as a result of variations in experimental input such as temperature, pressure, voltages, and physical constants and found that the uncertainty ranges between 2.7 and 4.6% for direct CCS calculation, and increases to 4.7–9.1% when performing calibration [104]. In TWIMS calibration for protein analysis, the CCS uncertainty through error propagation is 4–6%, two to three times higher than CCS standard deviations that are derived from replicate measurements [105]. These uncertainties explain why it is difficult to obtain high inter-laboratory reproducibility.

The reproducibility of CCS determination, therefore, needs to be improved. This can be done in several ways. First, instrumentation and instrument settings can be optimized to deliver accurate CCS values. Electric field strength, drift gas purity, temperature and pressure, and processing of unresolved fragment peaks were all found to influence ion mobility and moreover, ion optics before and behind the drift tube also influence the CCS values that will be found [106,107]. By taking these factors into account, CCS values can be determined up to 10 times more accurately. Morris et al. optimized instrument settings to deliver similar CCS values for different drift gases in DTIMS [108]. However, the order of compounds' mobilities was found to show some minor changes depending on the drift gas, so it seems unlikely that a complete CCS

reproducibility between drift gases can be achieved this way. Gabelica et al. introduced reporting standards to improve the exchangeability of CCS values between laboratories and platforms, including experimental prerequisites to deliver reproducible results [26]. They prescribe that the drift gas, temperature, and electric field over gas density ratio should be equal to compare CCS values. According to Hinnenkamp et al. solvent composition, solvent flow rate, desolvation temperature, and desolvation gas flow rate do not influence CCS values [109].

Second, CCS values will become more accurate by improving the calibration procedure usually performed for CCS determination via TWIMS and TIMS platforms because direct CCS calculation is difficult for these platforms. Since 2017 there have been several developments with regard to calibration. For example, the accuracy of calibrant mobility determination was improved, which allows calibration to become more accurate as well [107]. Haler et al. introduced a synthetic homopolymer-based calibration set with a single ionization moiety, such that all calibrants will behave inert and will be singly charged during IMS analysis [110]. This leads to vastly improved calibration curves and lower uncertainty in CCS determination. However, they discuss that the properties of a calibration set should always be chosen carefully to match relevant properties of the compounds of interest, such as their CCS over mass ratio. This was confirmed by Lim et al. (2019), as they found that IMS calibration for aromatic analytes could be improved by calibration with a set of aromatic compounds instead of polyalanine [111]. For TIMS, it turned out that calibration was already very accurate in comparison with DTIMS, with a relative error below 1% for 95% of the analyzed peptides [112]. In the same paper, a newly developed calibration procedure was presented that allows a single TIMS calibration for various instrument settings, compound classes or charge states, and possibly even various IMS platforms. Probably the most precise but most labor-intensive calibration procedure is directly coupling a DTIMS to the platform of interest, which was successfully performed for TIMS [113]. Calibration of TWIMS-based high-resolution IMS, however, poses a new challenge. Here, the accuracy of the calibration process is limited to DTIMS resolution, while the resolution of SLIM SUPER is an order of magnitude higher [114]. In many cases, a single DTIMS peak will even resolve into multiple peaks in SLIM SUPER, which hampers straightforward calibration. This problem still needs to be addressed. One should also consider that ion accumulation in SLIM applications can lead to CCS shifts due to Coulombic repulsion between ions in dense ion clouds [115].

The third strategy to improve the reproducibility of CCS determination is to improve the theoretical physics behind ion mobility, such that different platforms deliver the same, physically correctly calculated CCS without the need for calibration. This was successfully done at low TWIMS wave velocities with a set of protein ions, delivering an average relative error of only 0.3% for DTIMS [27]. Richardson et al. simplified the TWIMS waveform in their model and were able to identify two other important parameters for CCS determination: waveform anharmonicity and velocity relaxation [28]. Recently, the same group combined this strategy to improve CCS reproducibility with actual calibration. They used a calibration set spanning 3.5 orders of magnitude in ion size and incorporated the abovementioned theoretical insights in their calibration procedure [116]. This led to a generic calibration procedure where different calibration sets for different ion types seem unnecessary. However, this approach becomes significantly more difficult for meandering ion pathways as in SLIM.

