Analytica Chimica Acta 703 (2011) 114–123

Contents lists available at ScienceDirect

Analytica Chimica Acta

journal homepage: www.elsevier.com/locate/aca

Review

A review of recent, unconventional applications of ion mobility spectrometry (IMS)

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ARTICLE INFO

Article history:
Received 6 June 2011
Received in revised form 12 July 2011
Accepted 14 July 2011
Available online 23 July 2011

Keywords:
Ion mobility spectrometry
Pharmaceuticals
Food analysis
Environmental analysis
Clinical analysis
Process control

ABSTRACT

The applications of ion mobility spectrometry (IMS) have grown exponentially beyond its uses for explosive, illicit drug and chemical warfare agent monitoring in recent years. Instrumental developments including new drift tube materials and ionization sources have enabled the manufacturing of more sophisticated and affordable IMS equipment for the advantageous analysis of samples with no pretreatment. The most recent applications of IMS include quality control and cleaning validation procedures in the pharmaceutical industry; determinations of contaminants in food samples; clinical analyses of biological fluids; environmental analyses of contaminants in gaseous, liquid and solid samples; and (bio)process quality control monitoring. Coupling IMS with MS^n has enabled the analysis of very complex samples and the extraction of knowledge unavailable from isolated MS measurements, especially in the polymer and petroleomic industries.

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Dr. Blanco is Full Professor of the Applied Chemometrics Research group at the Universitat Autònoma de Barcelona. He is working in close collaboration with chemical and pharmaceutical industries for more than 25 years. He authored over 200 peer reviewed publications, including more than 90 devoted to near infrared spectroscopy and its applications. His main research fields are focused on the implementation of process analytical technology (PAT) and quality by design (QbD) in the pharmaceutical industry and the development of new analytical methods based on the use of vibrational spectroscopy techniques (NIR, Raman, IMS) combined with multivariate data analysis methods.

1. Introduction

Ion mobility spectrometry (IMS) an analytical technique for the determination of volatile and semivolatile compounds based on the gas-phase separation of the resulting ions under a weak electric field at ambient pressure reached its maturity between the late XX century and early XXI century [1]. Since then, IMS has been primarily used for the analysis of explosives, illicit drugs and chemical warfare agents with dedicated commercially available equipment. However, the analytical potential of IMS, particularly as regards operational speed and sensitivity, has extended its scope to the pharmaceutical, food and feed, clinical, polymer, petrochemical and environmental industries.

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doi:10.1016/j.aca.2011.07.021

The principle behind IMS is the separation of ionized analytes through a drift tube according to mass, charge, size and shape. The drift velocity, characteristic of each analyte, is proportional to the electric field strength and analyte mobility constant (K). Mobility values, which are usually normalized to standard environmental pressure and temperature conditions in the form of reduced mobility constants (K_0), are proportional to the time specific ions take to reach the detector, i.e. to drift times (t_d) [2]. Alternative ion mobility techniques such as differential mobility spectrometry (DMS) and field-asymmetric wavelength IMS (FAIMS) also exist the applications of which were recently reviewed [3] and are beyond the scope of this paper. Rather, the primary aim of this paper is to review the most recent contributions of IMS in the pharmaceutical, food and feed, clinical, environmental and process and bioprocess monitoring fields, with special emphasis on its advantages and shortcomings, and also on effective approaches to overcoming the latter.

2. IMS hardware development

2.1. Commercial and custom-made IMS equipment

The wide range of commercial IMS instruments currently available use a variety of sample introduction systems (direct air sampling, membrane extraction, GC injection, thermal desorption), ionization sources and drift tube lengths to provide specific solutions to particular problems. One advantage of IMS is that its closed design facilitates operation by unskilled workers. However, this can be a disadvantage for academic researchers seeking more advanced features and properties. In a product review article published in 2003 in Analytical Chemistry, K. Cottingham stated that "academic researchers are still not lining up in droves to purchase commercial machines" [4]. The literature scan performed to prepare this paper revealed that only 40% of the instruments used in IMS applications are commercially available, the remainder being custom-built by research laboratories and institutions. This can probably be ascribed to the impact of the paper by Cottingham, where H.H. Hill stated that some analytical features of custom-built instruments (e.g. resolving power) are frequently better than those of their commercial counterparts.

The following sections discuss the main advances in the development of ionization sources and drift tubes, two central components for IMS.

2.2. Ionization sources

The ionization source of an IMS instrument dictates to a great extent its performance. The most widely used ionization source for IMS, especially in commercial devices, is based on nickel (^{63}Ni), which makes it straightforward, stable and durable. However, various radioactive (^{241}Am, ^{3}H) and nonradioactive sources based on corona discharge, photoionization, laser and electrospray ionization have also been commonly used with IMS. Their main advantages and limitations are described elsewhere [5].

The ionization of analytes in different physical states under ambient conditions for analysis by mass spectrometry (MS), known as "ambient ionization MS", has become a fruitful research area affording significant advantages such as the fast analysis of samples with no prior preparation [6]. The main difficulty in adapting ambient desorption ionization sources for use in IMS spectrometers arises from the need to transfer ambient-generated ions against the uphill electric field at the instrument input while ensuring operator safety during the ionization operation. Overcoming this problem would open up new avenues for the development of a new generation of portable instruments for in-field measurements with no vacuum requirements.

A "nearly" ambient ionization technique named "secondary ESI" (SESI) was developed in 1994 [7]. SESI relies on the gas phase interaction between charged particles created by ESI and neutral gaseous molecules from gases or sample vapor. This is probably the precursor of other IMS ambient ionization methods successfully used to analyze compounds directly with no sample treatment such as desorption electrospray ionization (DESI) [8,9], direct analysis in real time (DART) [10], matrix-assisted laser desorption/ionization (MALDI) [11], atmospheric-pressure solid analysis probe (ASAP) [12], distributed plasma ionization source (DPIS) [13], low temperature plasma (LTP) [14] and direct current glow discharge (DCGD) [15].