2.4. CCS prediction

Besides experimentally obtaining accurate CCS data, research is also making progress in predicting CCS values. Reliable prediction of CCS values would be helpful in quickly generating large CCS databases. There are two general strategies for doing so: calculation and machine learning. Both strategies use so-called molecular descriptors, which are physical or chemical properties of a molecule or mathematical representations thereof, as the starting point for CCS prediction. Two recently described CCS calculation platforms, ISiCLE [117] and MOBCAL−MPI [118] are largely based on quantum chemistry and provide some significant improvements concerning the older MOBCAL (Mobility Calculation) platform. Both platforms use Boltzmann weighing of the most likely molecular conformations and improved computational speed compared with MOBCAL. Additionally, ISiCLE provides the possibility to process different adducts such as sodium and potassium. Its average relative CCS error was found to be 3.2%. MOBCAL−MPI uses van der Waals interactions between ions and the drift gas, in this case, nitrogen, resulting in a root mean square error of 2.3 and 2.6% in different experiments. Similarly, Graton et al. predicted 80% of steroids within a 2% deviation from the experimental CCS [119] using density functional theory to predict preferred ionization sites and adducts in order to subsequently estimate relevant conformers to calculate the CCS. Soper-Hopper et al. took a very different approach by calculating mathematical molecular descriptors from two-dimensional and three-dimensional structures and predicting CCS via linear multivariate regression [120]. They found that CCS prediction with 2D structures was at least as good as prediction with 3D structures, as median relative errors were all below 2% except for one of both 3D sets. The advantage of machine learning instead of CCS calculation is that no complicated physical-chemical theory is needed to predict CCS values. The computer can be fed with basic molecular descriptors such as simplified molecular line-entry system strings (SMILES). Plante et al. achieved a median relative CCS error of 2.7% with this strategy for many molecules [121]. However, other groups started to train algorithms based on physicochemical properties. Bijlsma et al. investigated 400 physicochemical molecular descriptors and trained an artificial neural network with the 8 most relevant ones, leading to median relative CCS errors of around 2%, although deviations up to 11% were found [122]. The introduction of molecular quantum numbers as molecular descriptors recently improved this result [97]. Moreover, unsupervised clustering to reduce structural diversity in each dataset further improved the performance of this algorithm, resulting in a median relative CCS error of 1.5%, with individual values up to 5%. A second very recent paper aimed to make CCS prediction by machine learning more generic: a standardization strategy was developed to overcome biases between labs and platforms, such that a broad and relatively smooth set of data could be used for algorithm training [123]. A ‘representative structure similarity’ was introduced to estimate the prediction accuracy for individual compounds. The median relative errors ranged from 1.66 to 2.25%, depending on compound classes. The authors expect their ‘All CCS’ platform to be further improved by introducing quantum chemistry to predict multiple relevant conformations.

The overall accuracy of CCS prediction is improving but not yet satisfying. Only a few groups could reach a median relative error just below 2%, but even then, a significant portion of individual compounds is still showing errors larger than 2%. Slightly better results are obtained experimentally, but reproducibility between IMS platforms is still a matter of concern. Moreover, physical differences in CCS might be caused by conformational changes during analysis, as we have seen earlier, depending on the platform and instrument settings. This problem has not yet been addressed in CCS calculations and predictions. For reliable non-targeted analysis in the future via all platforms, high confidence in databases is needed. Thus, both experimental CCS determination and CCS prediction need to become more accurate. As the resolution of IMS platforms steadily increases, the acceptable error of 2% moreover needs to decrease in the future, which demands an even larger improvement in CCS determination and prediction accuracy.

2.5. Other recent developments

Besides the aforementioned developments regarding resolution, sensitivity, CCS reproducibility and prediction, and the commercialization of high-resolution IMS platforms, a few other relevant

developments have emerged in recent years. One interesting development is the introduction of a dual DTIMS with separate drift tubes for positively and negatively charged ions [124]. This smart design improves response times and reaches a resolving power of 90.

A number of articles were recently published regarding portable IMS devices. The printed circuit board is currently becoming a popular choice to produce small and reproducible drift tubes [127,128] and even flexible drift tubes [129]. All three devices reach resolving powers >80. Commercially available portable IMS devices do already exist; they are typically used for rapid detection of chemical warfare agents, explosives, and narcotics [130], for example, at airports. However, they are not coupled to a mass spectrometer. Thus, not surprisingly, the biggest challenge in building portable IM−MS devices lies in building a portable mass spectrometer. In section 3.1 the applicability of portable, stand-alone IMS for food analysis will be discussed.

Besides, due to the need for quick and straightforward but reliable methods to reduce workload and increase high-throughput analysis, the number of direct ionization techniques is growing each year [131]. With direct ionization techniques, direct sampling and ionization of analytes from their native environment can be achieved, which is also easy to combine with portable devices for on-site analysis. Although direct ionization techniques can be based on different ionization principles (e.g. electrospray, plasma, laser), they have one thing in common: they lack selectivity. This is because the desorption/ionization of analytes from the sample is carried out simultaneously within a few seconds, and all arrive at the same time at the MS-inlet. So, in theory, combining a direct ionization technique with IM−MS would be highly beneficial due to the separation capabilities of IM−MS. Although there are numerous publications about direct ionization for food analysis, such as electrostatic field-induced tip-ESI [132], direct analysis in real-time (DART) [133,134], extractive electrospray ionization mass spectrometry (EESI−MS) [135], dipping probe electrospray ionization/mass spectrometry (dPESI−MS) [136], solid-phase microextraction (SPME) [137], atmospheric solid analysis probe (ASAP) [138] and paper spray (PS) [139], interestingly enough, none combines direct ionization and IM−MS. Combining direct ionization with IM−MS techniques will add selectivity and boost the applicability of both techniques.