Recently, nonradioactive pulsed electron sources have proved effective as IMS ionization sources. The concept is based on the production, within an electrical discharge tube, of electrons passing through a thin film of aluminum foil or a silicon nitride membrane [16]. Because electrons are not produced in a continuous manner, a delay time between ion formation and extraction can be easily inserted which allows ions to recombine before the extraction process and introduces a new variable (viz. the recombination time, which is typical of each analyte) to separate ionic species.

A novel bipolar UV radiation ionization source capable of efficiently operating as a negative ionization source while retaining its usefulness as a positive ionization source [17] uses UV light for soft ionization to obtain positive molecular ions. The core of the bipolar source for the negative ion mode relies on the ejection of electrons from a metal surface by UV radiation and their capture by electronegative compounds to form negative ions.

2.3. Drift tube materials

Drift tubes in commercially available IMS spectrometers consist of stacked ceramic or metal focusing rings containing alternating electrodes and insulators, the electrodes being connected by a resistor chain. These tubes are cumbersome and expensive to construct owing to the precision required in the manufacturing of components and the labor-intensive assembly of pieces. A number of materials have therefore been assessed as replacements for the ceramic and metal ring components. Thus, in 2006 Laprade patented the idea of constructing a drift chamber with one or more single-piece conductive glass tubes [18] where the inner surface of each tube was rendered electrically conductive by thermal or chemical treatment. Laprade's idea was converted into a prototype by Kwasnik et al. [19]. The main advantages of resistive-glass drift tubes over conventional tubes are as follows: (a) radial inhomogeneity in the electric field is minimized and the separation power theoretically increased as a result; (b) tubes are easier to construct; and (c) the need for periodic cleaning and maintenance is reduced [20].

Polymer materials such as zeonex encapsulated carbon-loaded nylon [21] have also proved useful for constructing drift tubes. Also, a planar IMS instrument was constructed by assembling two printed wiring boards with nine evenly spaced drift plates [22], which substantially reduced the cost of obtaining drift tubes with no ion losses or band broadening.

3. Applications of IMS

Ever since its development, IMS has been used for a wide variety of analytical purposes including the detection of explosives, illegal drugs and chemical warfare agents; environmental monitoring; process quality control; and biomedical and clinical determinations. The detection of narcotics and other illicit drugs, explosives

and chemical warfare agents is no doubt principal use of IMS and has been the subject of a number of state-of-the-art reviews [23–27], so it is not dealt with here.

3.1. Pharmaceutical applications: quality assurance (QA) and quality control (QC)

The low detection limits provided by IMS and its ability to ionize analytes under atmospheric pressure are two of its greatest advantages. Its ability to effectively detect and quantify amounts of sample smaller than a nanogram in a fast, accurate, precise manner makses it the most suitable choice for cleaning pharmaceutical processing equipment (see Table 1). Good manufacturing practices recommend avoiding cross-contamination between two consecutive production batches. After each instrument used during a manufacturing process has been cleaned, appropriate analytical methods are used to check that any traces of pharmaceutical components or residual detergents remaining are present at levels below the allowed limits.

IMS has been successfully used for cleaning validation purposes via the direct analysis of sampling swabs [28]. This affords the determination of smaller amounts of trace analytes as no prior dissolution of the sample is required. The key is to modify the operation conditions in order to insert the swabs into the IMS desorber.

Direct swab analysis was used in combination with rinse solution analysis [29]. The specific intermediate of a synthetic process and the two active ingredients obtained from the reaction concerned were analyzed by IMS. The manufacturing equipment downtime was significantly minimized through a reduction of the time needed for cleaning verification. Thus, the total analysis time for more than 30 samples with IMS was less than 2 h. The LOQs for the three methods used were 0.1, 0.54 and 1.1 μg, respectively.

IMS-based cleaning validation methods can also be considered total residue analysis methods; thus, the combination of active ingredients, excipients and cleaning agents remaining in industrial equipment will consume a fraction of the charged atmospheric gas reactant used for ionization (reactant ion consumption, RIC) [30]. A discussion about the organic and non-organic fraction of the sample is presented. The greatest limitations of this IMS method are its incompatibility with cleaners containing high concentrations of inorganic component and the limited ionization capacity of the instrument. However, the recoveries for 5 μg samples were accurate and precise (RSD < 2%).

Despite its high sensitivity and its ability to quantify trace level concentrations, the IMS technique has also been used for the quality control of major and minor components [31]. Thus, fourteen individual active ingredients in over-the-counter pharmaceutical formulations and commercial beverages were determined with electrospray-ion mobility spectrometry (ESI-MS) in combination with MS detection, which enabled the resolution and identification of analyte peaks after a simple dissolution step of composite samples containing 10–19 declared analytes.

Although IMS is not a chiral technique, exposing ions to a chiral modifier produces selective ion–molecule interactions which do not destroy the identity of the analytes. This approach enables true chiral separation of D- and L-enantiomers [32], and has been used with ESI-IMS-Time-of-Flight (TOF) MS for the expeditious separation of carbohydrates isomers [33,34].

3.2. Food and feed analyses

The responsiveness, sensitivity and selectivity of IMS make it highly suitable for food quality and safety control analyses including storage, process and quality control, and the characterization of foodstuffs (see Table 2). In recent years, the detection of metabolites from bacteria for purposes such as their identification and growth control [35], process control in beverage production [36], the detection of mould metabolites for process control during cheese production [37,38], the quality control of packaging materials during the production of polymers [35] and the characterization of wine have been accomplished with IMS [35,37]. Also, IMS has enabled the detection of rancid smelling metabolites formed as byproducts in production process with a view to assessing food quality. IMS has also been used as an identification tool for wines and liquors, which typically contain flavour volatiles that can be used as trace markers for origin. The plastic polymers used for packaging are the products of the polymerization of monomers which can cause allergic and lung diseases; therefore, IMS trace analyses of monomers can help control compliance with established concentration limits.

Meat analysis is one of the most cited applications of IMS. Basically, there are two types of IMS determinations. One involves controlling meat quality by determining biogenic metabolites produced during spoilage following bacterial degradation. Volatile amines such as trimethylamine can in fact be quantified with a LOD of 2 ng in less than 2 min with a long-term reproducibility of 15 or 25% [39]. There is a direct relationship between the qualitative and quantitative amine composition of samples depending on their storage time and temperature; as expected, the higher the temperature and the longer the time is, the faster is spoilage.