Direct ionization techniques are also used when performing mass spectrometry imaging (MSI); therefore, ion mobility can be of added value for MSI as well. MSI involves direct desorption or extraction of analytes from a surface such as a section of biological tissue and simultaneous or subsequent ionization and injection into MS. By scanning the surface, spatial concentration differences of one or more compounds of interest can be depicted with a resolution depending on the desorption or extraction technique. Some common surface desorption and extraction techniques that have shown great potential in the field of food analysis [131] are depicted in Fig. 5 [140]. Matrix-assisted laser desorption ionization (MALDI) is a method that is traditionally combined with MS for the ionization of biomolecules while keeping them intact. A UV laser simultaneously evaporates and ionizes molecules from the surface with a spatial resolution of 5–200 μm. Desorption electrospray ionization (DESI) desorbs and ionizes surface analytes by subjecting them to an electrospray ionization (ESI) spray of charged solvent droplets, with spatial resolutions ranging between 15 μm (for nanoDESI) and 150 μm. In liquid microjunction surface sampling (LMJ−SSP), a probe leads a constant solvent stream over the surface and then back into the probe for subsequent ionization and analysis. Liquid extraction surface analysis (LESA) makes use of a similar principle, but in this case, after solvent contact with the surface, the probe is withdrawn, and the solvent with analytes is injected in the MS [141]. The spatial resolution of LMJ−SSP and LESA is relatively low, 0.5–1 mm [140]. In laser ablation electrospray ionization (LAESI), at last, a laser pulse is used to desorb analytes from the surface while ESI intercepts the resulting plume for ionization. Spatial resolutions range between 15 and 350 μm [142].

Incorporating IMS in MSI workflows improves the identification and localization of compounds of interest [140,143]. At the same time, sensitivity can improve as a result of reduced chemical noise, but a decrease in sensitivity because of ion loss is possible as well, especially in the case of MS platforms that already suffer from low ion transmissionIM−MSI could be used to determine how compounds of interest or their metabolites are distributed in animal or plant tissues. This would provide a better understanding of which sampling and analysis strategies are relevant for different applications. As well, rapid imaging and identification of micro-organisms on food surfaces would be a possibility. However, only one paper has been published that reports on the application of IM−MS imaging for food safety or authenticity purposes. Claude et al. used DESI−TWIMS−MSI to image thin layer chromatography plates on which ecdysteroids from plants were pre-separated [144]. This interesting approach combines basic chromatography with rapid, sensitive, and high-resolution detection methods.

3. Applications in food safety and authenticity

The main developments and commercialization of IMS in recent years have increased its use in several areas such as clinical [157–159], pharmaceutical [160–162], environmental [163,164], and food analysis [6,165]. In food analysis, IMS can, on the one hand, provide quick, handheld screening and fingerprinting methods. On the other hand, it can increase the throughput, sensitivity, and resolving power of existing LC−MS and GC−MS methods. Thereby, the use of this technology is growing while increasing the number of available IMS-based methods, especially in the food safety and authentication field. To the best of our knowledge, few reviews have been published on these topics, and they are mainly focused on the determination of residues and contaminants [5,22,23]. Hence, this section aims to provide an overview of the recent potential application of IMS regarding the analysis of additives, allergens, biological and chemical contaminants, natural toxins, pesticides and veterinary drugs as well as authenticity approaches in food samples. Thereby, Table 1 summarizes recent publications (2017–2021) regarding the application of IMS for food safety and food authenticity purposes.

The aforementioned applications mainly aim at the identification/determination of specific compounds based on targeted analysis. Most of these targeted methods have introduced IMS as a new dimension for separation in traditional routine methods such as LC−MS and GC−MS. Nevertheless, IMS has also been applied to on-site analysis or mapping techniques such as imaging to improve selectivity and reduce the

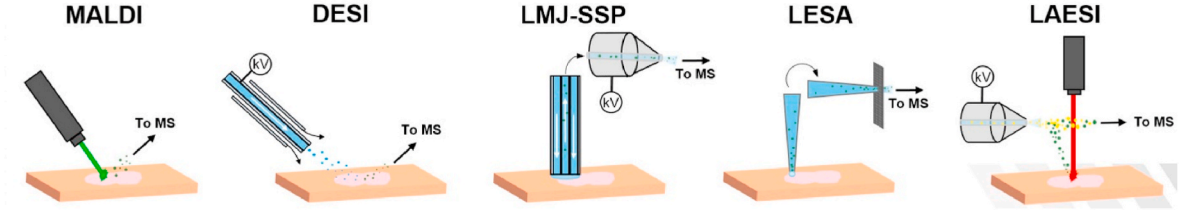

Fig. 5. Desorption-ionization and extraction-ionization techniques for MSI and IM−MSI. Reprinted and modified from Ref. [140]. Copyright (2019), with permission from Elsevier.

Table 1
Ion mobility spectrometry application in food safety and authenticity. (Publications from 2017 to 2021).

Application	Analyte	Matrix	Sample treatment	Ionization source	Ion mobility spectrometry	LODs	Data processing	Ref.
Additives								
	Sudan dyes	Tomato sauce and hot-pot seasoning	SPME	CD	DTIMS	0.005–0.25 μg g^{-1}	–	[166]
Allergens								
	Immunogenic and allergenic peptides	Wheat flour	SLE	nanoESI	LC-Q-TWIMS-TOF	–	Triticum aestivum database	[167]
Authenticity								
	VOC	Olive oil	–	^{3}H	HS-GC-DTIMS	–	PCA-LDA-kNN	[168]
	VOC	Olive oil	–	[a]#	HS-UV-DTIMS	–	PCA-LDA-kNN and PLS	[169]
	VOC	Olive oil	–	^{3}H	HS-GC-DTIMS	–	PCA-LDA-kNN	[170]
	VOC	Palm oil	–	^{3}H	HS-GC-DTIMS	–	–	[171]
	VOC, Fatty acids	Peanut oil	–	[a]#	HS-GC-DTIMS	–	PCA, CA	[172]
	VOC	Canola oil	–	^{3}H	GC-DTIMS	–	HOG-MPCA-CDA	[173]
	VOC	Patin fish oil	SLE	^{3}H	HS-GC-DTIMS	–	LDA, PLS	[174]
	VOC	Honey	–	He	HS-GC-DTIMS	–	PCA, PLS-DA	[175]
	VOC	Honey	–	^{3}H	HS-GC-DTIMS	–	LDA, HCA, PLS	[176]
	VOC	Honey	–	^{3}H	HS-GC-DTIMS	–	PCA-LDA-kNN	[177]
	Trisaccharides	Honey	SLE, Dilution	ESI	TIMS-TOF	–	PCA	[178]
	α-Dicarbonyl	Honey	SLE, Derivatization	ESI	LC-DTIMS-QTOF	–	PCA	[179]
	VOC	Honey	–	^{3}H	HS-GC-DTIMS	–	PCA, HCA, LDA	[180]
	VOC	Iberian ham	Puncture with a needle	^{3}H	GC-DTIMS	–	OPLS-DA	[181]
	VOC	Iberian ham	–	^{3}H	HS-GC-DTIMS	–	PCA-LDA-kNN and OPLS-DA	[182]
	VOC	Rice	–	^{3}H	HS-GC-DTIMS	–	Dynamic PCA	[183]
	Phenolic compounds	Red wine	Dilution	ESI	LC-DTIMS-TOF	–	–	[184]
Biological contaminants								
	VOC	Silver carp	Cut, SLE, HS	[a]#	GC-DTIMS	–	ANOVA	[185]
	mVOC of funghi	Barley	SPME	CD	GC-IMS	0.5–3 μmol L^{-1}	–	[186]
	Aspergillus fungus	Milled rice	SLE	^{3}H	GC-DTIMS	0.271–0.629 log (CFU g^{-1})	PCA, kNN	[187]
Chemical contaminants								
	Acrylamide	Potato food	HS-SPME	CD	DTIMS	4 ng g^{-1}	–	[188]
	Ethoxyquin transformation products	Salmon	SLE	ESI	LC-TWIMS-QTOF	–	CCS Database	[189]
	Ethoxyquin transformation products	Salmon	SLE	ESI	LC-TWIMS-QTOF	–	–	[190]
	PFASs	Water	–	nanoESI	DMS-LTQ-Orbitrap	–	–	[191]
	PFASs	Water	–	ESI	DMS-LTQ-Orbitrap	–	CCS Database	[192]
	NIAS	Food simulants	SLE	ESI	LC-TWIMS-QTOF	0.01–0.1 mg kg^{-1}	–	[106]
	NIAS	Food simulants	SLE	ESI	LC-TWIMS-QTOF	0.001–0.006 mg kg^{-1}	–	[193]
Natural toxins								
	Mycotoxins	Cereals	SLE	ESI	LC-TWIMS-QTOF	–	CCS Database	[92]
	Saponins	Horse chestnut	SLE	ESI	LC-TWIMS-QTOF cIMS-TOF	–	–	[194]
Pesticides								
	Pesticides	Salmon feed	SLE	ESI	LC-TWIMS-QTOF	≤0.05 mg kg^{-1}	CCS Database	[195]
	Pesticides	Cucumber, apple, cherry tomato	QuEChERS		DTIMS	0.03–3 μg kg^{-1}	–	[196]
	Pesticides	Plant-derived food	QuEChERS	ESI	LC-TWIMS-QTOF	0.001–0.1 mg kg^{-1}	CCS Database	[93]
	Pesticides	Plant-derived food	SLE	ESI	LC-TWIMS-QTOF	≤0.01 mg kg^{-1}	In house library, CCS Database	[94]
	Pesticides and their metabolites	*Brassica* species	SLE	ESI	LC-TWIMS-QTOF	0.001–0.1 mg kg^{-1}	In house library	[197]
	Organophosphorus pesticides	Water	UA-DSPE	CD	HS-GC-DTIMS	–	PCA, PLS-DA	[198]
	Organophosphorus pesticides	Water, cucumber, apple	halloysite nanotube extraction + SPME	CD	GC-DTIMS	0.01–0.5 μg L^{-1}	–	[199]
	Organophosphorus pesticides	Water and vegetables	Magnetic DSPME	CD	GC-DTIMS	0.46–1 μg L^{-1}	–	[200]
	Organophosphorus pesticides	Chinese cabbage	SLE	Kr lamp (10.6 eV)	PP-IMS	0.2–0.6 mg L^{-1}	–	[53]
	Diazinon	Water and apple	Stir-bar sorptive extraction	CD	DTIMS	1.5 μg L^{-1} and 7.5 μg kg^{-1}	–	[201]