Multivariate calibration modeling was used as a data processing technique to calculate IMS regression slopes [40]. A set of trimethylamine solutions was prepared and a set of peak analyte spectra used to construct partial least-squares calibration models with a view to quantifying the amines in fresh, fair and bad chicken meat. Pattern recognition methods of the IMS signal were also used as classification tools for meat freshness [40].

Total volatile basic nitrogen (TVB-N) was determined by IMS in the headspace of fish samples, using an inexpensive sample introduction system based on a membrane and two switching valves [41]. Volatile compounds from gill samples after hexane extraction were used to estimate fish quality and shelf-life [42]; the results testified to the capabilities of the IMS–chemometric analysis combination for food quality assessment. Also, freshness in a pizza topping product (cooked sausages) was assessed in terms of the concentration of volatile organic compounds (VOCs) in the headspace as a marker of freshness [43]. Partial Least Squares (PLS) and Anova-PLS multivariate regressions were used to predict maximum storage periods from electronic nose data.

The determination of veterinary drug residues is a critical quality control method for fresh meat. Corona discharge ion mobility spectrometry (CD-IMS) was used to develop a quantitative method for the determination of furazolidone, chloramphenicol and enrofloxacin in poultry [44]. The sample was extracted with appropriate solvents and a secondary solid phase extraction of the analytes performed. The determinations of the three antibiotics were linear over ranges spanning about three orders of magnitude, and their LOQs all below 20 $\mu g\,kg^{-1}$.

Aflatoxin B1 and B2 in pistachios were determined with CD-IMS to monitor spoilage status [45]. Samples were introduced into the spectrometer via a GC headspace (HS) device. The resulting LOQ was 0.1 ng, which is the value for the reference method.

IMS has proved as a powerful tool for quality and safety control analyses of food samples such as that of ochratoxin by CD-IMS in liquorice roots following extraction and purification by passage through an immunoaffinity column [46].

One other application of IMS to meat quality control is origin authentication based on animal feeding. The assurance of food origin is one of the main objectives in characterizing some natural and traditional foods with a strong economic impact such as Iberian pig fat [47] by using a simple gas chromatography head space device connected to an IMS spectrometer in order to establish the fatty

Table 1
Recent applications of IMS in the pharmaceutical sector.

Group	Matrix	Compound	IMS mode	LOD values	Ref.
Cleaning verification	Water MeOH	Duloxetine HCl Surfactant	^{63}Ni-IMS	5–100 μg per 25 cm^2	[25]
	Acetonitrile Isopropanol	Synthesis intermediate Two active principle ingredients	^{63}Ni-IMS	0.1, 0.54 and 1.1 μg	[26]
		Duloxetine HCl Excipients Surfactant	^{63}Ni-IMS	5 μg	[27]
Final product quality control		Acetaminophen Aspartame Bisacodyl Caffeine Dextromethorphan Diphenhydramine Famotidine Glucosamin Guaifenesin Loratadine Niacin Phenylephrine Pyridoxine Thiamin Tetrahydrozoline Aspartame	ESI-IMS-MS	0.05–44 mM	[28]
Resolution of isomers		D/L-Atenolol D/L-Serine D/L-Methionine D/L-Threonine D/L-Penicillamine D/L-Valinol D/L-Phenylalanine D/L-Tryptophan	ESI-IMS-MS	–	[32]
		Carbohydrates	ESI-IMS-MS	–	[33,34]

Table 2
Recent applications of IMS in the food and feed sector.

Group	Compound	Separation	IMS mode	Ref.
General	Bacteria metabolites	–	^{63}Ni-IMS	[35]
Beer	Diacetyl 2,3-pentandione	HS-GC	^{63}Ni-IMS	[35]
	Diacetyl 2,3-pentandione	HS-GC	UV-IMS	[36]
Cheese	Metabolites from mould	HS-GC	^{63}Ni-IMS	[37]
	Metabolites from mould	–	^{241}Am-IMS	[38]
Wine and liquor	Flavour and taste volatiles	–	^{63}Ni-IMS	[35]
	Flavour and taste volatiles	HS-GC MCC	UV-IMS ^{63}Ni-IMS	[37]
General	Packaging monomers	-	^{63}Ni-IMS	[35]
Meat & Fish	Trimethylamine	HS-GC	^{63}Ni-IMS	[39]
	Trimethylamine	Dissolution	^{63}Ni-IMS	[40]
	TVB-N	HS-membrane	UV-IMS	[41]
	Volatile markers	Hexane extraction	^{241}Am-IMS	[42]
	Volatile markers	-	^{241}Am-IMS	[43]
	Furazolidone Chloramphenicol Enrofloxacin	SPE	CD-IMS	[44]
Pistachio	Aflatoxines	HS-GC	CD-IMS	[45]
Licorice roots	Ochratoxine A	Immunoaffinity columns	CD-IMS	[46]
Fat	Fatty acids	HS-GC	UV-IMS	[47]

HS-GC, head space gas chromatography; MCC, multicapillary column; TVB-N, total volatile basic nitrogen; SPE, solid phase extraction.

acid profile. Principal component analysis (PCA) and discriminant analysis (DS) methods allow the construction of a training library with predictive identification criteria for unknown samples. The fatty acid profile for nonIberian pig fat varies markedly with origin. This method enables accurate discrimination even when pigs are fed in a way mimicking the fatty acid profile for Iberian pigs.

3.3. Clinical analysis

IMS have been widely used in the clinical sector for two main purposes, namely: (a) the determination of drugs and drug metabolites; and (b) medical diagnoses based on the analysis of volatile biomarkers. In both cases, the sample is either a biological fluid or exhaled air (see Table 3).

IMS with thermal desorption for sample introduction has been used to the direct determination of γ-hydroxybutyrate, γ-butyrolactone and their degradation products in urine and breath [48] with detection limits in the low parts-per-million range. Saliva has also been directly analyzed by ESI-IMS for the determination of thiocyanate with a view to distinguishing between smokers and nonsmokers in a simple, rapid, inexpensive manner without the need for separation or sample preparation [49].

The main problems faced in the direct analysis of complex biological samples such as urine and serum by IMS arise from

Table 3
Recent applications of IMS in the clinical sector.