(*continued on next page*)

Table 1 (*continued*)

Application	Analyte	Matrix	Sample treatment	Ionization source	Ion mobility spectrometry	LODs	Data processing	Ref.
	Diazinon and phosalone	Pistachio	SLE, LLE	CD	DTIMS	0.1 and 0.5 mg L^{-1}	–	[202]
	Chlorpyrifos	Pistachio oil	QuEChERS	CD	DTMS	0.1 μg g^{-1}	–	[203]
	Malathion and chlorpyrifos	Water, food and serum	Nanofiber extraction SPME	CD	GC-DTIMS	0.019 and 0.032 μg L^{-1}	–	[204]
	Ethion and chlorpyrifos	Water and bell pepper	LPME	SESI	DTIMS	0.09 and 0.21 μg L^{-1}	–	[205]
	Acetamiprid	Pistachio	QuEChERS	CD	DTIMS	0.5 μg g^{-1}	–	[206]
	Imidacloprid	Chili and tomato plants	MIP extraction	^{63}Ni	DTIMS	0.03 μg g^{-1}	–	[207]
	Thiabendazole	Fruit juice	Electromembrane extraction	CD	IMS	0.9 ng mL^{-1}	–	[208]
	Glyphosate	Drinking water	–	CD	HS-IMS	10 μg L^{-1}	–	[209]
	Propoxur	Water	Molecular-imprinted graphite extraction	CD	DTIMS	0.3 ng mL^{-1}	–	[210]
Veterinary drugs								
	Veterinary drugs	Fish and bovine liver	SLE	ESI	LC-TWIMS-QTOF	–	–	[211]
	Veterinary drugs	Bovine urine	Dilution	ESI	LC-TWIMS-QTOF	–	CCS Database	[88]
	Veterinary drugs	Porcine urine	QuEChERS	ESI	LC-DTIMS-QTOF	–	CCS Database	[89]
	Antibiotics	Sausage	LLE-DLLME	CD	DTIMS	1.52–2.73 ng g^{-1}	–	[212]
	Antibiotics	Bovine liver and hamburger	LLE-DLLME	CD	DTIMS	1.7–2.8 ng g^{-1}	–	[213]
	Steroids	American eel	SLE	ESI	LC-DMS-QqQ	72 pg g^{-1}	–	[214]
	Steroids	Bovine urine	Dilution	ESI	LC-TWIMS-QTOF	–	–	[215]
	Non-steroidal SARMs	Bovine urine	LLE	ESI	(SFC)-Q-TWIMS-TOF	<0.05 ng mL^{-1}	–	[216]
	Nandrolone	Calf urine	–	ESI	LC-TWIMS-QTOF	–	CCS Database	[91]
	Clenbuterol	Bovine urine	MIP-DLLME	^{63}Ni	DTIMS	2 μg L^{-1}	–	[217]
	Fluoroquinolones	Porcine muscle	SLE	ESI	LC-TWIMS-QTOF cIMS-TOF	–	CCS Database	[218]
	Ecdysteroids	Plant tissue	–	DESI	TLC/DESI-TWIMS-QTOF DESI-MSI	–	–	[144]
	Diclofenac and metabolites	Edible plants	SLE	ESI	LC-DTIMS-QTOF	–	–	[219]