Group	Matrix	Compound	Sample treatment	Separation	IMS mode	LOD values	Ref.
Drugs	Serum and breath	γ-hydroxybutyrate and γ-butyrolactone	TD	None	^{63}Ni-IMS	Low ppm range	[48]
	Saliva	Thiocyanate	Flow injection	None	ESI-IMS	3 μg L^{-1}	[49]
	Urine	Cocaine and metabolites	SPE	None	^{63}Ni-IMS	4–10 μg L^{-1}	[51]
	Urine	Ephedrine	SPME	None	^{63}Ni-IMS	50 μg L^{-1}	[52]
	Serum	Methamphetamines	HS-SPME	None	CD-IMS	0.04–8 μg L^{-1}	[54]
	Plasma	Captopril	HS-SPME	None	CD-IMS	6.3 μg L^{-1}	[55]
	Blood	Se(IV)	HS-SPME	None	CD-IMS	12 μg L^{-1}	[56]
	Urine	Verapamil	SPME	None	SELDI-IMS	2 μg L^{-1}	[57]
	Urine and plasma	Trimipramine and desipramine	HF-LPME	None	ESI-IMS	1 μg L^{-1}	[59]
	Urine and plasma	Pentazocine	HF-LPME	None	ESI-IMS	2 μg L^{-1}	[60]
	Urine	Testosterone	MIP-SPE	None	CD-IMS	0.9 μg L^{-1}	[62]
	Spiked plasma	Caffeine and theophylline	MIP-SPE	None	ESI-IMS	0.2–0.3 mg L^{-1}	[63]
	Serum	Phenazopyridine	MIP-SPE	None	ESI-IMS	0.2 μg L^{-1}	[64]
	Serum	Primidone	MIP-SPE	None	ESI-IMS	5.1 μg L^{-1}	[65]
	Serum	Metronidazole	MIP-SPE	None	CD-IMS	10 μg L^{-1}	[66]
	Exhaled breath	Propofol	None	MCC	^{63}Ni-IMS	–	[67]
Biomarkers	Breath	Sarcoidosis	Exhalation	MCC	^{63}Ni-IMS	Ppb level	[71]
		Sarcoidosis	Exhalation	MCC	^{63}Ni-IMS	Ppb level	[72]
		Lung diseases	Exhalation	MCC	^{63}Ni-IMS	Ppb level	[70]
		Diseases	Exhalation	MCC	^{63}Ni-IMS	Ppb level	[68]
		Diseases	Exhalation	MCC	^{63}Ni-IMS	Ppb level	[69]
		Cancer	Exhalation	MCC	^{63}Ni-IMS	0.1–2.1 μg L^{-1}	[73]
		Lung cancer	Exhalation	MCC	^{63}Ni-IMS	Ppb level	[74]
		Diseases	Adsorption on Tenax – TD	None	ESI-IMS-MS	ng level	[75]
	Urine	Acetone	HS	None	UV-IMS	3 mg L^{-1}	[76]
	Serum	N-linked glycans	Flow injection	None	ESI-IMS-MS ESI-IMS-IMS-MS	–	[77]
	Blood	Metabolites	Flow injection	None	ESI-IMS-MS	–	[78]
	Lymph extracts	Metabolites	Flow injection	None	ESI-IMS-MS	–	[79]

TD, thermal desorption; ESI, electrospray; SPE, solid phase extraction; SPME, solid phase microextraction; HS-SPME, head space solid phase microextraction; CD, corona discharge; SELDI, Surface enhanced laser desorption ionization; HF-LPME, Hollow fiber liquid phase microextraction; MIP-SPE, molecularly imprinted polymer solid phase extraction; MCC, multi-capillary column.

suppressed ionization due to charge exchange reactions, and competitive ionization of salts and other polar compounds present in the sample [50]. Both traditional (solid phase extraction, SPE) and more recent sample preparation techniques (solid phase microextraction, SPME; molecularly imprinted polymer SPE, MIP-SPE) have been used to overcome the interferences of biological matrices with IMS analyses.

IMS has been used in combination with SPE to retain the target analytes and remove salts and other polar compounds potentially interfering with volatilization or ionization processes—and improve detection limits as a result. Thus, SPE-IMS was used for the determination of cocaine and its metabolites in urine with spectral data analysis by alternating least squares (ALS) methodology to resolve the ion peak for the reactant from those for the product [51].

Solid-phase microextraction (SPME) is a simple, fast, solvent-free sample preparation technique integrating sampling, extraction, concentration and sample introduction in a single step, all without the need for organic solvents. Both direct immersion and headspace extraction methods have been thoroughly explored in combination with IMS. For example, the determination of ephedrine in urine by direct SPME immersion and IMS analysis has provided a useful tool for the fast, sensitive on-site monitoring of drugs in biological samples [52].

Headspace SPME (HS-SPME) provides several advantages over direct immersion including the obtainment of a neat IMS plasmagram and protection of the fiber from irreversible damage by nonvolatile concomitants present biological matrices [53]. The feasibility of HS-SPME coupled to IMS for the simple, rapid determination of methamphetamines in human serum [54], captopril in plasma [55], and selenite [Se(IV)] (by derivatization with 1,2-diaminobenzene) in human blood [56] has been demonstrated. The analytes are introduced into the IMS instrument by thermal desorption, so the methodology is unsuitable for nonvolatile and/or thermally labile compounds. The introduction of SPME/surfaced enhanced laser desorption/ionization (SELDI) fibers has expanded the scope of SPME-IMS to the analysis of nonvolatile and/or large molecules. The procedure involves direct ionization from polypyrrole coated fiber by a Nd:YAG laser and was validated with the IMS determination of verapamil in urine samples with no further sample cleanup [57].

A combination of hollow-fiber based liquid phase microextraction (HF-LPME) and IMS was used to circumvent the greatest shortcomings of SPME (viz. a high cost, sample carry-over, fiber fragility, limited lifetime) [58]. HF-LPME combines extraction, concentration and sample cleanup in a single step. Because the hollow fibers typically used in HF-LPME are inexpensive, they can be disposed of after a single use to avoid the risk of sample carryover. A methodology based on three-phase HF-LPME was developed for the determination of trimipramine and desipramine [59], and that of pentazocine [60], in urine and plasma samples by ESI-IMS analysis of the acceptor phase.