[a] #, no specified; CA, Cluster Analysis; CD, Corona discharge; CDA, Canonical Discriminant Analysis; cIMS, cyclyc Ion Mobility Spectrometry; ESI, Electrospray ionization; HCA, Hierarchical Cluster Analysis; HOG, Histogram of Oriented Gradient; HS, Headspace; kNN, k-Nearest Neighbors; LDA, Linear Discriminant Analysis; LPME, Liquid-phase microextraction; MIP, Molecularly Imprinted Polymers; MPCA, Multiway Principal Component Analysis; mVOC, microbrial Volatile Organic Compounds; NIAS, Non Intentionally Added Substances; PCA, Principal Component Analysis; PFASs, Per/Polyfluoroalkyl; PP, Positive Photoionization; SARMs, Selective Androgen Receptor Modulators; SFC, Supercritical Fluid Chromatography; UA-DSPE, Ultrasound-Assisted Dispersive Solid-Phase Extraction; VOC, Volatile Organic Compounds.

complexity of data treatment quickly. For instance, combining IM−MS with direct ionization techniques for on-site analysis, which are believed to have enormous potential [220], could add the necessary selectivity for on-site MS measurements. It is expected that portable MS capable of doing so will significantly change working routines of food inspectors and other stakeholders. Also the fingerprinting approach shows great potential for food authentication. Moreover, increasing the use of non-targeted methods is also observed to enhance the performance of routine laboratories as well as the identification of new compounds that might pose a food safety risk.

3.1. Stand-alone IMS: on-site screening and fingerprinting

Because IMS is very fast and portable equipment is available, it is a very suitable detection method for on-site screening purposes. Rapid on-site screening would drastically increase the throughput of monitoring food safety while decreasing the costs of a single analysis. However, suitable IMS equipment alone is not enough for most matrices to perform on-site screening since simple sampling and extraction methods are necessary. To improve the selectivity of the screening method and prevent the generation of many suspected samples, additional equipment such as GC or MS would be helpful. Portable GC−IMS devices do exist, as well as portable GC−MS, which theoretically clears the way to portable GC−IM−MS, but until today no portable GC−IM−MS is described in the literature, so we focus on portable stand-alone (GC−) IMS. Many papers have been published on existing and new sampling and extraction methods for IMS or GC−IMS in the past years. Some new methods are very elegant but not yet very practical. For instance, Saei et al. synthesized a water-immiscible deep eutectic solvent with a melting point near room temperature for the extraction and concentration of antibiotics from meat products [212,213]. By placing the mixture on ice, the solvent solidifies, allowing easy isolation. However, like conventional extraction methods, the whole procedure is still elaborate and involves organic solvents; it thus needs considerable adjustments to be applied on-site. A few other methods seem suitable for concentrating compounds of interest, which is beneficial in combination with portable equipment that lacks high sensitivity and high resolution. However, at the same time, these extraction methods are still too complex for on-site application. Examples are molecular-imprinted polymer extraction [207,217], mesoporous nanosorbent extraction [198], supported liquid extraction with a solvent-holding aerogel [205] and magnetic extraction with porous magnetized carbon sheet nanocomposites that can be catched onto a stir bar for easy isolation [200].

More efficient methods apply adsorption onto a material suitable for direct injection in IMS or GC−IMS equipment. For analysis of water samples, this is relatively straightforward. For example, Zargar et al.

immersed a preconditioned cellulose paper with an immobilized aptamer in codeine and acetamiprid samples for 30 min, after which the paper could be used for direct DTIMS injection via paper spray ionization [221]. The authors used a similar procedure for extracting propoxur with molecular-imprinted graphite blades for graphite spray ionization [210]. In contrast, Pourmand et al. still applied grinding and sonication of potato products in methanol before adsorbing samples containing acrylamide onto a solid-phase microextraction fiber, followed by direct DTIMS injection [188]. Such sample preparation steps are not very suitable for on-site application. Saraji et al. [199] and Jafari et al. [204] made use of a water bath and centrifuge to prepare fruit samples before performing solid-phase microextraction (SPME) of pesticides on a nanoparticle-modified SPME fiber and direct insertion of the fiber into the injection port for GC−DTIMS. Simultaneously, Jafari et al. reported stir bar extraction of diazinon. Via diazinon absorption into a thermal desorption coating on a stir bar during sample preparation, the centrifugation step could be skipped [201]. The stir bar was subsequently transferred to a specially designed thermal desorption unit on a DTIMS apparatus for easy injection. The thermal desorption unit can also be coupled to GC−IMS.

Few publications already describe the on-site application of IMS or claim that on-site application is possible. Zou et al. used swab sticks to sample pesticides on surfaces [196]. Before analysis by DTIMS, the swabs are vortexed in acetonitrile for a few minutes, and subsequently, the acetonitrile extract is filtered. Son and Choi claim that their method can be used for on-site polyaromatic hydrocarbon detection via DTIMS, but they use halogenated solvents for extraction, which is not convenient for environmental and health reasons [33]. Sun et al. developed a polydopamine coating on nickel foam with a large surface area to extract Sudan dyes from tomato sauce and hot-pot seasoning in a water bath [166]. Subsequently, the Sudan dyes are eluted from the foam with only 200 μl acetonitrile for DTIMS analysis. The same group developed a pipette-tip solid-phase extraction for DTIMS screening for benzodiazepines in supplements [222], which provides a very easy extraction method. However, it should be taken into account that supplements are a relatively non-complex matrix and that sample preparation was still time-consuming. Erler et al. performed a 1-h on-site extraction of volatiles from barley for fungus detection via fingerprinting [186]. Volatiles were captured on an SPME fiber at elevated temperature for direct injection into a GC−IMS apparatus. Only Jiang et al. performed a truly fast on-site analysis method by directly injecting sesame oil in a portable DTIMS device for fingerprinting [223]. However, this approach is only suitable for a small number of matrices and purposes. Thus, before on-site screening via IMS is efficient, more developments are necessary.