IMS has also been successfully used in combination with molecularly imprinted polymer (MIP) solid phase extraction. MIP has the ability to selectively extract a single molecule or a group of structurally related molecules from a relatively complex matrix [61]. IMS has proved compatible with this pre-separation technique and facilitated the highly selective determination of biochemical compounds such as testosterone in urine [62]; caffeine and teophylline in spiked plasma [63]; and phenazopyridine [64], primidone [65] and metronidazole [66] in serum. Although MIPs are rapidly built and their components usually stable, their preparation requires a prior knowledge of the polymerization process, functional monomers and cross-linkers involved.

IMS has also been used to determine propofol in exhaled air consistently with its concentrations in serum [67] by on-line coupling a multicapillary column (MCC) to IMS for enhanced separation

capabilities; the limit of detection (LOD) thus obtained was 0.7 $\mu g\,L^{-1}$ and the within-day precision 2.5%.

One other area explored by IMS in the clinical sector is the use of volatile metabolites from breath and biological fluids as biomarkers for diagnostic purposes. Usually, this requires coupling IMS to a pre-separation technique such as MCC and/or a selective detector such as an MS. In both cases, information is obtained as a complex three-dimensional dataset which requires using an effective chemometric tool for evaluation, classification and analyte quantification. Disease-specific peaks can be identified by comparing the plasmagrams for patients with a particular disease and others in a control group. The relationships of such peaks to specific diseases such as airway and lung infections or bacterial colonization have been examined [68–70]. Thus, MCC-IMS allowed patients with sarcoidosis to be accurately discriminated from healthy individuals [71,72]. Similarly, MCC-IMS breath analyses of patients with various types of cancer were compared with those for healthy persons to identify biomarkers for specific cancer diseases and facilitate an early diagnosis [73,74]. Breath analyses have also been performed by retaining volatile metabolites in a tenax adsorbent and interfacing a thermal desorption unit to an ESI-IMS-MS spectrometer [75]. The combination of temperature programmed thermal desorption (TD) and IMS improved the response of selected species and enabled the identification of breath metabolites from ion mobilities and accurate mass measurements.

IMS has also been applied to other body fluids such as urine and serum for diagnostic purposes. For instance, human and cow urine samples were used to identify acetone as a potential biomarker for fat metabolism-related diseases [76]. The headspace of urine samples was transferred to a UV-IMS spectrometer via two switching valves, which afforded a LOD of 3 $mg\,L^{-1}$ and recoveries of $109 \pm 3\%$ from spiked urine samples. IMS-MS and IMS-IMS-MS were used to study *N*-linked glycans isolated from human serum of healthy and diseased patients [77]. Statistical analyses of the IMS data suggested that aberrations in isomer distributions might be indicative of some diseases. The additional IMS dimension provided information about isomer and conformer compositions which cannot be obtained by MS alone; therefore, this hyphenated methodology appears to be especially useful for studying diseases involving different isomeric forms of glycoproteins.

High resolution IMS-MS has been successfully used to determine metabolites in blood with the aim of gaining insight into many human disease mechanisms and identifying diagnostic biomarkers [78]. This methodology, which requires no preconcentration, can detect and resolve over 1100 metabolites in methanol extracts of blood including amino acids, carbohydrates, amines, organic acids, sterols, estrogens, prostaglandins, phosphocholines, mono- and diacylglycerophosphoethanolamines, mono- and diacylglycerols, sphingolipids, isoprenoids and various metabolic intermediates. A similar approach based on high resolution ESI-IMS-MS and multivariate processing of the results was successfully evaluated for analytical purposes in metabolomics with a view to identifying changes in metabolite concentrations in lymph extracts from animals on a fasting regimen or fed with a mixed meal [79]. A total of 165 and 78 metabolites were detected in the positive and negative mode, respectively, in lymph samples.

3.4. Environmental analysis

Some features of IMS such as its low cost, portability, flexibility, sensitivity and selectivity make it the ideal technique for on-site, real-time environmental applications [80]. IMS has in fact been successfully used for environmental analyses based on (a) monitoring of outdoor and indoor air to automate the detection of hazardous organic vapors; (b) measurements of contaminants present in water and discharge effluents; and (c) analysis of VOCs and semivolatile organic compounds present in headspace vapor evolved from potentially contaminated soil and solid samples (see Table 4).

By virtue of the ease with which samples can be introduced in IMS, the determination of VOCs in air samples is its most direct application in environmental analysis. Thus, IMS has been used for the on-site monitoring of VOCs produced during tile baking in the ceramic industry, using an air-flow permeation setup with reference compounds for calibration [81]; the monitoring of emissions from surfaces in indoor air with a UV lamp as ionization source and MCC for pre-separation of analytes [82]; and the direct determination of VOCs in air with a custom-built UV-ion mobility spectrometer [83]. Also, BTEX compounds were determined in air by using a bipolar ionization source based on a UV lamp [17], and ambient ammonia in urban air was measured to monitor emissions from fertilizer manufacturing facilities [84].

Most environmental samples analyzed by IMS are aqueous. Depending on the nature of the particular water sample (natural, tap, river, sea, ground), its matrix can be complex enough to require cleanup and preconcentration prior to IMS analysis. For example, methyl *tert*-butyl ether (MTBE) was determined in water and gasoline samples by using a membrane extraction unit prior to IMS analysis [85], and also by HS-SPME with a dodecylsulfate-doped polypyrrole coated fiber [86]. Likewise, halogenated substances in water samples have been determined by using various sample treatments including membrane extraction [87], ionic liquid based HS-single drop microextraction (SDME) and room temperature GC separation prior to IMS analysis [88], HS-SPME with MCC-IMS [89] and ESI-IMS after LC large-bore pre-separation [90]. Pesticide residue analyses have also been accomplished by IMS without any prior separation. Malathion, ethion and dichlorovos [91]; sevin, amitraz and metalaxyl [92]; and ethyl parathion and toluene 2,4-diisocyanate [93] standards were successfully analyzed by thermal desorption followed by IMS with a β-radiation ionization source. However, none of the ensuing methods was applied to real samples. Atrazine and ametryn in water and soil samples were successfully determined by IMS with no chromatographic separation [94]. The analytes were extracted from environmental samples by HS-SPME, using a dodecylsulfate-doped polypyrrole film; the results for samples spiked with 200 $ng\,g^{-1}$ concentrations of the two analytes were quite acceptable.