As we have seen earlier in this section, IMS methods can be used to detect pathogens via fingerprinting. Several groups have already done this: the presence of biological contaminants, such as bacteria or fungi, can be detected by GC−IMS fingerprinting of volatile organic compounds (VOCs) that are excreted from infected food [185–187]. Taylor et al. demonstrated that Listeria bacteria could be differentiated via GC−DTIMS fingerprinting methods, which also could be of interest for food safety applications [224]. Besides, IMS fingerprinting is also widely explored to determine food authenticity, with satisfactory results. In most cases, it is performed with headspace-GC−IMS to generate a two-dimensional fingerprint where volatiles are plotted depending on their retention time and ion mobility. Subsequently, chemometric methods such as principal component analysis (PCA) are used to classify samples based on their authenticity. In some cases, a small number of markers are then identified for future authenticity analysis [170,175,182,184].

Most stand-alone IMS fingerprinting publications in food authenticity are on edible oils, such as olive oil [168–170,225], palm oil [171], and sesame oil [223]. Gerhardt et al. reported that GC−DTIMS is a fast, robust, and inexpensive method for determining olive oil origin, with a high separation power [168]. Tian et al. detected adulteration of peanut oil with as little as 1% of canola oil by GC−DTIMS [172]. Quantification of the amount of added adulterant was demonstrated in canola oil [173], olive oil [169] and patin fish oil [174]. The same can be done for honey [176], a popular matrix for authenticity determination by IMS. While Gerhardt et al.) [177], Wang et al. [175], and Przybylski and Bonnet [178] used IMS to identify the floral origin of honey, Aliaño-González et al. [176,180] used it to detect adulteration with additives such as high fructose corn syrup. Besides oils and honey, IMS was used to classify Iberian ham for pig feed and breed [181,182], to identify rice variants and adulteration [183] and to classify raw-milk cheese [226], although for the latter no satisfying distinction between cheese types was obtained.

3.2. IM−MS: high throughput, high resolving power

One of the promises of IMS is the possibility to perform high-throughput, non-targeted analysis in combination with LC− or GC−MS, especially using high-resolution MS (HRMS) such as TOF. The exceptionally high peak capacity of LC− or GC−IM−HRMS methods allows the generic pre-processing of food and food-related matrices as well as the simultaneous analysis of almost all components present in the extract. This approach also permits retrospective analysis. Hernández-Mesa et al. showed that almost no matrix effect is visible for veterinary drugs in urine when analyzed via LC−TWIMS−QTOF, which underlines the possibility of effectively separating matrix and interest compounds in such workflows [215]. Xu et al. used a generic Quick, Easy, Cheap, Effective, Rugged, and Safe (QuEChERS) extraction method to analyze 250 veterinary drugs in urine by LC−DTIMS−QTOF [89]. The authors found improved sensitivity and fewer false positives after data processing compared with LC−QTOF. QuEChERS is also an approved extraction method for pesticides in plant-based food [227] and was used to prepare scallion and celery with pesticides for high-throughput LC−DTIMS−QTOF analysis [228]. Bauer et al. analyzed pesticides in plant-based food with QuEChERS and LC-TWIMS-QTOF [93], but in contrast to Xu et al. found a decrease in sensitivity. The detection rate according to European SANTE criteria could not be improved, unless the criterium of detecting one fragment ion was dropped, which shows how important it is that CCS will be accepted as an identification point. Also Kaufmann et al. found that the number of false positives decreases upon incorporation of IMS, but the number of missed detects might increase at the same time, at least for IMS platforms with a resolving power up to 50 [229]. Nevertheless, the same group used the clean LC−TWIMS−QTOF spectra for suspect identification of veterinary drugs in fish and bovine liver via screening of computationally determined fragments [211]. Of 98 added veterinary drugs, 94 were detected by the software. If this approach becomes more reliable in the future, it can be used for screening without the need for reference standards. As discussed earlier, reproducible CCS determination or reliable CCS prediction is one of the critical elements in non-targeted analysis.