Inorganic compounds in environmental matrices can be also determined with IMS. Thus, nitrite and nitrate in real water samples were determined with a detection limit of 10 and 40 ppb, respectively, by using an ESI ionization source [95]. Also, ESI-IMS was used to obtain the distinct peak patterns and reduced mobility constants for arsenate, phosphate, sulfate, chloride, formate and acetate. Ammonia nitrogen in water samples was quantified by IMS, using a corona discharge as ionization source and pyridine as reagent gas to create alternate reactant ions to further enhance the selectivity [96]. The principal advantage of corona discharge over ^{63}Ni as an ionization source is the increased total ion current it provides (about an order of magnitude greater), which leads to improved sensitivity, signal-to-noise ratio and dynamic range. Selenite ion [Se(IV)] in blood and water samples was determined by IMS after derivatization with 1,2-diaminobenzene for conversion into its piaselenol form, which was extracted and preconcentrated by HS-SPME prior to injection into the IMS instrument [56]. The derivatization step was necessary because nonvolatile compounds cannot be processed with commercial or conventional IMS injection-ionization systems, which inevitably entails converting metal ions into volatile forms amenable to IMS detection.

Environmental soil samples have been also successfully analyzed by IMS. Thus, halogenated compounds in the vadose soil zone were determined by inserting a specially developed small subsurface IMS spectrometer into a cone penetrometer [97,98]. Soil gas

Table 4
Recent environmental applications of IMS published in the scientific literature.

	Group	Compound	Sample introduction	Separation	IMS mode	LOD values	Ref.
Air quality	VOCs	VOCs	None	None	^{63}Ni-IMS	–	[81]
		VOCs	Aspiration	MCC	UV-IMS	5–1200 μg L^{-1}	[82]
		VOCs	None	None	UV-IMS	1 μg L^{-1}	[83]
		BTEX	None	None	^{63}Ni-IMS	40–65 μg L^{-1}	[17]
					UV-IMS	50–63 μg L^{-1}	
	Inorganic compounds	Ammonia	Membrane inlet	None	^{63}Ni-IMS	0.10 μg L^{-1}	[84]
Water & liquid samples	VOCs	MTBE	Water-Air membrane extraction unit	None	^{63}Ni-IMS	0.1–4 mg L^{-1}	[85]
					UV-IMS		
					CD-IMS		
		MTBE	HS-SPME	None	CD-IMS	0.7–4.9 μg L^{-1}	[86]
	Halogenated substances	Tetrachloroethylene and trichloroethylene	PDMS membrane	None	^{63}Ni-IMS	74–80 μg L^{-1}	[87]
		Trihalomethanes	IL-HS-SDME	RTGC	^{3}H-IMS	100–910 ng L^{-1}	[88]
		Chloroethenes, chlorobenzenes and aromatics	HS-SPME	MCC	UV-IMS	Upper μg L^{-1} range	[89]
		Chlorophenols	None	LC large bore	ESI-IMS	0.135–2.23 mg L^{-1}	[90]
	Pesticides	Malathion, ethion and dichlorovos	None	None	^{63}Ni-IMS	0.21–0.94 ng	[91]
		Sevin, Amitraz, and Metalaxyl	None	None	^{63}Ni-IMS	0.45–0.58 ng	[92]
		Ethyl parathion and toluene 2,4-diisocyanate	Vapor generation	None	^{241}Am-IMS	4.9–30 μg L^{-1}	[93]
		Atrazine and ametryn	HS-SPME	None	CD-IMS	37–23 ng g^{-1}	[94]
	Inorganic compounds	Nitrite and nitrate	None	None	ESI-IMS	10–40 mg L^{-1}	[95]
		Ammoniacal nitrogen	Purge system	None	CD-IMS	9.2 μg L^{-1}	[96]
		Se	HS-SPME	None	CD-IMS	12 μg L^{-1}	[56]
Solids & aerosols	Halogenated substances	Chlorocarbons	Exponential dilution	None	^{63}Ni-IMS	6–8 nL L^{-1}	[97]
	Halogenated substances	Gaseous VOCs	Exponential dilution	None	^{63}Ni-IMS	-	[98]
	Pesticides	Malathion	UV photolytic vapor generation	None	^{63}Ni-IMS	<0.01 mg m^{-3}	[99]
		Atrazine and ametryn	HS-SPME	None	CD-IMS	37–23 ng g^{-1}	[94]
	VOCs	α-pinene	None	None	^{63}Ni-IMS	Ppb range	[100]

VOC, volatile organic compound; BTEX, benzene, toluene, ethylbenzene and xylene; MCC, multi-capillary column; TD-SPME, thermal desorption-solid phase microextraction; PDMS, polydimethylsiloxane; ESI, electrospray ionization; IL-HS-SDME, Ionic liquid-head space-single drop microextracion; RT-GC, room temperature-gas chromatography; HS-SPME, head space-solid phase microextraction; MTBE, methyl tert butyl ether; CD, corona discharge.

Table 5
Recent applications of IMS in processes and bioprocesses monitoring and quality control.

			Analytes	IMS	Ref.
Processes	Polymer industry	Synthesis (emulsion polymerization)	VA, BA and MMA	UV-IMS	[103]
				^{63}Ni-IMS	
		Synthesis (radical polymerization)	PMMA	IMS-MS	[104]
		Reaction monitoring	7-fluoro-6-hydroxy-2-methylindole	ESI-IMS-MS	[105]
		Composition of mixtures	PEGs	ESI-IMS-MS	[106]
			PEGs	ESI-IMS-MS/MS	[107]
			PEGs and PEGylated proteins	ESI-IMS-MS	[108]
			Branched and linear aramid fibers	MALDI-IMS-MS	[109]
			PEGs, PTMEG, PEMA, Pn-BMA, Pt-BMA, PMMA, PPG, and Jeffamine®	ESI-IMS-MS	[110]
				ESI-IMS-IMS-MS	
		Outgassing	Zeonor, conductive polystyrene, Zeonex, nylon and conductive nylon	IMS	[18]
	Petroleum industry	Quality control	Markers	LDI-IMS-MS	[114]
		Quality control	Markers	LDI-IMS-MS	[115]
		Composition of mixtures	Asphaltenes and dealphaltenes oils	LDI-IMS-MS	[116]
		Composition of mixtures	Hydrocarbons	ASAP-IMS-MS	[12]
	Carbon nanotubes production	Impurities determination	Fullerenes	LDI-IMS-MS	[117]
	Wood industry	Quality control of Preservatives	Propiconazole and tebuconazole	TD-^{63}Ni-IMS	[118]
	Natural gas industry	Odorization	Sulfur free odorants	^{63}Ni-IMS	[119]
Bioprocesses	Enzyme reactions	Acetylcholinesterase	Acetylcholine and choline	^{63}Ni-IMS	[122]

VA, vinyl acetate; BA, butyl acrylate; MMA, methyl methacrylate; PMMA, poly(methyl methacrylate); ESI, electrospray ionization; PEG, polyethyleneglycol; MALDI, matrix assisted laser desorption ionization; PTMEG, poly(tetramethylene glycol); PEMA, poly(ethyl methacrylate); Pn-BMA, poly(n-butyl methacrylate); Pt-BMA, poly(tert-butyl methacrylate); PPG, poly(propylene glycol); LDI, laser desorption ionization; ASAP, atmospheric solids analysis probe; MCC, multi-capillary column; TVB-N, total volatile basic nitrogen; TMA, trimethylamine.

contaminants were thus separated and detected in environmental subsurface samples with good sensitivity and selectivity. Malathion residues in organic and inorganic aerosol dust were analyzed by IMS with UV photolytic vaporization [99]. Dust was collected with various methods to characterize its UV photolytic vaporization signature. Malathion and related photolysis products were successfully determined in a direct manner in untreated dust particle samples by using IMS with a ^{63}Ni ionization source. The usefulness of IMS for studying the formation of organic aerosols from biogenic and anthropogenic VOCs with atmospheric oxidants was evaluated on a model aerosol formed by oxidation of α-pinene [100]. IMS was found to provide a useful tool for monitoring and analyzing the gas phase in parallel with aerosol measurements during aerosol particle formation. Also, it provided additional time-resolved information about the compounds involved in the in situ formation of new particles in real time.

3.5. Process and bioprocess monitoring

Process understanding is an essential requirement to assure quality and purity in the pharmaceutical, petrochemical, polymer and food industries, as well as to obtain detailed information about the course of a reaction, its intermediates and its end products. Process monitoring has evolved from chromatographic to spectroscopic techniques, where specific chemical or physical properties can be measured instantaneously, thereby improving product quality and saving costs. IMS is a powerful tool for process control by virtue of its ability to monitor chemical and biochemical reactions in near-real time (see Table 5). This section discusses the uses IMS for monitoring technical and biological processes.

The polymer industry has expanded rapidly worldwide in response to the increasing demand of the global market across a wide range of areas [101]. Thus, increasingly complex polymeric structures have been developed to provide desirable properties and functions that depend on a number of factors including end group composition, molecular weight distribution (MWD) and 3D conformation [102]. This has raised the need for powerful, selective analytical technologies for characterizing such complex polymeric structures.

The main advantages of IMS (particularly its sensitivity, selectivity and quasi real-time response capabilities) make it a highly useful tool for monitoring polymer reactions. Thus, IMS has been used for the online monitoring of vinyl acetate concentrations in semibatch emulsion polymerizations [103]. A LOD of ca. 1% vinyl acetate was obtained by using UV light as ionization source and HS sampling in a continuous recirculating system. The radical polymerization reaction of poly(methyl methacrylate) (PMMA) in butyl acetate in the presence of a peroxide initiator was monitored by high resolution IMS-MS [104], which provided detailed end group information and discrimination of molecules with identical nominal masses without the need for previous, time-consuming LC separation. IMS was also successfully used to monitor the polymerization reaction of 7-fluoro-6-hydroxy-2-methylindole in the presence of sodium hydroxide, air and light [105]. Aliquots withdrawn from the reaction vessel at hourly intervals were measured by ESI-IMS-MS to determine the concentrations of monomer, dimer, trimer and higher-order molecules.

IMS in combination with tandem MS-ESI enabled the resolution of polymers with an identical nominal *m/z* ratio but a different structure [106]. The ESI-IMS-MS procedure was used to examine distributions of PEGs with average molecular masses of 6550 and 17900 Da, and provided useful information about polymer size distributions and smaller oligomers spanning wide ranges of charge states and sizes. Using IMS significantly reduced spectral congestion relative to ESI-MS alone and enabled the resolution of structures with dissimilar gas phase volumes. In addition, ESI-IMS-MS/MS was used to study mixtures of synthetic polymers, PEG 1000 and PEG monooleate, plus stearyl alcohol initiated PEG and PEG *bis*(2-ethyl hexanoate) [107]. Once again, ESI-IMS provided an additional dimension of fast, sensitive, gas-phase, ion separation enabling the discrimination of isobaric synthetic polymers by size, shape and charge. In another application, ESI-IMS-MS facilitated the characterization of large PEGs and PEGylated proteins [108]. Low abundance free PEG in a PEGylated peptide preparation, which is not directly detectable by MS, was easily observed and accurately quantified by IMS-MS.

The MALDI-IMS-MS combination has a great potential for separating and identifying different branched and linear species of aramid fibers [109]. IMS exhibited a greater discriminating power than gel permeation chromatography (GPC) and dispensed with the need for fraction collection.

IMS-MS and IMS-IMS-MS have been successfully used for complex blend and copolymer characterization, instantaneous recognition and even quantification of differences between samples [110]. Multidimensional IMS-MS analysis is cost effective in terms of equipment, analysis and reagent consumption—it virtually avoids the need for the consumables typically used in liquid separation methods. These methodologies extract information based on molecular shape and size, and hold promise for predicting changes in polymer physical properties.