The increased peak capacity by incorporating IMS allows for separating highly similar compounds, such as allergens or per- and polyfluoroalkyl substances (PFAS). Alves et al. were able to produce the most comprehensive overview of immunogenic compounds in wheat flours at the time by incorporating TWIMS in their analysis [167]. Ahmed et al. [191] and Dodds et al. [192] reported PFAS analysis via DMS−LTQ−Orbitrap and LC−DTIMS−QTOF, respectively, and showed that IMS incorporation in the workflow facilitates the identification of a larger number of compounds while the analysis time can be significantly reduced.

Metabolites of active substances, or impurities that arise during the production of compounds of interest, are often found in food or food-related matrices. In many cases, such metabolites or impurities can be isomers of each other or the active compound, or two active substances can be isomers of each other. Because such isomers typically have very few structural differences, retention times will often be similar, and separation via LC−MS or GC−MS is not possible in some cases, which sometimes leads to incorrect identification during food safety routine

analysis. Incorporating IMS in routine analysis, particularly high-resolution IMS, could potentially reduce the risk of such incorrect results. Diastereoisomeric steroids [91], environmental pollutants [90] and diclofenac acyl glucuronides [230] are examples of compounds that were shown to have different CCS values. Some compounds can form protomers that can be separately detected via IM–MS, which, importantly, provides another identification possibility. This was shown for fluoroquinolones by McCullagh et al. [218]. Moreover, IM−MS can be used to identify metabolites or other transformation products that cannot be identified with other methods. Examples of such compounds identified by IMS are ethoxyquin transformation products in fish feed [189,190], pesticide metabolites in Brassica species [197], boldenone metabolites in urine [215], mycotoxin glucuronides [231] and drug metabolites [232] produced by human liver microsomes, and diclofenac metabolites in plants [219]. This, in turn, could result in new ways to demonstrate the presence or unauthorized use of certain substances.

Finally, IM−MS methods have also sometimes been used for fingerprinting purposes. IM−MS fingerprinting is more expensive than standalone (GC−)IMS, butit is much more powerful since almost any compound can be detected whereas with (GC−)IMS fingerprinting up to now most studies were almost exclusively performed for VOCs (section 3.1). As well, the selectivity becomes much higher when MS is incorporated in the analysis. Yan et al. [179] used LC−DTIMS−QTOF fingerprinting to detect honey adulteration with high fructose corn syrup. Causon et al. used LC−DTIMS−QTOF for red wine fingerprinting to separate the large number of phenolic compounds found in wine and were able to identify markers for each grape variety that they investigated [184].

4. Conclusion and perspectives

Ion mobility spectrometry is a rapidly developing technology that separates molecules by their gas-phase dimensions in ionized form. Incorporating IMS as an extra separation dimension improves peak capacity and reduces matrix effects in complex food samples. IMS can be used as a stand-alone detector, coupled to an MS for MSI workflows, or coupled to a GC- or LC-MS.

IMS approaches that are not coupled to MS seem to be rather mature compared to IM-MS applications and can be readily implemented in laboratories. Direct IMS mostly relies on fingerprinting purposes for food authentication, permitted to improve the characterization of several food products such as edible oils and honey, achieving a complete fingerprint and enabling the identification of biomarkers. The use of stand-alone IMS for food analysis purposes is relatively cheap compared to IM-MS.

When IMS is coupled to an MS, the CCS value can be obtained from the drift time, which can be used for compound identification in addition to the retention index and mass spectra. In this context, the development of publicly available CCS databases and the calculation of the CCS are essential. By incorporating this information, emerging (unknown) compounds can be identified, and the effectiveness of food safety control can be increased. However, the equipment to perform this type of analysis is expensive, CCS databases are not complete, and the CCS calculations need to be further improved. As well, CCS still has to be accepted as an identification point to effectively implement it in routine analysis. This is still a point of discussion for example in the European Union.

IMS has already demonstrated its potential in improving selectivity and thereby reducing data complexity. For LC and GC-MS, peaks can be more easily detected due to spectral clean-up whereby interfering compounds are filtered out. Also, the added selectivity can be especially beneficial for coupling with imaging MS. However, one should take into account that the likelihood of missing detects can increase as a result of IMS hyphenation. Nevertheless we believe there is also an enormous potential for coupling of IM-MS with direct ionization techniques; however, examples in literature are lacking. Another area in which the added selectivity can be beneficial is for on-site analysis. At the moment, lack of portable MS equipment is limiting on-site screening methods. Sample preparation and extraction need to be optimized rather than available IMS methods themselves since, for many applications, IMS can be directly implemented with equipment that is already commercially available.

Besides, as can be observed by the present review, the sensitivity and resolving power in IMS platforms are still remarkably increasing. New high resolving IMS techniques, cyclic IMS and SLIM, recently became commercially available. With these IMS techniques, in-depth insight in food samples can be obtained which will help to identify new food safety-related compounds. Although IMS is an old technique, the application of IMS in the food safety and authenticity field still needs to be explored to a large extent. But with new high resolving IMS techniques, improved software and databases, and coupling with (onsite) direct ionization, there are numerous food applications that will benefit from IMS.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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