IMS has also been successfully used to detect outgassing of VOCs in the polymer industry. The pioneering work reported in 1979 [111] was followed by in-depth studies of the outgassing characteristics of various polymer materials used in the semiconductor technology such as polypropylene (PP), polycarbonate (PC), perfluoroalkoxy polymer (PFA), polyvinylidene fluoride (PVDF), acrylonitrile butadiene styrene copolymer (ABS) and polytetrafluoroethylene (PTFE) [112]. Recently, the outgassing feasibility of conditioned and unconditioned polymeric materials including Zeonor, conductive polystyrene, Zeonex, nylon and conductive nylon for use in IMS drift tubes was studied [21].

Petroleomics studies and characterizes petroleum at the molecular level. Petroleum is a complex oil mixture containing thousands of chemical compounds which require fast, accurate chemical fingerprinting with a view to assessing the characteristics of the refining process, the production efficiency and, ultimately, the economic value of oil and the level of environmental pollution to be expected upon combustion. Ultrahigh resolution MS has shown potential to resolve components in crude oil; however, it is difficult to assign unique elemental formulas to ions with *m/z* ratios above 300 [113]. The unique ability of IMS-MS to resolve complex polymer mixtures, and hence its potential for complete conformational and chemical characterization of petroleum samples, were exploited for the direct desorption and ionization from a stainless steel sample plate with a laser desorption-ionization (LDI) [114,115]. A similar methodology was used to study petroleum asphaltene and deasphaltened oils [116] that exposed differences in MW distribution between the two types of oil. Petroleomic studies have also been addressed by using an atmospheric pressure solid analysis probe (ASAP) source and a high-resolution IMS-MS instrument [12]. In the ASAP source, the sample was heated, volatilized with a nitrogen stream and ionized by corona discharge (CD). The results obtained by IMS-MS analysis of crude oil can be used to investigate structural relationships between crude oil molecules.

Additional industrial applications of IMS include the detection of fullerene impurities in the production of carbon nanotubes by IMS-MS with laser desorption ionization [117]; the detection and determination of preservatives such as propiconazole and tebuconazole in wood by thermal desorption (TD)-IMS [118]; and the detection of sulfur-free odorants such as Gasodor® S-Free®, and a mixture of methylacrylate, ethylacrylate and methylethylpyrazine, in less than 80 s in the gas industry by means of a handheld IMS

placed directly at the gas pipe [119]. This methodology is the basis for two portable, miniaturized IMS spectrometers named IMS®-ODOR and μIMS®-ODOR which have been specially designed by G.A.S. Gesellschaft für Analytische Sensorsysteme mbH to determine sulfur-free odorants in natural gas [120].

As noted in Section 3.2, IMS is also useful for monitoring and controlling bioprocesses (i.e. reactions governed by microbial metabolism). Enzymatic reactions can also be considered bioprocesses since enzymes are required for a wide variety of functions in living organisms including signal transduction, cell regulation, movement and transport. The fact that many diseases are directly linked to the aberrant activities of one or several enzymes has aroused growing interest among health researchers in enzymology and led to a substantial fraction of modern pharmaceutical research relying on the search for potent, specific inhibitors of the disease related enzymes [121]. The capabilities of IMS for determining enzyme activity inhibition has been demonstrated with acetylcholinesterase inhibition by neostigmine and galanthamine, which has provided a new, efficient tool for studying enzyme reactions with a view to drug screening or the facilitation of enzymological studies [122].

4. Conclusions and future trends

The operational simplicity and expeditiousness, and exceptionally high sensitivity of IMS, have turned it into a highly useful analytical tool for use alone or in combination with MS and/or chromatography.

Ionization sources originally developed for ambient MS (e.g. DART, DESI) have been successfully adapted for IMS analysis. Available interfaces between the two systems afford the analysis of intact samples without the need for dissolution or extraction. Drift tube materials and designs have received renewed attention and some IMS instruments are now constructed with drift tubes made from glass or polymers, which are less expensive and difficult to operate than their conventional counterparts.

Close inspection of the scientific literature exposes a wide range of IMS applications beyond explosive, illicit drug and chemical warfare agent monitoring. In fact, IMS is by now a mature technique for quality control of end products and cleaning validation in the pharmaceutical sector. In addition, IMS has strongly emerged in other analytical fields including clinical, food and environmental analysis, and is bound to continue to expand in other chemical industrial areas. Coupling IMS with MS^n has introduced a new dimension facilitating the analysis of highly complex mixtures with improved sensitivity and selectivity in the polymer and petroleomic industries, where it provides information about the sample not available from MS measurements alone; this affords a 3–5 fold increase in separation efficiency compared to one-stage low-resolution MS analysis. One other advantage of coupling IMS to MS is the ability to separate multiple compounds having the same nominal molecular weight by size, shape, and charge.

However, IMS still has some major drawbacks such as the risk of charge exchange reactions and competitive ionization, which can result in strong or even complete signal suppression for some analytes (especially in the direct analysis of complex samples, where interferent concentrations may exceed those of the target analytes). This, together with the decreased separation efficiency of commercial IMS instruments, has so far required the use of a selective detector and prior sample cleanup and/or chromatographic separation. On the other hand, IMS is more affordable and mechanically robust, and easier to operate, than MS. Also, it provides sensitivity on a par with that of a flame ionization detector in GC and usually better than that of a UV–vis absorption detector in LC [123].

Another advantage of IMS over MS in the absence of preliminary separation is that use of the latter is hindered by its varying sensitivity, which usually requires internal standards for quantitation. Both techniques, however, are exposed to suppression of ionization by effect of matrix interferences.

Future improvements in instrumentation design and drift tube materials is bound to improve the resolution power of IMS and bring them closer to its theoretical capabilities. Also, additional developments in multidimensional IMS can be expected to raise its sensitivity, resolving power and selectivity.

In summary, the dramatic recent expansion of its applications and developments anticipates a promising future for IMS and demonstrates that technical barriers can usually be successfully overcome.

Acknowledgments

The authors gratefully acknowledge funding by Spain's Ministry of Science and Technology (Project CTQ2009-08312). S. Armenta is also grateful for award of a *Juan de la Cierva* grant by the Ministry.

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